To protect the identities of pediatric transgender, nonbinary, and gender diverse patients, city names and clinical sites where research subjects have been treated are redacted from this version of the report.

COLLEGE OF PHARMACY
UNIVERSITY OF UTAH
L. S. SKAGGS PHARMACY INSTITUTE

GENDER-AFFIRMING MEDICAL TREATMENTS FOR PEDIATRIC PATIENTS WITH GENDER DYSPHORIA

PART I:

PHARMACOLOGICAL AGENTS
GUIDELINES
SYSTEMATIC REVIEWS
BIBLIOGRAPHY OF INCLUDED STUDIES
EXPERIMENTAL AND OBSERVATIONAL STUDIES
DESCRIPTIVE STUDIES

PART II:

LONG-TERM OUTCOMES

Submitted to

Utah Department of Health and Human Services

Jennifer Strohecker, PharmD, BCPS
Medicaid Director
Director, Division of Integrated Healthcare
jstrohecker@utah.gov

Michelle Hofman, MD, MPH, MHCDS, FAAP
Medical Director
Utah Department of Health and Human Services
mhofmann@utah.gov

Submitted by

Joanne LaFleur, PharmD, MSPH
Director, Drug Regimen Review Center
Associate Professor, Department of Pharmacotherapy
University of Utah, College of Pharmacy
Joanne.LaFleur@pharm.utah.edu

August 6, 2024

University of Utah College of Pharmacy, Drug Regimen Review Center.

CONTENTS

LIST OF FIGURES

In Part I

In Part II

LIST OF TABLES

In Part I Report Body

In Part I Appendixes

In Part II Report Body

In Part II Appendixes

REPORT CONTRIBUTORS

- Joanne LaFleur, PharmD, MSPH — Director, DRRC
- Lauren Heath, PharmD, MS, BCACP — Clinical Pharmacist, DRRC
- Valerie Gonzales, PharmD — Clinical Pharmacist, DRRC
- Monet Luloh, PharmD — Clinical Pharmacist, DRRC
- Rebecca Henkels, PharmD candidate — Pharmacist Intern
- Ary Vadipour, PharmD candidate — Pharmacist Intern
- Danielle Nguyen, PharmD, PhD candidate — Graduate Research Assistant
- Xi Liang, PharmD, PhD candidate — Graduate Research Assistant
- Tami Haines, RPh — Clinical Pharmacist
- Kristin Knippenberg, MFA — Project Administrator

FUNDING AND FINANCIAL CONFLICTS OF INTEREST

The writing of this report was sponsored by funding from the Utah Department of Health and Human Services. The report contributors have no other conflicts of interest to declare.

ABBREVIATIONS

Alphabetized by Abbreviation

AAP	American Academy of Pediatrics
ABCL	Adult Behavior Checklist
aBMD	Areal bone mineral density
ACOG	American College of Obstetricians and Gynecologists
ACoG	Amsterdam Cohort of Gender Dysphoria
ADHD	Attention deficit hyperactivity disorder
AFAB	Assigned female at birth
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMA	American Medical Association
AMAB	Assigned male at birth
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews, Version 2
Amsterdam UMC	Amsterdam University Medical Center
aOR	Adjusted odds ratio
ASQ	Ask Suicide Screening Questions
ASR	Adult self-report
AST	Aspartate transaminase
BA	Bone age
BCE	Before common era
BDI	Beck Depression Inventory
BDI-(Y)	Beck Depression Inventory (for Youth)
BDI-II	Beck Depression Inventory-II
BES	Body Esteem Scale for Adolescents and Adults
BIS	Body Image Scale
BMAD	Bone mineral apparent density
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BTM(s)	Bone turnover marker(s)
C-SSRS	Columbia Suicide Severity Rating Scale
CA	Chronological age
CADTH	Canada's Drug and Health Technology Agency
CBCL	Child Behavior Checklist

Return to TOC

CBD	Cortical BMD
CCT	Controlled clinical trial
CD-RISC	Connor-Davidson Resilience Scale
CDC	Center for Disease Control and Prevention
CDI	Children's Depression Inventory
CEGD	Center of Expertise on Gender Dysphoria
CEOAE(s)	Click-evoked otoacoustic emission(s)
CESD-R	Center for Epidemiologic Studies Depression Scale
CF	Cystic fibrosis
CGAS	Children's Global Assessment Scale
CHEO	Children's Hospital of Eastern Ontario
CHLA	Children's Hospital Los Angeles
CI	Confidence interval
cLDL	Low-density lipoprotein cholesterol
cm	Centimeter(s)
CML	Chronic myelogenous leukemia
COI	Conflict of interest
CPP	Central precocious puberty
CSH	Cross-sex hormones
CSHT	Cross-sex hormone therapy
DC	District of Columbia
DFAB	Designated female at birth
dL	Deciliter
DLPFC	Dorsolateral prefrontal cortex
DM	Diabetes mellitus
DMAB	Designated male at birth
DRRC	Drug Regimen Review Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision
DVT	Deep vein thrombophlebitis
DXA	Dual-energy radiograph absorptiometry
ED	Endocortical diameter
EDE-Q	Eating Disorders Examination Questionnaire
EROS	Erotic Response and Orientation Scale
ES	Endocrine Society
ESSM	European Society for Sexual Medicine
ET-FMR	Extremities/Trunk fat mass ratio
FBeK	Fragebofen zur Beurteilung des eisenen Körpers (Body image assessment questionnaire)
FDA	US Food and Drug Administration

Return to TOC

FDAMA	Food and Drug Administration Modernization Act of 1997
FEV	Forced expiratory volume
fMRI	Functional magnetic resonance imaging
FN	Femoral neck
FTM	Female-to-male, or assigned female at birth transitioning to male
GAD-7	General Anxiety Disorder-7
GAET	Gender-affirming estrogen treatment
GAH	Gender-affirming hormone(s)
GAHT	Gender-affirming hormone therapy
GAS	Gender-affirming surgery
GD	Gender dysphoria
GDAAY	Gender Diversity and Affirming Action for Youth Clinic of the Health Sciences Center, Winnipeg, Manitoba
GENECIS	Children's Health GENder Education and Care Interdisciplinary Support program
GGT	Gamma-glutamyl transferase
GIDS	Gender Identity Development Service
GIDYQ	Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults
GIQ-Ad	Gender Identity Questionnaire for Adolescents
GIS	Gender Identity Service
GMSR-A	Gender Minority Stress and Resilience Measure for Adolescents
GnRH	Gonadotropin-releasing hormone
GnRH analog	Gonadotropin-releasing hormone analog/analogue/agonist
GnRH antagonist	Gonadotropin-releasing hormone antagonist
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
GRS	Gender reassignment surgery
GWBS	General Well-being Schedule
HB	Hemoglobin
HCP(s)	Healthcare professional(s)
HCT	Hematocrit
Hg	Mercury
HRQOL	Health-related quality of life
HT	Hormonal therapy
HTN	Hypertension
ICD	International Classification of Diseases
IOM	Institute of Medicine
IQ	Intelligence quotient
IRB	Institutional Review Board
ISRCTN	International Standard Randomized Controlled Trial Number Register
ITS	Interrupted time series
IUD	Intrauterine device

Return to TOC

IV	Intravenous
K6	Kessler Psychological Distress Scale
kg	Kilogram(s)
KIDSCREEN-27	KIDSCREEN Health Related Quality of Life Questionnaire for Children and Young People and their Parents, Short Version
KP	Kaiser Permanente
KZcG	Kennis- en Zorgcentrum Genderdysforie
L	Liter(s)
LA	Long-acting
LBM	Lean body mass
LGBTQ	Lesbian gay bisexual transgender queer
LGI	Leeds General Infirmary
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
LOE(s)	Level(s) of evidence
LS	Lumbar spine
LSAS	Liebowitz Social Anxiety Scale
LT-FMR	Legs/Total fat mass ratio
LTH	Left total hip
LUMC	Leiden University Medical Center
m	Meter(s)
MA	Meta-analysis
MacCAT-T	MacArthur Competence Assessment Tool for Treatment
mBMI	Median body mass index
MDC	Medical decision-making competence
MDS	Modified Depression Scale
MeSH	Medical Subject Headings for National Library of Medicine
mFG	Modified Ferriman-Gallwey
MHP(s)	Mental health professional(s)
MI	Myocardial infarction
mIU	Milli-international unit(s)
mL	Milliliter(s)
mm	Millimeter(s)
mmol	Millimole(s)
MRI	Magnetic resonance imaging
MRT	Mental rotation task
MSPSS	Multi-dimensional Scale of Perceived Social Support
MTF	Male-to-female, or assigned male at birth transitioning to female
N/A	Not applicable
N/R	Not reported

Return to TOC

N/S	Not significant
ng	Nanogram(s)
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service
NIH	National Institutes of Health
NOS	Newcastle-Ottawa Scale
NRI	Network of Relationships Inventory—Relationship Qualities
NRSI	Non-randomized studies of interventions
NSSI	Non-suicidal self-injury
OASIS	Overall Anxiety Severity and Impairment Score
OATP	Organic anion transporting polypeptide
OC	Osteocalcin
OGD	Other gender-diverse
OR	Odds ratio
OTC	Over-the-counter
PAH	Predicted adult height
PAQ-C	Physical Activity Questionnaire for Older Children
PB	Puberty blocker(s)
PE	Pulmonary embolism
PEDSnet	A Clinical Research Network in the National Patient-Centered Clinical Research Network
pg	Picogram(s)
PHQ	Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire Modified for Teens
PICO	Population Intervention Control Group and Outcome
POTS	Postural orthostatic tachycardic syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRL	Prolactin
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Puberty suppression
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form
QIDS	Quick Inventory of Depressive Symptoms
QOL	Quality of life
QRS	A Q wave (downward deflection), followed by an R wave (upward deflection), followed by an S wave (another downward deflection after the R wave), on an electrocardiogram
QT	Time from the beginning of the QRS complex to the end of the T wave on electrocardiogram
QTc	Rate-corrected QT interval
RCGI	Recalled Childhood Gender Identity/Gender Role Questionnaire

Return to TOC

RCMAS-2	Revised Children's Manifest Anxiety Scale, Second Edition
RCT(s)	Randomized controlled trial(s)
REP	Rochester Epidemiology Project
RLPFC	Rostrolateral prefrontal cortex
ROB	Risk of bias, or risk-of-bias
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
ROI	Region of interest
SAIFI	Italian Gender Identity Development Service
SB	Senate Bill
SBP	Systolic blood pressure
SBQ-R	Suicide Behaviors Questionnaire-Revised
SCARED	Screen for Child Anxiety Related Disorders
SCr	Serum creatinine
SD	Standard deviation
SERM(s)	Selective estrogen receptor modulator(s)
SHI	Self-harm Index
SHQ	Sexual History Questionnaire
SHS	Subjective Happiness Scale
SI	Suicidal ideation
SOC	Standard of care
SOE	Strength of evidence
SPPA	Harter Self Perception Profile for Adolescents
SPRM(s)	Selective progestin receptor modulator(s)
SPW	Subperiosteal width (SPW)
SR(s)	Systematic review(s)
SRMA(s)	Systematic review(s) and meta-analysis(es)
SRS-2	Social Responsiveness Scale, Second Edition
STAI	Spielberger State-Trait Anxiety Inventory
STRONG cohort	Study of Transition Outcomes and Gender cohort of Kaiser Permanente
SubQ	Subcutaneous
SWLS	Satisfaction With Life Scale
T	Testosterone
T1DM	Type 1 diabetes mellitus
TBD	Trabecular BMD
TBF	Total body fat
TBLH	Total body less head
TC	Total cholesterol
TCS	Transgender Congruence Scale
TG	Triglycerides
TGD	Transgender/Gender diverse

Return to TOC

TGF	Transgender female
TGM	Transgender male
TGNB	Transgender non-binary or gender-diverse
TGNB	Transgender/Nonbinary
TH	Total hip
TIAB	Title and Abstract
TOL	Tower of London
TPI	Spielberger State-Trait Anger Expression Inventory
TRICARE	Healthcare payer for US military personnel and their families
TT-FMR	Trunk/Total fat mass ratio
TYC	Transgender Youth Clinic
UCLH	University College London Hospital
UCSF	University California San Francisco
UDHHS	Utah Department of Health and Human Services
UGDS	Utrecht Gender Dysphoria Scale
UK	United Kingdom
UMC, VUmc	VUmc location of Amsterdam University Medical Center
US	United States
USC	University of Southern California
UTIGPA	Unidad de Tratamiento de Identidad de Género del Principado de Asturias
VTE	Venous thromboembolism
VUMC	Vrije Universiteit Amsterdam, VU University Medical Center
WHO-QOL-Brief	World Health Organization Quality of Life Brief Version
WHR	Waist-hip ratio
WISC	Wechsler Intelligence Scale for Children
WPATH	World Professional Association for Transgender Health
yr	Year(s)
YSR	Youth Self Report
µg	Microgram(s)

Alphabetized by Name

Acquired immune deficiency syndrome	AIDS
Adjusted odds ratio	aOR
Adult Behavior Checklist	ABCL
Adult self-report	ASR
Alanine transaminase	ALT
Alkaline phosphatase	ALP
American Academy of Pediatrics	AAP

Return to TOC

American College of Obstetricians and Gynecologists	ACOG
American Medical Association	AMA
Amsterdam Cohort of Gender Dysphoria	ACoG
Amsterdam University Medical Center	Amsterdam UMC
Areal bone mineral density	aBMD
Ask Suicide Screening Questions	ASQ
Aspartate transaminase	AST
Assigned female at birth	AFAB
Assigned male at birth	AMAB
Attention deficit hyperactivity disorder	ADHD
Beck Depression Inventory	BDI
Beck Depression Inventory (for Youth)	BDI-(Y)
Beck Depression Inventory-II	BDI-II
Before common era	BCE
Blood pressure	BP
Body Esteem Scale for Adolescents and Adults	BES
Body Image Scale	BIS
Body mass index	BMI
Bone age	BA
Bone mineral apparent density	BMAD
Bone mineral content	BMC
Bone mineral density	BMD
Bone turnover marker(s)	BTM(s)
Canada's Drug and Health Technology Agency	CADTH
Center for Disease Control and Prevention	CDC
Center for Epidemiologic Studies Depression Scale	CESD-R
Center of Expertise on Gender Dysphoria	CEGD
Centimeter(s)	cm
Central precocious puberty	CPP
Child Behavior Checklist	CBCL
Children's Depression Inventory	CDI
Children's Global Assessment Scale	CGAS
Children's Health GENder Education and Care Interdisciplinary Support program	GENECIS
Children's Hospital Los Angeles	CHLA
Children's Hospital of Eastern Ontario	CHEO
Chronic myelogenous leukemia	CML
Chronological age	CA
Click-evoked otoacoustic emission(s)	CEOAE(s)
A Clinical Research Network in the National Patient-Centered Clinical Research Network	PEDSnet

Return to TOC

Columbia Suicide Severity Rating Scale	C-SSRS
Confidence interval	CI
Conflict of interest	COI
Connor-Davidson Resilience Scale	CD-RISC
Controlled clinical trial	CCT
Cortical BMD	CBD
Cross-sex hormone therapy	CSHT
Cross-sex hormones	CSH
Cystic fibrosis	CF
Deciliter	dL
Deep vein thrombophlebitis	DVT
Designated female at birth	DFAB
Designated male at birth	DMAB
Diabetes mellitus	DM
Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision	DSM-IV-TR
Diagnostic and Statistical Manual of Mental Disorders, 5th Edition	DSM-5
District of Columbia	DC
Dorsolateral prefrontal cortex	DLPFC
Drug Regimen Review Center	DRRC
Dual-energy radiograph absorptiometry	DXA
Eating Disorders Examination Questionnaire	EDE-Q
Endocortical diameter	ED
Endocrine Society	ES
Erotic Response and Orientation Scale	EROS
European Society for Sexual Medicine	ESSM
Extremities/Trunk fat mass ratio	ET-FMR
Female-to-male, or assigned female at birth transitioning to male	FTM
Femoral neck	FN
Food and Drug Administration Modernization Act of 1997	FDAMA
Forced expiratory volume	FEV
Fragebofen zur Beurteilung des eisenen Körpers (Body image assessment questionnaire)	FBeK
Functional magnetic resonance imaging	fMRI
Gamma-glutamyl transferase	GGT
Gender Diversity and Affirming Action for Youth Clinic of the Health Sciences Center, Winnipeg, Manitoba	GDAAY
Gender dysphoria	GD
Gender Identity Development Service	GIDS
Gender Identity Questionnaire for Adolescents	GIQ-Ad
Gender Identity Service	GIS

Return to TOC

Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults	GIDYQ
Gender Minority Stress and Resilience Measure for Adolescents	GMSR-A
Gender reassignment surgery	GRS
Gender-affirming estrogen treatment	GAET
Gender-affirming hormone(s)	GAH
Gender-affirming hormone therapy	GAHT
Gender-affirming surgery	GAS
General Anxiety Disorder-7	GAD-7
General Well-being Schedule	GWBS
Gonadotropin-releasing hormone	GnRH
Gonadotropin-releasing hormone analog/analogue/agonist	GnRH analog
Gonadotropin-releasing hormone antagonist	GnRH antagonist
Grading of Recommendations, Assessment, Development, and Evaluations	GRADE
Harter Self Perception Profile for Adolescents	SPPA
Health-related quality of life	HRQOL
Healthcare payer for US military personnel and their families	TRICARE
Healthcare professional(s)	HCP(s)
Hematocrit	HCT
Hemoglobin	HB
Hormonal therapy	HT
Hypertension	HTN
Institute of Medicine	IOM
Institutional Review Board	IRB
Intelligence quotient	IQ
International Classification of Diseases	ICD
International Standard Randomized Controlled Trial Number Register	ISRCTN
Interrupted time series	ITS
Intrauterine device	IUD
Intravenous	IV
Italian Gender Identity Development Service	SAIFI
Kaiser Permanente	KP
Kennis- en Zorgcentrum Genderdysforie	KZcG
Kessler Psychological Distress Scale	K6
KIDSCREEN Health Related Quality of Life Questionnaire for Children and Young People and their Parents, Short Version	KIDSCREEN-27
Kilogram(s)	kg
Lean body mass	LBM
Leeds General Infirmary	LGI
Left total hip	LTH
Legs/Total fat mass ratio	LT-FMR

Return to TOC

Leiden University Medical Center	LUMC
Lesbian gay bisexual transgender queer	LGBTQ
Level(s) of evidence	LOE(s)
Liebowitz Social Anxiety Scale	LSAS
Liter(s)	L
Long-acting	LA
Low-density lipoprotein cholesterol	cLDL
Lumbar spine	LS
Luteinizing hormone	LH
Luteinizing hormone-releasing hormone	LHRH
MacArthur Competence Assessment Tool for Treatment	MacCAT-T
Magnetic resonance imaging	MRI
Male-to-female, or assigned male at birth transitioning to female	MTF
A MeaSurement Tool to Assess systematic Reviews	AMSTAR
A MeaSurement Tool to Assess systematic Reviews, Version 2	AMSTAR-2
Median body mass index	mBMI
Medical decision-making competence	MDC
Medical Subject Headings for National Library of Medicine	MeSH
Mental health professional(s)	MHP(s)
Mental rotation task	MRT
Mercury	Hg
Meta-analysis	MA
Meter(s)	m
Microgram(s)	µg
Milli-international unit(s)	mIU
Milliliter(s)	mL
Millimeter(s)	mm
Millimole(s)	mmol
Modified Depression Scale	MDS
Modified Ferriman-Gallwey	mFG
Multi-dimensional Scale of Perceived Social Support	MSPSS
Myocardial infarction	MI
Nanogram(s)	ng
National Health and Nutrition Examination Survey	NHANES
National Health Service	NHS
National Heart, Lung, and Blood Institute	NHLBI
National Institutes of Health	NIH
Network of Relationships Inventory—Relationship Qualities	NRI
Newcastle-Ottawa Scale	NOS
Non-randomized studies of interventions	NRSI

Return to TOC

Non-suicidal self-injury	NSSI
Not applicable	N/A
Not reported	N/R
Not significant	N/S
Odds ratio	OR
Organic anion transporting polypeptide	OATP
Osteocalcin	OC
Other gender-diverse	OGD
Over-the-counter	OTC
Overall Anxiety Severity and Impairment Score	OASIS
Patient Health Questionnaire	PHQ
Patient Health Questionnaire Modified for Teens	PHQ-9
Patient Reported Outcomes Measurement Information System	PROMIS
Physical Activity Questionnaire for Older Children	PAQ-C
Picogram(s)	pg
Population Intervention Control Group and Outcome	PICO
Postural orthostatic tachycardic syndrome	POTS
Predicted adult height	PAH
Preferred Reporting Items for Systematic Reviews and Meta-analyses	PRISMA
Prolactin	PRL
Puberty blocker(s)	PB
Puberty suppression	PS
Pulmonary embolism	PE
A Q wave (downward deflection), followed by an R wave (upward deflection), followed by an S wave (another downward deflection after the R wave), on an electrocardiogram	QRS
Quality of life	QOL
Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form	Q-LES-Q-SF
Quick Inventory of Depressive Symptoms	QIDS
Randomized controlled trial(s)	RCT(s)
Rate-corrected QT interval	QTc
Recalled Childhood Gender Identity/Gender Role Questionnaire	RCGI
Region of interest	ROI
Revised Children's Manifest Anxiety Scale, Second Edition	RCMAS-2
Risk Of Bias In Non-randomised Studies - of Interventions	ROBINS-I
Risk of bias, or risk-of-bias	ROB
Rochester Epidemiology Project	REP
Rostrolateral prefrontal cortex	RLPFC
Satisfaction With Life Scale	SWLS
Screen for Child Anxiety Related Disorders	SCARED

Return to TOC

Selective estrogen receptor modulator(s)	SERM(s)
Selective progestin receptor modulator(s)	SPRM(s)
Self-harm Index	SHI
Senate Bill	SB
Serum creatinine	SCr
Sexual History Questionnaire	SHQ
Social Responsiveness Scale, Second Edition	SRS-2
Spielberger State-Trait Anger Expression Inventory	TPI
Spielberger State-Trait Anxiety Inventory	STAI
Standard deviation	SD
Standard of care	SOC
Strength of evidence	SOE
Study of Transition Outcomes and Gender cohort of Kaiser Permanente	STRONG cohort
Subcutaneous	SubQ
Subjective Happiness Scale	SHS
Subperiosteal width (SPW)	SPW
Suicidal ideation	SI
Suicide Behaviors Questionnaire-Revised	SBQ-R
Systematic review(s)	SR(s)
Systematic review(s) and meta-analysis(es)	SRMA(s)
Systolic blood pressure	SBP
Testosterone	T
Time from the beginning of the QRS complex to the end of the T wave on electrocardiogram	QT
Title and Abstract	TIAB
Total body fat	TBF
Total body less head	TBLH
Total cholesterol	TC
Total hip	TH
Tower of London	TOL
Trabecular BMD	TBD
Transgender Congruence Scale	TCS
Transgender female	TGF
Transgender male	TGM
Transgender non-binary or gender-diverse	TGNB
Transgender Youth Clinic	TYC
Transgender/Gender diverse	TGD
Transgender/Nonbinary	TGNB
Triglycerides	TG
Trunk/Total fat mass ratio	TT-FMR

Return to TOC

Type 1 diabetes mellitus	T1DM
Unidad de Tratamiento de Identidad de Género del Principado de Asturias	UTIGPA
United Kingdom	UK
United States	US
University California San Francisco	UCSF
University College London Hospital	UCLH
University of Southern California	USC
US Food and Drug Administration	FDA
Utah Department of Health and Human Services	UDHHS
Utrecht Gender Dysphoria Scale	UGDS
Venous thromboembolism	VTE
Vrije Universiteit Amsterdam, VU University Medical Center	VUMC
VUmc location of Amsterdam University Medical Center	UMC, VUmc
Waist-hip ratio	WHR
Wechsler Intelligence Scale for Children	WISC
World Health Organization Quality of Life Brief Version	WHO-QOL-Brief

Return to TOC

PART I

PHARMACOLOGICAL AGENTS
GUIDELINES
SYSTEMATIC REVIEWS
BIBLIOGRAPHY OF INCLUDED STUDIES
EXPERIMENTAL AND OBSERVATIONAL STUDIES
DESCRIPTIVE STUDIES

Return to TOC

I.1.0 INTRODUCTION

I.1.1 Gender Dysphoria and the Utah Context

In recent years, there has been a growing public awareness about the challenges faced by individuals suffering from *gender dysphoria*. According to the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), this condition is defined as a disparity between an individual's perceptions about their own gender identity relative to their assigned gender at birth, resulting in psychological distress. The incorporation of the diagnostic term *gender dysphoria* into the DSM-5 was added only recently (2013).[1] However, that diagnostic term was preceded by the term *gender identity disorder* in the DSM-3 (1980),[2] and the condition itself has been reported in the medical literature as long ago as the 1800s.[3] Outside the medical literature, transgender individuals have been mentioned in western literature for more than 2 thousand years; for example, as early as the 1st century BCE, the Roman poet Ovid wrote a collection of stories and myths, The Metamorphoses, which included a myth about a transgender figure, Tiresias.[4]

The recent increase in public awareness has coincided with a great deal of public discourse in which individuals from across the political spectrum have opined publicly and privately about whether gender dysphoria should be medically treated, and if so, how. Much of the discourse has focused on the issue of whether transgender children should receive the same medical interventions that are offered to adult patients.[5,6] A 2018 guideline by the American Academy of Pediatrics (AAP) advocated for the importance of gender-affirming medical care in transgender adolescents,[7] citing evidence that gender-affirming care may reduce depression, anxiety, eating disorders, self-harm, and suicide.[8-13]

Utah state legislators passed a law on January 28, 2023 prohibiting newly-diagnosed transgender and gender-diverse minors from receiving gender-affirming medical interventions;[14] Utah was the fifth state to pass legislation banning gender-affirming care for transgender minors.[15] Senate Bill (SB) 16 refers to the ban as a *moratorium*, and charges the Utah Department of Health and Human Services (UDHHS) to undertake a systematic review of the medical evidence about gender-affirming hormonal and hormone-blocking agents and to use that as the basis for making a recommendation to the legislature about whether the moratorium on use of these treatments in minors should be lifted.[14]

I.1.2 Objectives

The purpose of this review is to provide evidence to support the UDHHS in its recommendations about gender-affirming care in transgender, nonbinary, or other gender diverse (TGNB) adolescents, including the questions listed below:

1. **<u>Objectives addressed by the compilation of Pharmacological Agents:</u>**
    a. What hormones and hormone blockers are used in gender-affirming care of pediatric patients with gender dysphoria (GD)?
    b. What is the regulatory status of the treatments? (ie, are they approved by the US Food and Drug Administration [FDA] for use in pediatric patients?)
    c. What are the indications and contraindications for their use?
    d. What are off-label pediatric indications listed in pharmacy compendia for hormones and hormone blockers?

Return to TOC

2. **Objectives addressed by the compilation of Guidelines:**
    a. What recent clinical practice guidelines address medical interventions for gender-affirming treatment in pediatric gender dysphoria patients?
    b. What recommendations related to hormonal and hormonally active medications for treatment of GD are made in the guidelines?
    c. What are the levels of evidence (LOEs) that support the guideline recommendations?
3. **Objectives addressed by the compilation of Systematic Reviews and Clinical Studies (ie, Experimental Studies, Observational Studies, and Descriptive Studies):**
    a. What systematic reviews and meta-analyses (SRs/MAs), randomized controlled clinical trials (RCTs), and observational studies address short- and long-term safety and efficacy outcomes of hormonal and hormone-blocking agents used for gender-affirming care in pediatric patients?
    b. What are the primary and secondary findings of primary studies, including experimental, observational, and descriptive studies?
    c. What is the quality (or risk-of-bias [ROB]) of the evidence?
4. **Additional objectives:**
    a. Among pediatric patients who initiate a hormone or hormone blocker, what are the short- and long-term rates of discontinuation?

I.1.3 Deliverables Based on a Hierarchy of Evidence

This work was completed on a short timeline. With the goal of providing the highest-quality evidence as quickly as possible, the work was organized into the following deliverables, in this order:

1. The first deliverable comprised the identification of all specific **hormonal and hormonally-active pharmacological agents** that are approved for any use in the US, and that are used (or recommended for use) as a component of gender-affirming care in the US, based on secondary and tertiary literature sources. FDA-approved pediatric indications, relevant off-label uses, and contraindications are provided for each drug. This step was an essential prerequisite to the remaining work.
2. The second deliverable comprised a tabular summary of recent **clinical practice guidelines** (since 2010) that address treatment of pediatric gender dysphoria, as identified in bibliographic database searches. Guidelines were included if they were intended for an audience of practicing clinicians, and if they were released by organizations that are widely regarded as authorities in their given specialty (eg, the Endocrine Society for the treatment of endocrine diseases). Authors of these guidelines typically rate the strength of evidence behind their recommendations, and they may provide a high- to low-ranking of the recommendations that they make based on the quality of the underlying evidence. To create high-quality guidelines, such authors often utilize systematic reviews and primary studies to inform their recommendations, and tend to comprise one of the most rigorous compilations of evidence for clinical care available. Clinicians rely on guidelines for standard courses of treatment, to determine options available for nonstandard patients and certain populations, and to understand which aspects of treatment are uncertain.
3. The third deliverable comprises evidence tables of **systematic reviews and/or meta-analyses (SRMAs)**, as identified in bibliographic database searches. Systematic reviews have, ideally, rigorous search terms and attempt to capture all primary studies meeting criteria that will help answer their

given research questions. If enough primary studies comparing the same interventions and outcomes in similar populations are available, these reviews may also include meta-analyses, which quantitatively analyze and synthesize outcomes across studies to obtain more precision in estimates of treatment effects, and to improve power for small treatment effects. In this deliverable, a summary of SRMA findings and an appropriate risk-of-bias (ROB) assessment are provided for each review.

The guidelines and SRMAs together represent the **highest order of available evidence**, in that they draw on the consensus of all the patient-level evidence that their authors found in searches like ours. To the extent that our highly exhaustive searches experimental, observational, and descriptive studies yielded many studies that were not cited by many guidelines and SRs, our report has the potential to more reliably capture the true consensus of the evidence compared to some of the other top-of-the-pyramid evidence summaries found in guidelines and SRMAs. The conventional wisdom has long been that there is not a great deal of evidence to support use of these treatments for pediatric gender dysphoria, but the results of our searches are likely to undermine that particular narrative. The body of evidence that we have uncovered exceeds the amount of evidence that often serves as the basis of FDA approval for many high-risk, new drugs approved in pediatric populations in the US, including recent gene therapies.

4. Of greater urgency to our timeline was a **complete bibliography of all included studies** identified in our systematic search bibliographic databases, grouped into relevant publication types. This bibliography includes all guidelines, systematic reviews, and experimental, observational, and descriptive/qualitative studies that met our inclusion criteria, even if we did not ultimately perform data extraction on all of them due to time restrictions for this report. The studies in this bibliography have passed all of the eligibility screenings: highly sensitive searches, duplicate title and abstract screening, and duplicate full-text screening.
5. We next delivered detailed evidence tables for all explanatory studies, including **experimental** (eg, randomized controlled trial) and **observational** (ie, cohort, case-control, and cross-sectional) studies. These evidence tables summarize primary and secondary safety and efficacy findings, as well as an ROB assessment of comparisons between treated and untreated TGNB adolescents, and between TGNB adolescents and cisgender peers.
6. Finally, we submitted detailed evidence tables for relevant **descriptive** studies identified in bibliographic database searches. These include the notably important, longitudinal, pre-post studies from The Netherlands that follow pediatric transgender patients into adulthood, as much as 40 years of follow-up in some cases. These also include a large body of evidence from US populations comprising well over 18,000 TGNB children and adolescents.

I.1.4 Terms Used in This Report

I.1.4.1 Populations

For the purposes of this evidence synthesis, we consider those who have not started puberty as "children" and those who have started puberty as "adolescents." This distinction matters more than an exact age because puberty onset (variable as to age) is consistently the time at which one's appearance and hormones become more gendered, which in turn is a major factor in the intensification or alleviation of gender dysphoria.

Because the terms used to refer to gender-diverse people change over time and across place, there is no consistent naming terminology in the evidence presented. We do not attempt to correct these terms in the data we extract from primary studies; rather, we present here the terms we have chosen to use. We use the acronym "TGNB", short for transgender non-binary, as an inclusive, umbrella term that indicates we are talking about a population of gender-diverse patients, or all patients who may identify as transgender, nonbinary, or otherwise gender diverse. Where it is otherwise ambiguous, we use the term "natal" to qualify the terms "male" or "female" when referring to assigned-at-birth gender. We may also use acronyms for "assigned male at birth" (AMAB) and "assigned female at birth" (AFAB). The terms "FTM" (female-to-male) and "MTF" (male-to-female) are used to refer, respectively, to natal females who identify as transgender males, and natal males who identify as transgender females.

Much of the literature may lead readers to believe that the goal for most gender transitions is from entirely female to entirely male, or vice versa. Although such TGNB patients may be the easiest for study purposes, their majority is shrinking.[16,17] Many gender-diverse patients may need treatments and procedures so that they are *neither* male- *nor* female-presenting, or so they present with the traits of both genders. In the clinical presentation of gender dysphoria and transgenderism, it should be noted that gender identity, presentation, and embodiment are highly individual and are guided by the patient's ultimate alleviation of dysphoria, and ideally, quality of life.

I.1.4.2 Treatment protocols and agents

Numerous means are available to TGNB people wishing to transition. "Social transition"—meaning everything from wearing gender non-conforming clothes, to hair and makeup, to mannerisms, habits, and activities, to name and pronoun changes—is flexible, reversible, and available to anyone, including pre-pubertal children. Gender-affirming surgery (GAS) is another well-known means. **In this report, we address only pharmacologic/hormonal means of transition, also referred to as "medical," for pubertal adolescent GD patients <18 years. This evidence synthesis found no evidence that pharmacologic/ hormonal treatments are offered to pre-pubertal children with GD.**

The terms referring to pharmacologic protocols for puberty suppression, cross-sex hormone therapy, or both also vary from study to study. For example, some studies use "gender-affirming hormone therapy" (GAHT) to refer to cross-sex hormone therapy only, while other studies use this term to refer to the arc starting with puberty-delaying hormones and ending with cross-sex hormones.

The terms we use throughout this report are "puberty suppression" (PS) for the phase of treatment typically done with GnRH analogs; "cross-sex hormone therapy" (CSHT) for treating natal males with estrogen-based hormones and natal females with testosterone-based hormones; and "gender-affirming hormone therapy" (GAHT) to refer to the full arc encompassing both phases.

Finally, we address the various terms referring to gonadotropin-releasing hormone agents used to suppress puberty: agonists, analog(ue)s, or their abbreviations, GnRHa or GnRH(a). **The term we use throughout the report for these puberty-suppression agents is "GnRH analog,"** rather than agonists, analogues, GnRHa, or GnRH(a). "GnRH antagonists" are used for puberty *initiation* and are referred to as such the few times they appear in this report.

I.2.0 AGENTS USED OR RECOMMENDED FOR USE IN PEDIATRIC TGNB PATIENTS

I.2.1 Off-label Use of Drugs in Pediatric Patients

Off-label use of drugs is commonplace in the US.[18] "Off-label use" refers to the practice of prescribing drugs that are approved for use in the United States (US), by the Food and Drug Administration (FDA), but using them to treat indications that are not expressly approved by the FDA.[19] Off-label use of medications is widely accepted and often becomes a standard of care.[19]

The extent of off-label use varies across populations, but worldwide estimates range from 3.2% to 95%.[18,20] In US pediatric patients, estimates for off-label use are reportedly as high as 38.1% of prescriptions,[20] and as many as 78.9% of children.[21,22] Common medications used off label in pediatric patients include antibiotics, anticoagulants, beta blockers, and psychiatric drugs.[20] Studies examining the safety of pediatric off-label prescribing in the US are limited, but one study showed no differences in the risk of adverse events.[23]

A key driver of this high off-label use prevalence is the substantial financial investment required to get additional uses approved; because off-label use is otherwise common and legal, drug companies rarely go to the effort without a financial incentive to offset this cost burden.[19,24]

The Pediatric Studies of Drugs, Section 505A of the Food and Drug Administration Modernization Act (FDAMA)(1997), was one attempt to incentivize the practice of getting additional approved indications for pediatric patients.[25] This act allows drug companies to obtain a 6-month patent extension for a product (upon FDA approval), effectively preventing competitors from marketing generic versions within that timeframe.[25,26] However, many drugs used in pediatric gender dysphoria were off patent long before that law came into existence, which makes them ineligible for the incentive.

I.2.2 Methods

We first compiled a list of US drugs that, according to reputable pharmacy compendia, are used or recommended for use in the treatment of pediatric patients diagnosed with gender dysphoria, or who are transgender, nonbinary, or gender-diverse (ie, TGNB). We also summarize the FDA-approved indications of these agents in children and adults, as well as off-label indications that are indexed in reputable pharmacy compendia.

Standard tertiary databases (eg, Micromedex, UpToDate, and the FDA Orange Book) were searched to identify a comprehensive list of all drug product hormones and hormonally active agents that are used in pediatric TGNB patients in the United States. Information in these databases that addresses the relevant questions above will be extracted; for example, the FDA Orange Book was the primary source for identifying FDA-approved indications.

We identified medications that are used for gender-affirming hormone therapy (GAHT) from recommendations in clinical practice guidelines, and from relevant citations identified during the full-text screening of bibliographic database search results. The US FDA-approved indications, off-label uses, and contraindications for each agent were obtained from the pharmacy compendia, Micromedex[27] and

Lexicomp.[28] We included any pediatric off-label uses for identified agents of interest; but we only included adult off-label uses that specifically addressed a gender transition-related use, including menstrual suppression.

Generally, the FDA approval date for each agent was obtained from Lexicomp. If Lexicomp did not provide an FDA approval date for an agent, it was then obtained from the *Approved Drug Products with Therapeutic Equivalence Evaluations*[29] (commonly referred to as the Orange Book) by noting the oldest approval date among all entries for a particular agent. Notably, the Orange Book does not provide a specific date for agents approved prior to 1982, which was the year that the FDA began requiring approval dates on New Drug Applications. If a discrepancy in the initial date of approval existed between Lexicomp and the Orange Book, we deferred to the date listed in the Orange Book, which is published by the FDA.

Agents were arranged into multiple tables, organized by drug class. Agents in some drug classes may not be included in the tables for several reasons:

- They were not found to be used for GAHT, including combination products of included individual agents (eg, letrozole in combination with ribociclib, finasteride in combination with tadalafil).
- They were withdrawn from the market in the US before the date of this report (eg, leuprolide in combination with norethindrone, oxandrolone).
- They were not approved for any use by the FDA (eg, esterified estrogens in combination with methyltestosterone, cyproterone acetate).

I.2.3 Results

I.2.3.1 Agents used for gender-affirming hormonal therapy (GAHT) in TGNB adolescents

We identified 66 unique prescription drug entities from 10 different therapeutic classes that are used off label or recommended for off-label use (according to Micromedex and/or Lexicomp) in patients with gender dysphoria, and that are available in the US. These are summarized below and detailed in **Appendix I.A**.

- Gonadotropin releasing hormone (GnRH) analogs (5 agents)
- GnRH antagonists (5 agents)
- Antiandrogens (6 agents)
- Single-ingredient estrogen and testosterone products (10 agents)
- Single-ingredient progestin agents (ie, not in combination with another agent; 7 agents)
- Combination sex hormone/progestin products (20 agents)
- Aromatase inhibitors (3 agents)
- Selective estrogen receptor modulators (SERMs; 6 agents)
- Androgens (2 agents)
- Vasodilators (1 agent)
- Selective progestin receptor modulators (SPRMs; 1 agent)

I.2.3.1.1 FDA-approved indications

None of the identified agents have specifically been approved by the FDA to treat gender dysphoria in pediatric or adult patients. However, these agents have other various FDA-approved indications; note that some labeled indications may be approved for use in both adult and pediatric patients or in only one of these populations.

I.2.3.1.1.1 Pediatric FDA indications

Of the identified agents, 24 have at least one FDA-approved, pediatric labeled indication, as listed below:

- Central precocious puberty (4 agents)
- Abnormal uterine bleeding (1 agent)
- Post-menarche contraception, including emergency (17 agents)
- Acne vulgaris (4 agents)
- Premenstrual dysphoric disorder (2 agents)
- Folate supplementation (1 agent)
- Hypogonadism (3 agents) or delayed puberty (2 agents)
- Endometriosis (1 agent)
- Hypertension (1 agent)

I.2.3.1.1.2 Adult FDA indications

All 66 identified agents have at least one FDA-approved indication in adults. The various indicated disease states for these are listed below with the corresponding count of included agents:

- Breast cancer (12 agents) or fibrocystic breast changes (1 agent)
- Endometriosis, including treatment of associated pain (8 agents)
- Hypoplasia of the endometrium (1 agent)
- Prostate cancer (13 agents)
- Anemia related to uterine leiomyomata (1 agent)
- Female infertility (3 agents) or assisted reproductive technology (1 agent)
- Benign prostatic hyperplasia (2 agents)
- Male pattern alopecia (2 agents)
- Ascites due to cirrhosis (1 agent)
- Edema (nephrotic syndrome) (1 agent)
- Heart failure with reduced ejection fraction (1 agent)
- Hypertension (2 agents)
- Hyperaldosteronism (1 agent)
- Menopause-related symptoms (dyspareunia, vasomotor, atrophy) (15 agents)
- Postmenopausal osteoporosis (9 agents)
- Hypogonadism (7 agents), hypoestrogenism (5 agents), or delayed puberty (1 agent)

- Abnormal uterine bleeding (5 agents)
- Contraception, including emergency (18 agents)
- Menorrhagia (3 agents)
- Acene vulgaris (4 agents)
- Premenstrual dysphoric disorder (2 agents)
- Folate supplementation (1 agent)
- Endometrial cancer (1 agent)
- Prevention of estrogen therapy-associated endometrial hyperplasia (3 agents)
- Renal cell carcinoma (1 agent)
- Secondary amenorrhea, diagnostic aid (3 agents)
- Prevention of hereditary angioedema (1 agent)

I.2.3.1.2 Indications for off-label use from reputed pharmacy compendia

Overall, 19 agents had off-label indications indexed in Micromedex, and 24 had off-label indications in Lexicomp.

I.2.3.1.2.1 Pediatric off-label indications

In Micromedex, 14 identified agents had a pediatric off-label indication, and no pediatric off-label indications were listed in Lexicomp. Of these, the following 6 agents specifically had an indexed off-label use related to gender dysphoria:

- Triptorelin pamoate
- Estradiol
- Testosterone
- Testosterone undecanoate
- Testosterone cypionate
- Testosterone enanthate

Except for triptorelin, which is classified as "effective," all others are classified as "evidence favors efficacy" and are recommended based on Category B evidence[a] (per Micromedex).

Other recommended pediatric off-label indications for the remaining agents[b] include the following:

- Precocious puberty (1 agent)
- Hyperaldosteronism (1 agent)
- Bronchopulmonary dysplasia of newborn (1 agent)
- Hemorrhagic cystitis (1 agent)
- Postoperative hemorrhage (1 agent)

---

[a] *Category B evidence is based on meta-analyses of randomized controlled trials (RCTs) with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.*
[b] *Note that some agents may be indexed for ≥ 1 off-label indication*

- Turner syndrome (1 agent)
- Alveolar hypoventilation (1 agent)
- Central precocious puberty (1 agent)
- Gynecomastia (1 agent)
- Polyostotic fibrous dysplasia of bone (1 agent)
- Retinoblastoma (1 agent)
- Retroperitoneal fibrosis (1 agent)

Note that 4 agents had recommendations against their use for certain off-label uses in the pediatric population due to inconclusive evidence for that particular indication(s), as listed below:

- Triptorelin pamoate: growth hormone deficiency, short stature disorder (idiopathic)
- Flutamide: congenital adrenal hyperplasia
- Danazol: thrombocytopenic purpura (idiopathic or immune)
- Anastrozole: pubertal gynecomastia

I.2.3.1.2.2 Adult off-label indications

All 24 agents indexed in Lexicomp and 13 of the 19 agents indexed in Micromedex had an off-label use related to GAHT in adults. Both Micromedex and Lexicomp recommended the use of 6 agents in male-to-female (MTF) transgender adults with gender dysphoria, as listed below:

- Goserelin
- Leuprolide
- Spironolactone
- Estradiol
- Estradiol cypionate[c]
- Estradiol valerate

For female-to-male (FTM) transgender individuals with gender dysphoria, the following agents were recommended to be used off-label in both Micromedex and Lexicomp:

- Testosterone
- Testosterone undecanoate
- Testosterone cypionate
- Testosterone enanthate

Although the listed agents with an adult off-label use for GAHT tended to be the same across the 2 pharmacy compendia, slight variations were observed. For example, conjugated estrogens and nilutamide were only indexed in Micromedex with an off-label GAHT use in adults. Furthermore, none of the agents indexed in Micromedex were specifically for the off-label use of menstrual suppression in FTM transgender adults, but 14 agents were listed in Lexicomp, listed below:

---

[c] *Although Micromedex and Lexicomp list a off-label use for this agent in male-to-female transgender adults with gender dysphoria, no efficacy or recommendation is reported in Micromedex, but this use is supported by guideline evidence as noted in Lexicomp.*

- Estradiol valerate and dienogest
- Ethinyl estradiol and drospirenone
- Ethinyl estradiol and desogestrel
- Ethinyl estradiol and norethindrone
- Ethinyl estradiol and norgestimate
- Ethinyl estradiol and levonorgestrel
- Ethinyl estradiol and norelgestromin
- Ethinyl estradiol and norgestrel
- Ethinyl estradiol and ethynodiol diacetate
- Ethinyl estradiol, drospirenone, and levomefolate
- Medroxyprogesterone (acetate)
- Norethindrone
- Norethindrone acetate
- Levonorgestrel, specifically the intrauterine device

Notably, despite that included agents are recommended in reviewed sources, use of a few is discouraged in some compendia. For example, Micromedex recommends against the use of finasteride in MTF transgender adults with gender dysphoria, citing a lack of efficacy.

I.3.0 EVIDENCE SYNTHESIS METHODS

I.3.1 Protocol

We conducted the current work according to pre-specified, internal protocols for the searches, eligibility assessment, and data extraction tasks.

I.3.2 Systematic Search Methods

We planned a systematic search to address most of the questions specified in Senate Bill (SB) 16, including those addressed by guidelines, prior systematic reviews, and inferential and descriptive studies. We planned a comprehensive search of at least 2 standard bibliographic medical databases, including Medline and Embase. While we also considered options to search Cochrane CENTRAL, PsycInfo, and ClinicalTrials.gov if time allowed, and if needed, but as of the date of this report, we have conducted bibliographic database searches only in Ovid Medline, Embase, and ClinicalTrials.gov.

Several organizations have articulated standards for systematic reviews (SRs) such as the present study. The most common such guideline is the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[30] We have followed the PRISMA guidance as closely as possible given the abbreviated timeline and the broad scope of the current work.

I.3.2.1 Eligibility criteria

Details of the broad eligibility criteria used to identify studies of interest during the search and screening phases are summarized in **Table I.1**. In short, after identifying the comprehensive list of pharmacological agents, we planned to search for full-text publications that addressed these treatments as either study exposures/interventions/comparators, study eligibility criteria, or study outcomes (or a function of an outcome). We identified 66 agents in 10 different drug classes, including sex hormones (testosterones and estrogens), progestins, gonadotropin-releasing hormone (GnRH) analogs and antagonists, selective estrogen/progestin inhibitors (SERMs/SPRMs), and others.

The study population of interest was adolescents (ie, patients < 18 years of age, or cohorts with a mean age of < 18 years, or long-term follow-up studies of patients who initiated treatment at < 18 years of age or in cohorts with a mean age of < 18 years, and who were transgender, nonbinary, or gender diverse). Publication types of interest included guidelines, systematic reviews (SRs), experimental studies, observational studies, and descriptive studies.

We limited study eligibility to papers that were published since 2010 to facilitate the identification of modern studies, to include those that may have informed the addition of the diagnostic term for gender dysphoria in DSM-5, and to include recent studies that likely inform modern treatment choices. We chose not to restrict eligibility based on comparator, outcome, or publication language; however, some otherwise eligible studies were included but did not undergo data collection for these reasons and others. These are nonetheless provided in the bibliography of included studies.

After relevant studies were identified in the search and screening phases of the work, further eligibility criteria were applied by the lead author for each category of evidence (ie, guideline, systematic review, or experimental, observational, or descriptive study) before the data extraction phase in order to ensure

Table I.1. Eligibility criteria for relevant publications in the search and screening phases

Publication types and study designs
Guidelines
We included guidelines that met the IOM definition of a clinical practice guideline,[31] listed below, if they were written or published by a *well-recognized medical authority*, and if they provided recommendations about the use of treatments of interest in the population of interest. For treatments and populations of interest, see below under *Intervention* and *Population*, respectively. • Clinical practice guideline definition: "…statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."
Clinical studies
Study designs (S) of interest included systematic reviews or cohort-type reviews, experimental studies, observational studies, and descriptive studies. To simplify the task of classifying patient-level clinical studies, we used simple categories devised by Gehlbach,[32] summarized in **Figure I.1**. In short, each publication type or study design of interest is defined as follows: • Systematic reviews: We included review articles that described a systematic search in 1 or more bibliographic database, which were described by authors as a "systematic review" or has having a "systematic search" or a "comprehensive search," or reviews that were cohort-type meta-analyses (eg, prospective meta-analyses or other full cohort of studies identified before any results were known) • Experimental studies: We included any RCTs or pseudo-randomized studies (ie, those that were not randomized, but in which the intent was to randomize patients), or non-randomized experimental studies. We also included single-arm clinical trials, but these were grouped with descriptive studies (below) in keeping with our chosen study design taxonomy (ie, Gehlbach's taxonomy).[32] • Observational studies: We included all eligible cohort, case-control, and cross-sectional studies. Because these may not use standard terminology to describe the study designs (eg, a "retrospect database analysis"), we used definitions from Gehlbach's taxonomy for making these classifications.[32] In short, observational studies included any non-experimental study in which inferential statistics were used to compare either (a) study outcomes between 2 or more exposure groups, or (b) study exposures between 2 or more outcome groups. These were included if subjects from our population of interest (see below under Population) were included in one or more exposure or outcome group, and in which study exposures or outcomes included an intervention of interest (see below under Intervention). • Descriptive studies: We included all eligible case reports and case series if they addressed the population and interventions of interest. Initially we had planned to extract data for all descriptive study designs, including case reports that contained a statement about IRB (or other ethics board) review and approval/exemption, or specified that informed consent was obtained from study subjects for research or publication. However, due to time constraints and the number of relevant publications, only longitudinal, pre-post descriptive studies underwent data collection. Other descriptive studies lacking such pre-post comparisons were included in the bibliography only.
Population
The population of interest was pediatric patients (ie, ages < 18 years) described as having gender dysphoria/transition/diversity or being non-binary and/or transgender (ie, pediatric TGNB patients). We included studies that mixed TGNB children and adults if the studies met at least one of the following conditions: • Findings were reported separately for minors (ie, ages < 18 years).

Table abbreviations: IOM, Institute of Medicine; RCT, randomized controlled trials; IRB, investigational review board; US, United States; TGNB transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; SERM, selective estrogen receptor modulator; SPRM, selective progestin receptor modulator

Return to TOC

Figure I.1. Relevant clinical study designs included in the report grouped according to Gehlbach's taxonomic definitions [32]

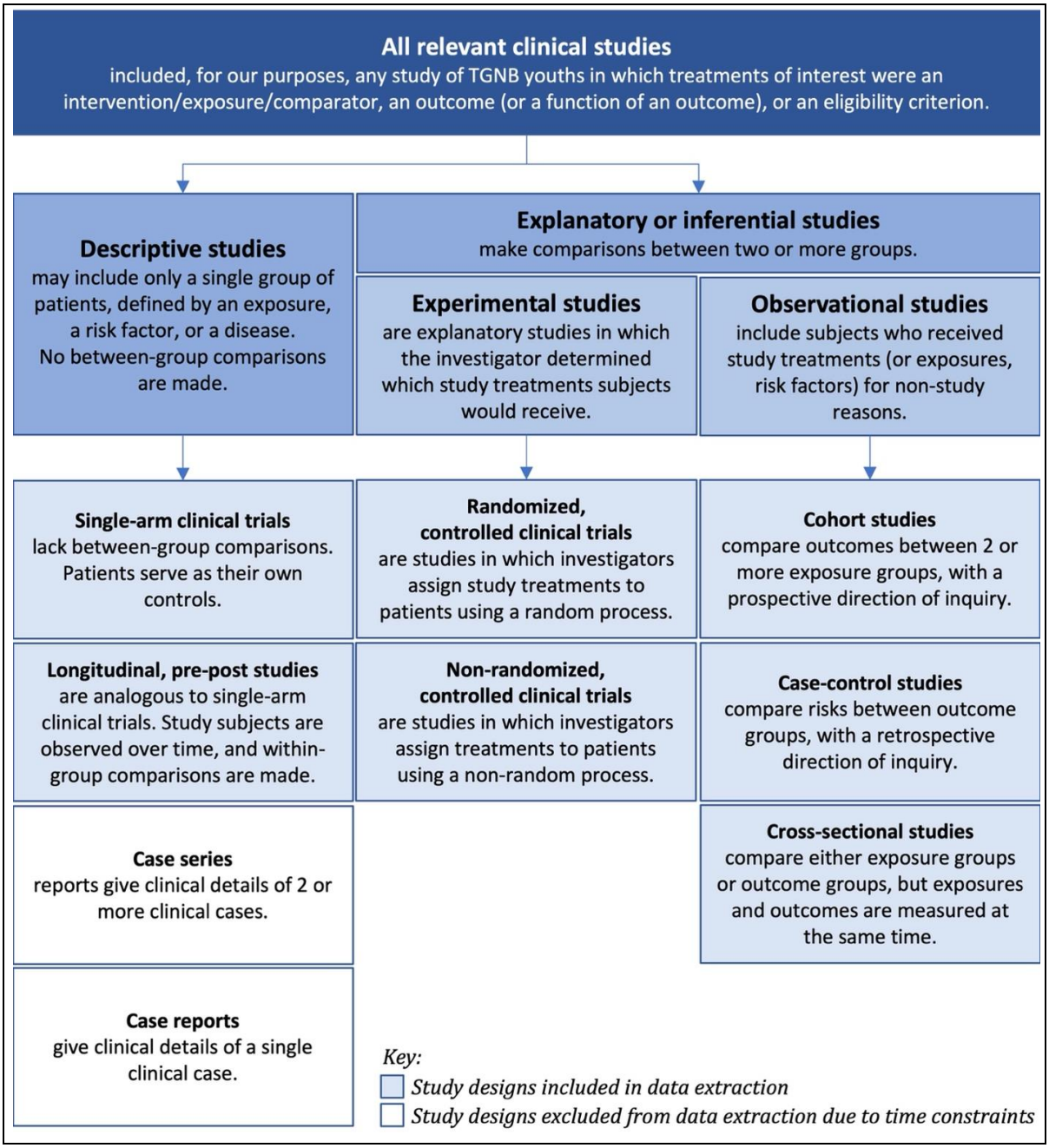


Table abbreviations: TGNB, transgender, nonbinary, or other gender diverse

that the most relevant evidence was highlighted, and to ensure that the scope of the work was manageable within our abbreviated timeline. These additional eligibility criteria are described in the methods sections specific to guidelines, SRs, experimental studies, observational studies, and descriptive studies.

Return to TOC

I.3.2.2 Search strategies

Search strategies for bibliographic databases were developed and conducted according to best-practice standards. We planned to employ both structured vocabulary searches (eg, medical subject headings [MeSH] for Medline and Emtree for Embase) and unstructured keyword terms in relevant database fields. Searches were implemented in phases, including structured-vocabulary-only searches in the first phase, and complete searches in the second.

The relevant citations identified in the structured-vocabulary-only searches are collectively referred to as "first-corpus" citations where applicable throughout this narrative. These included structured vocabulary terms for gender dysphoria (eg, Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/), pediatrics (eg, Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/), and interventions of interest (eg, Gonadotropin-releasing hormone/ or Gonadal Steroid Hormones/ or Hormone Replacement Therapy/ or Androgens/ or Estrogens/ or exp Progesterone/).

Complete searches, which were designed to find remaining studies, are collectively referred to as "second- corpus" citations. These included a combination of all structured-vocabulary terms from first-corpus searches, plus free-text terms. The inclusion of free-text terms ensures the identification of relevant in-process citations and citations that were incorrectly or incompletely indexed.

All searches, including both first- and second- corpus searches, were limited to relevant citations published since 2010 to ensure that studies leading up to the 2013 addition of the term *gender dysphoria* in the DSM-5 were retrieved. Search strategies also used validated, high-quality filters for publication types (ie, guidelines, systematic reviews, experimental studies, observational studies, qualitative studies, and descriptive studies).[33-37] We also used a validated filter to exclude non-human studies.[38] Searches were conducted between March 9 and June 5, 2023. All searches were peer reviewed internally before implementation. Complete searches for Medline and Embase are summarized in **Appendix I.B**.

I.3.3 Study Relevance Assessment Methods

As searches were completed, meta-data for potentially relevant bibliographic references were downloaded into Covidence, an online tool designed to support systematic review work (Covidence.org, Veritas Health Innovation, Melbourne, Australia). Two phases of study eligibility screening were then conducted, including (1) title/abstract screening, and (2) full-text screening, described below.

I.3.3.1 Title/Abstract screening

Title and abstract (TIAB) screening was conducted in duplicate in Covidence using the eligibility criteria given in **Table I.1**. Reviewers were instructed to assess eligibility on the basis of the population, intervention, and study design (or publication type) only. Studies that otherwise met population and study-design eligibility criteria were included if treatments of interest were included in any of the following ways:

1. It was an intervention or comparator
2. It was an outcome or a function of an outcome
3. It was an eligibility criterion

At this stage, all potentially-relevant studies were included, regardless of outcomes and language of publication. Disagreement between reviewers about the relevance of any citations was resolved by consensus or by a third reviewer.

I.3.3.2 Full-text screening and tagging

All citations that were deemed to be potentially relevant in TIAB screening were retrieved in full text and underwent duplicate full-text screening in Covidence. While eligibility criteria did not change for the identification of relevant studies, we began to identify studies that would be included in the bibliography, but that would not undergo data collection. These are defined as follows:

- Potentially-relevant, non-English studies of all types did not undergo data extraction, but were included in the bibliography.
- Descriptive studies (ie, case reports and case series) that lacked a statement about ethics review or institutional review board (IRB) review and approval/exemption, or a statement about obtaining informed consent for research, did not undergo data extraction, but were included in the bibliography.

Disagreement about eligibility between two independent authors at the full-text screening stage was resolved by consensus or by a third reviewer when consensus could not be reached.

Studies that did not meet eligibility criteria as defined in **Table I.1** were excluded at this stage, and a reason for exclusion was selected. Included studies underwent additional full-text screening before data extraction, as described in the study design-specific methods below.

A single study design category was assigned to each primary study using a simple taxonomy (Gehlbach's).[32] While many studies can meet the criteria for multiple study designs, we used a *gestalt* method of assigning the design, which was based on which types of comparisons seemed to be the major point of the paper. Studies in which the major point of the paper seemed to be to make between-group comparisons were assigned as experimental or observational studies, and studies in which the major point seemed to be to make within-group comparisons were assigned as descriptive studies.

I.3.4 Study Design-specific Methods

Study design-specific methods (including additional study design-specific full-text eligibility assessments), data-collection methods, and risk-of-bias assessment methods for each study design are summarized in the sections below.

I.3.4.1 Guideline-specific methods

I.3.4.1.1 Final full-text eligibility assessment

Included guidelines met eligibility criteria in **Table I.1**. The published guideline text, supplementary materials, and publishing organization website, when available, were assessed to determine guideline inclusion. To meet the inclusion criteria of performing a systematic review, guidelines were required to report performing a systematic review for at least 1 part of the guideline. If a guideline did not report

performing a systematic review for a section in which recommendations were extracted, we required that the guideline at least cite and discuss published literature supporting each recommendation.

Guidelines with recommendations that were not formed by the publishing organization were excluded (eg, publication from a medical authority that summarized recommendations from another authority's guideline). Guidelines that only addressed intervention/outcome pairs that were excluded after the stage of full-text eligibility were also excluded at this stage. For example, we excluded from consideration any evidence that addressed menstrual suppression with common treatments that would also be offered to cis women who required menstrual suppression. Consequently, we only considered guidelines that addressed menstrual suppression if they included recommendations about use of testosterone for menstrual suppression, as testosterone is the only one of the available options that would not be offered to cisgender women.

I.3.4.1.2 Data collection

Published guideline text, supporting appendices, and the guideline organization's website (for guideline construction methodology only) were searched for relevant information to extract. A single author of this report reviewed guidelines for relevant information. Formal guideline recommendations (ie, recommendations or statements created by consensus of the guideline authors, and when part of the guideline methodology, assigned a risk-of-bias [ROB] or level-of-evidence [LOE] rating) or informal recommendations (eg, non-consensus statements provided as supplementary text) were eligible for extraction.

The primary extraction focus was hormonal/hormone-blocking (see list in **Table I.1**) treatment information about *who* should be treated, *which* agent(s) are recommended, and *when* the treatment should be started and/or stopped for the target population (TGNB youth). In addition, guideline development methodology was extracted. Recommendation strengths and/or LOE ratings for each hormonal treatment recommendation were extracted when provided. Lastly, an overview of guideline recommendations about safety and efficacy monitoring for hormonal/hormone-blocking therapies, and the recommended population to receive the monitoring were extracted.

Some reviewed guidelines addressing both youth and adults do not state whether a hormonal therapy recommendation is intended for youth, adults, or both. When applicable, only recommendations pertaining to youth were extracted (eg, relevant recommendations from the section of the guideline devoted to adolescents). If a guideline including all ages did not specify an age for a hormonal therapy recommendation, we interpreted that recommendation as applying to both adolescents and adults.

Extracted information other than about guideline development methodology is from the following guideline chapters or sections:

- World Professional Association for Transgender Health (WPATH; 2022): chapter 2 (medical necessity of treatment), chapter 7 (lack of hormonal therapy for pre-pubertal TGNB children), chapter 6 (assessment and treatment of TGNB adolescents), and chapter 12 (hormonal therapy treatment recommendations for adolescents and adults).[39]
- American College of Obstetricians and Gynecologists (ACOG; 2022): This guideline only addresses menstrual suppression. Information on the section about transgender and gender-diverse patients was extracted.[40]

- European Society for Sexual Medicine (ESSM; 2020): sections "Assessment of gender diverse children and adolescents," "Hormone therapy in trans AFAB [assigned female at birth] people," and "Hormone therapy in trans AMAB [assigned male at birth] people."[41]
- Endocrine Society (ES; 2017): sections "Evaluation of youth and adults," "Treatment of adolescents," "Adverse outcome prevention and long-term care," and "Surgery for sex reassignment and gender confirmation" (for a single non-graded statement about the recommended duration of GAHT).[42]

I.3.4.1.3 Risk of bias assessment

A risk-of-bias assessment was not conducted on guidelines as part of the current work because we restricted inclusion to recognized medical authorities who published evidence-based guidlines. However, we exctracted information about any ROB assesssment of the primary evidence that was made by guideline authors.

I.3.4.2 Systematic review-specific methods

I.3.4.2.1 Final full-text eligibility assessment

Systematic reviews (SRs) that met the eligibility described in **Table I.1** were included in the SR deliverable. Further full-text eligibility assessment was then conducted by one author of this review to limit data collection to the highest-quality subset of reviews, including the following criteria:

- Potentially relevant SRs that were published in a non-English language, but which had an English-language abstract suggesting they met inclusion criteria, were listed in the bibliography only and did not undergo data extraction.
- SRs that did not include one or more of the following highest-priority outcomes were included in the bibliography only and did not undergo data extraction:
    - Mental health (eg, depression, anxiety, suicidality)
    - Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
    - Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
    - Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
    - Bone health (eg, bone density, bone turnover measures)
    - Cardiovascular risk factors (eg, thrombotic changes, insulin sensitivity, blood pressure, obesity)
    - Cancer
- SRs that did not report results of their search, such as those that only included a narrative synthesis but without descriptions of the primary studies included, were included in the bibliography only and did not undergo data extraction.
- SRs that did not search at least 2 bibliographic databases were included in the bibliography only and did not undergo data extraction. (For this criterion, Medline was considered a single database, whether it was searched via PubMed or Ovid; Ovid Medline contains a subset of all PubMed citations.)

I.3.4.2.2 Data collection

Data collection was conducted by a single author. Data that were extracted included for each SR included a purpose statement, the type of synthesis conducted (ie, narrative vs quantitative), bibliographic databases that were searched, dates of the searches, numbers of primary studies that examined treatments in TGNB children and/or adolescents, total numbers of TGNB children and/or adolescents that were represented in the primary studies, the treatments examined in each SR, the outcomes examined in each SR along with the specific measures that were used in the primary study, and relevant study-level findings reported in each SR.

I.3.4.2.3 Risk-of-bias assessment

An ROB assessment of each SR was conducted by a single author using the complete AMSTAR-2, a 16-item checklist designed to assist readers of SRs in assessing the ROB.[43] Relevant items in AMSTAR are summarized in **Table I.2**. A subset of the items deemed "critical" by the AMSTAR-2 authors are also indicated.

Table I.2. Explanations for ROB items included in the AMSTAR-2 tool for SR quality [43]

Item number	Item description Explanation	Critical domain
1	**Did the authors use a well-specified research question and inclusion criteria?** The PICO framework (ie, (population, intervention, control group, and outcome) is commonly used to define a focused research question for systematic reviews. A well-specified research question reduces the risk that the search strategy and the authors' objectives will not be well-matched, and it reduces the risk that the authors will make biased study eligibility decisions.	
2	**Did the authors use methods that were established prior to beginning the work?** SRs are observational studies of other studies. Best practices for all observational studies are that a protocol should be created in advance, reducing the risk of bias in the findings.	√
3	**Did the authors justify their study design restrictions?** Some questions can only be answered with nonrandomized studies, such as effects of a policy change, or studies of interventions in a vulnerable population without other treatment options. Other questions require only experimental studies. However, most research questions can only be well-answered by including all study types. If authors restrict eligibility to only a particular study design, they should give a justification for that restriction.	
4	**Did the authors use a comprehensive search strategy?** SRs can only reveal the true consensus of the evidence if one of 2 conditions is met: (1) they must include all the relevant studies; or (2) they must include a completely random sample of all relevant studies. Because of the difficulty obtaining the second type of sample, the best practice is to find everything. Because of bias in publishing, it can be	√

Return to TOC

Table I.2. Explanations for ROB items included in the AMSTAR-2 tool for SR quality [43]

Item number	Item description Explanation	Critical domain
	very difficult to find all the relevant studies without a comprehensive and exhaustive search strategy.	
5	**Did the authors perform duplicate study selection?** Authors can easily make mistakes in determining study eligibility, or can inadvertently allow bias to creep into their eligibility assessment. To minimize the risk of this happening, best practice for SRs are that review authors should conduct title/abstract and full-text eligibility screening in duplicate.	
6	**Did the authors perform duplicate data extraction?** Data extraction can be very complex and error-prone. For this reason, best practice is that data collection should be performed in duplicate, with a plan for resolving any disagreement.	
7	**Did the authors provide a list of excluded studies?** Because of the subjectivity inherent in evidence synthesis, best practice for review authors is that they should provide a list of studies excluded at the stage of full-text review along with reasons for exclusion. This enables readers to determine whether some excluded studies should have been included.	√
8	**Did the authors adequately describe included studies?** Heterogeneity of included studies (eg, major differences in population characteristics across studies) can distort review findings. That's why best practices for review authors are that they should provide key details about the populations, interventions, comparators, outcome measures, study designs, and settings of included studies. The provision of these details enables readers to make judgments about study heterogeneity.	
9	**Did the authors assess study-level ROB?** All primary studies are subject to bias. A good systematic review will make assessments of ROB in the primary studies so that they can consider whether bias is distorting the review's findings.	√
10	**Did the authors report on the sources of funding for primary studies?** Funding source tends to be highly correlated with systematic differences in the nature and direction of study results. That's why best practice for review authors is that they examine sources of funding in the primary studies.	
11	**Did the authors use appropriate methods for statistical combination of results?** In the presence of heterogeneity, review authors should be very careful about which approach they use to calculate quantitative summaries of treatment effects, if it is even appropriate to do so. This item may be irrelevant when authors use a narrative or qualitative synthesis only.	√
12	**Did the authors assess the impact of primary-study ROB on their findings?**	

Return to TOC

Table I.2. Explanations for ROB items included in the AMSTAR-2 tool for SR quality [43]

Item number	Item description Explanation	Critical domain
	Because study-level ROB can distort a review's finding, review authors should go beyond just assessing study-level ROB; they should conduct sensitivity and subgroup analyses to examine the extent to which study-level ROB is distorting their findings. This item may be irrelevant when authors use a narrative or qualitative synthesis only.	
13	**Did the authors address study-level ROB when interpreting/discussing their findings?** Because of the importance of study-level ROB, investigators should go beyond assessing primary-study ROB and examining its impact on their findings. They should discuss its effects on their findings in their narrative. This item may be irrelevant when authors use a narrative or qualitative synthesis only.	√
14	**Did the authors explain and discussion any observed heterogeneity?** Because heterogeneity can distort review findings, review authors should go beyond simply measuring heterogeneity; they should also examine potential sources of heterogeneity, and theorize about the impact it may have on their findings. This item may be irrelevant when authors use a narrative or qualitative synthesis only.	
15	**Did the authors investigate small study bias and discuss its impact on their findings?** The effects of several reporting biases, such as publication bias, can be seen by examining funnel plot asymmetry. A statistical or visual examination asymmetry can reveal the presence of bias in the review's findings. This item may be irrelevant when authors use a narrative or qualitative synthesis only.	√
16	**Did the authors report their own funding sources or conflict of interest?** Because of the strong correlation between funding source and study findings, review authors are asked to report any financial conflicts of interest.	

I.3.4.3 Methods for the bibliography of all relevant studies

To compile this bibliography, all relevant sources passed 3 levels of screening: search screening, title and abstract screening, and full-text screening. The eligibility criteria specific to guidelines and systematic reviews are detailed above in Sections I.3.3.1 and I.3.3.2, respectively. The eligibility criteria specific to experimental studies, observational studies, and descriptive studies are presented in Sections I.3.3.4, I.3.3.5, and I.3.3.6, respectively.

I.3.4.4 Experimental study-specific methods

I.3.4.4.1 Clinicaltrials.gov search

While it was not a part of the contracted work, we planned to search ClinicalTrials.gov if few clinical trials were found in bibliographic database searches.

Return to TOC

I.3.4.4.2 Final full-text eligibility

Experimental studies that met eligibility criteria according to **Table I.1** were to be included in this review. Experimental studies that did **not** examine relevant outcomes of interest (listed below) were tagged for inclusion in the bibliography only.

- Mental health (eg, depression, anxiety, suicidality)
- Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
- Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
- Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
- Bone health (eg, bone density, bone turnover measures)
- Cardiovascular risk factors (eg, thrombotic changes, insulin sensitivity, blood pressure, obesity)
- Cancer

I.3.4.4.3 Data collection

Data collection for experimental studies was combined with data collection for other study designs. Experimental studies that made between-group comparisons underwent data collection with observational studies based on the comparison type (ie, between-TGNB-group or TGNB vs peer-group comparisons). Single-arm experimental studies underwent data collection with descriptive studies (ie, longitudinal, pre-post, within-group comparisons).

I.3.4.4.4 Risk-of-bias assessment

When it was possible to do so, ROB assessment for non-randomized experimental studies was combined with ROB assessment for other study designs. Experimental studies that made between-group comparisons (eg, TGNB patients who received an intervention vs cisgender patients who did not) underwent ROB assessment with similar observational studies as described below. Single-arm experimental studies underwent data collection with descriptive studies as described below.

I.3.4.5 Observational study-specific methods

I.3.4.5.1 Final full-text eligibility assessment and tagging

Observational studies that met eligibility according to **Table I.1** were included in this review. Potentially-relevant, non-English publications with English-language abstracts that met inclusion criteria were also assigned to the bibliography only. Observational studies that did ***not*** examine high-priority outcomes of interest (listed below) were tagged for inclusion in the bibliography only.

- Mental health (eg, depression, anxiety, suicidality)
- Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
- Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
- Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
- Bone health (eg, bone density, bone turnover measures)

- Cardiovascular/metabolic risk factors: thrombotic/thromboembolic, insulin sensitivity, obesity, blood pressure, cholesterol, liver, and kidney outcomes
- Cancer

Included studies were further examined to determine the study design (ie, cohort study, case-control study, or cross-sectional study), and were categorized further according to the types of between-group comparisons made, including the following:

A. Between-TGNB-group comparisons: These studies made inferential comparisons between 2 or more TGNB groups. For example, a study that compared treated TGNB children with untreated TGNB children (eg, comparisons between treated and untreated TGNB children).
B. TGNB vs cisgender peer group comparisons: These studies made inferential comparisons between 1 or more TGNB groups and one or more cisgender control groups from the general population.
C. TGNB vs other populations: These studies made inferential comparisons between 1 or more TGNB groups and one or more special populations, such as patients with sex developmental disorders.

Comparison types A and B above (ie, between-TGNB-group comparisons and between TGNB-group vs peer group comparisons) were considered 2 of the 3 highest-priority comparisons to evaluate for this evidence synthesis and were tagged for data extraction, as long as they also examined the identified high-priority outcomes. Those studies that lacked high-priority outcomes, along with type C above (ie, studies in which TGNB patients were compared to special populations, such as patients with a developmental sex disorder) were assigned to the bibliography only. For type C studies, the decision to exclude them was a function of the large number of higher-priority studies with relevant comparisons of interest in the context of the limited time available for this review.

Some observational studies had comparisons that met more than 1 of the group comparison types listed above. If these had high-priority outcomes, these were assigned to data collection in multiple stages.

I.3.4.5.2 Data extraction and record annotation

Because there were so many observational studies, data extraction was conducted by a team of authors in multiple phases, staged according to the comparison types described above.

For each phase, a data collection tool was developed in Excel and piloted to standardize the data collection process among the multiple authors. There were 5 steps in the data collection, listed below:

1. **Confirm data collection tasks**: During this data collection step, authors collected 3 types of data:
    a. **Confirmation of *between-group* comparisons:** Authors confirmed that there was 1 or more or more between-group comparison of the type specified, regardless of outcomes. For example, during the phase of data extraction for between-TGNB-group comparisons, authors were asked to confirm that there was one or more inferential finding reported that compared 1 group of TGNB subjects to another.
    b. **Identification of *relevant* comparisons**: Authors listed each inferential between-group comparison reported of the type specified (ie, comparison type A, B, and/or C), regardless of outcomes. For example, during the phase of data extraction for between-TGNB-group comparisons, authors were asked to list the comparisons in the following format: [Outcome list] was compared between [exposure group] vs [comparator group] at [time]. Bracketed phrases

were replaced by the outcome, exposure definition, comparator definition, or timeframe for follow-up (eg, baseline or 6 months).

c. **Identification of *included* comparisons**: Authors were asked to indicate which between-group comparisons required data collection (ie, comparison type A and/or B) because they pertained to a high-priority outcome (ie, outcomes 1-6, above). For example, during the phase of data extraction for between-TGNB-group comparisons, and if a study reported findings for 2 inferential between-TGNB-group comparisons, but only one included an outcome of interest, authors highlighted only the one that included the outcome of interest.

4. **Extract details for the *included* comparisons**: During this data collection step, authors collected 3 types of data:
   a. **Give the number of included comparisons**: Authors were asked to indicate the number of relevant inferential comparisons that required data extraction. This number should match the number of highlighted comparisons described in step 1c, above.
   b. **Extract details of included comparisons**: For each included comparison, authors extracted data on the population studied; number of subjects included; eligibility criteria; setting; sampling method; subset definition (if the extracted comparison was conducted in a subset of the whole study population); and summary baseline characteristics overall, for the subset (if relevant), and for each comparison group. They also extracted details of exposure and comparator definitions and numbers in each group, outcome definitions and numbers with each outcome (if dichotomous) or mean values (if continuous), and a summary of the hypothesis test findings.
   c. **Manuscript annotation**: Authors were asked to annotate the PDFs of each study to highlight relevant and included comparisons, including additional comparisons to be addressed in other data extraction phases. For example, during between-TGNB group data collection, authors highlighted comparisons that would need to be extracted during the phase of TGNB vs peer data collection, if any.
5. **Complete ROB assessment**: Authors completed the ROB assessment for the study overall, or for a primary included comparison if no included comparisons were conducted in the full study cohort, using an appropriate tool as described below.
6. **Identify any other treatment-related, inferential comparisons** that will need to be extracted in other phases. Authors were asked to indicate what other inferential comparisons were reported in the study that would need to be examined during other data-extraction phases. For example, during between-TGNB-group data extraction, if authors saw an inferential pre-post comparison (eg, a value at follow-up was compared to a value at baseline in the same group), then they would indicate that a "pre-post descriptive" comparison remained to be addressed during the data collection task for descriptive studies.

I.3.4.5.3 Risk-of-bias assessment

The Newcastle-Ottawa Scale (NOS) was used for ROB assessment.[44] The NOS has two versions: one for cohort studies, and another for case-control studies. We applied the NOS to all observational study types, adapting it for cross-sectional studies by excluding items that were relevant to the duration of follow-up. We decided not exclude items related to the temporality requirement for cohort and case-control studies (ie, that all measured exposures must precede measured outcomes), as this is a clear weakness of cross-sectional studies that increases the ROB for those studies relative to cohort studies.

The NOS is a validated tool with good inter- and intra-rater reliability. It comprises 8 items each for cohort and case-control studies, as described in **Table I.3**. The NOS contains items in each of 4 domains, including 3 each for cohort studies (selection bias, comparability, and outcome assessment) and case-control studies (selection bias, comparability, and exposure assessment). A summary score for each domain can be calculated, ranging from 0-5 stars for the selection domain with cohort studies, and 0-4 stars for the selection domain with case-control studies, 0-1 star for the; comparability domain for both study types, and 0-3 stars for the outcome domain for both study types. Overall scores range from 0 to 8 stars for cohort studies, and 0-7 stars for case-control studies.

Table I.3. Explanations for ROB items included in the NOS tool for observational study quality [44]

Domain Item #	Cohort study items	Case-control study items	Scoring
	Domain: Selection		
Item 1	**Representativeness of the exposed cohort** Asks whether the exposed cohort was representative of the larger population from which the sample was drawn. This relates to *selection bias* as a question of generalizability.	**Case definition** Asks whether the case definition is with regards to identifying the outcome. This relates to a question of accurate outcome classification, an issue of *information bias*.	0-1 stars
Item 2	**Selection of the nonexposed cohort** Asks whether the comparator group was drawn from the same community as the exposed cohort. This relates to a type of selection bias that can introduce *confounding bias* into the study.	**Representativeness of cases** Asks whether all cases were included, or whether a cherry-picked subset of cases were included. This concerns *confounding bias*, which occurs when other causes of the outcome are ignored.	0-1 stars
Item 3	**Ascertainment of exposure** Asks how the exposure was assessed, whether by secure records, interviews, self-report, or other. This item is in the selection bias domain for the NOS, but misclassified exposures (or outcomes) are classically a concern about *information bias.*	**Control selection** Asks how controls were selected, whether they came from the same population that gave rise to the cases, or whether they came from different populations. The latter can introduce *confounding bias.*	0-1 stars
Item 4	**Outcome temporality requirement** Asks if the authors of the primary study demonstrated that the outcome was not present at the beginning of the study; including patients not at risk for the outcome is classic *selection bias.*	**Control definition** Asks whether controls were selected from all non-cases (eg, cumulative sampling), or whether some other sampling method was used (ie, case-cohort or risk-set sampling). Cumulative sampling may bias a study away from the null hypothesis if the outcome is	0-1 stars

Table I.3. Explanations for ROB items included in the NOS tool for observational study quality [44]

Domain Item #	Cohort study items	Case-control study items	Scoring
		common, but this item awards a point for that method.	
	Domain: Comparability		
Item 1	**Comparability of (exposure/comparator) cohorts** Asks if study investigators controlled for one or more key confounding factors, whether by a study design method (ie, matching, restriction, stratification), or a statistical method.	**Comparability of (case/control) groups** Asks if study investigators controlled for one or more key confounding factors, whether by a study design method (ie, matching, restriction, stratification), or a statistical method.	0-1 stars
	Domain: Outcome		
Item 1	**Outcome assessment** Asks how outcomes were classified, a factor that concerns *information bias.*	**Exposure ascertainment** Asks about the data source used for exposure ascertainment; this item concerns *information bias.*	0-1 stars
Item 2	**Duration of follow-up** Asks whether the study duration is sufficiently long for an outcome to occur as a result of the exposure.	**Comparability of exposure ascertainment method** This item asks whether exposure ascertainment was the same in both cases and controls; this item concerns either *differential information bias* or *confounding bias* or both.	0-1 stars
Item 3	**Attrition** Asks whether any patients were lost to follow-up during the study period; if so, *confounding bias* can be introduced.	**Non-response rate** This item asks about percentage of study subjects who do not respond to surveys, or who lack data on exposures. Depending on how a lack of response is handled by investigators, nonresponse may introduce either *information bias* or *selection bias*.	0-1 stars

I.3.4.6 Descriptive study-specific methods

I.3.4.6.1 Descriptive study full-text eligibility assessment

Descriptive studies that met eligibility according to **Table I.1** were included in this review. Potentially-relevant, non-English publications with English-language abstracts that met inclusion criteria were also assigned to the bibliography only. Descriptive studies that did not examine high-priority outcomes (listed below) were tagged for inclusion in the bibliography only.

1. Mental health (eg, depression, anxiety, suicidality)
2. Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
3. Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
4. Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
5. Bone health (eg, bone density, bone turnover measures)
6. Cardiovascular/metabolic risk factors: thrombotic/thromboembolic, insulin sensitivity, obesity, blood pressure, cholesterol, liver, and kidney outcomes
7. Cancer

Due to an overwhelming volume of descriptive studies to examine within our very limited time constraints, we ultimately restricted data extraction to only 2 types of descriptive studies (ie, single-arm clinical trials and longitudinal, pre-post descriptive studies). All case series, case reports, and other descriptive studies that did not assess high-priority outcomes at 2 or more time points did not undergo data extraction. Potentially relevant, non-English descriptive studies were also assigned to the bibliography only.

In the bibliography, we also distinguish between case series/reports that include a statement about IRB/ethics board review or subjects' consent, and those that do not have such statements. This is to indicate which studies certainly used real patients and those that may or may not have used fictional or composite patients; the latter studies are sometimes written for educational purposes.

I.3.4.6.2 Data extraction and record annotation

A data collection tool was developed in Excel and piloted to standardize the data collection process, which was to be completed by multiple authors. There were 5 steps in the data collection, listed below:

1. **Confirm data collection tasks:** During this data collection step, authors collected 3 types of data:
    a. **Confirmation of relevant and/or included comparisons:** Reviewers confirmed that there was 1 or more or more within-TGNB-group comparison, regardless of outcomes. For example, reviewers were asked to confirm that there was one or more inferential finding reported that compared mean outcome measures in a TGNB study sample both before and after a treatment was initiated.
    b. **Identification of relevant comparisons:** Reviewers listed each inferential within-group, pre-post comparison that was reported, regardless of outcomes. For example, reviewers were asked to list the comparisons in the following format: [Outcome list] was compared at [time 1 (eg, "12 months")] vs [time 0 (eg, "baseline")] in [population] who received [exposure]. Bracketed phrases were replaced by the outcome, exposure definition, population, or timeframe for follow-up.
    c. **Identification of included comparisons:** Authors were asked to indicate which within-group, pre-post comparisons required data collection. For example, if a study reported findings for 2 inferential within-TGNB-group comparisons, but only one included an outcome of interest, authors highlighted the one that included the outcome of interest.
8. **Extract details for the included comparisons:** During this data collection step, reviewers collected 3 types of data:

a. **Give the number of included comparisons:** Reviewers were asked to indicate the number of relevant inferential comparisons that required data extraction. This number should match the number of highlighted comparisons described in step 1c, above.
b. **Extract details of included comparisons:** For each included comparison, reviewers extracted data on the population studied; number of subjects included; eligibility criteria; setting; sampling method; subset definition (if the extracted comparison was conducted in a subset of the whole study population); and summary baseline characteristics overall, for the subset (if relevant), and for each comparison group. They also extracted details of exposure definitions and numbers in each treatment group, outcome definitions and numbers with each outcome (if dichotomous) or mean values (if continuous), and a summary of the hypothesis test findings.
c. **Manuscript annotation:** Reviewers were asked to annotate the PDFs of each study to highlight relevant and included comparisons, including additional comparisons to be addressed in other data extraction phases. For example, reviewers highlighted comparisons that would need to be extracted during the phase of TGNB vs peer data collection, if any.

9. **Complete ROB assessment:** Reviewers completed an ROB assessment for the study overall, or for a primary included comparison if no included comparisons were conducted in the full study cohort, using the National Institutes of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group,[45] as described below.
10. **Extract information on funding and financial conflicts of interest:** Reviewers extracted data from the manuscript about 2 types of financial conflicts of interest: (A) funding for the study, and (B) other financial conflicts of interest.
11. **Identify any other treatment-related, inferential comparisons that will need to be extracted in other phases:** Reviewers were asked to indicate what other inferential comparisons were reported in the study that would need to be examined during other data-extraction phases. For example, during between-TGNB-group data extraction, if authors saw an inferential pre-post comparison (eg, a value at follow-up was compared to a value at baseline in the same group), then they would indicate that a "pre-post descriptive" comparison remained to be addressed during the data collection task for descriptive studies.

I.3.4.6.3 Risk-of-bias assessment

The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group was used for ROB assessment of longitudinal, pre-post descriptive studies.[45] This tool was developed jointly by methodologists from the National Heart, Lung, and Blood Institute (NHLBI) and Research Triangle Institute International. This NIH tool is a 12-item questionnaire, with questions designed to help reviewers focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list from which to add up items to judge a study's quality (ie, a "summary score.") The questions in this quality assessment tool, as well as their descriptions, are listed in **Table I.4**.

The tool includes items for evaluating potential flaws in study methods or implementation, including sources of bias (eg, patient selection, performance, attrition, and detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and other factors. Reviewers could select "yes," "no," or "cannot determine/not reported/not applicable" in response to each item on the tool. For each item where "no" was selected, reviewers were instructed to consider

the potential risk of bias that could be introduced by that flaw in the study design or implementation. "Cannot determine" and "not reported" were also noted as representing potential flaws. The greater the risk of bias, the lower the quality rating of the study.

Table I.4. Explanations for ROB items included in the NIH/NHLBI tool for longitudinal, pre-post descriptive studies [45]

Domain *(Item no)* Question	**Description**
Study question *(Item 1)* Was the study question or objective clearly stated?	This item asks reviewers to assess whether the authors adequately and clearly described their research goal for the study. High-quality research studies should have a hypothesis, defined a priori, and an a priori research plan that is designed to test the prespecified hypothesis. It is easy to come up with a hypothesis after-the fact that fits the study's findings, but such hypotheses are usually biased.
Eligibility criteria and study population *(Item 2)* Were eligibility/selection criteria for the study population prespecified and clearly described?	This item asks reviewers to assess whether the authors adequately and clearly described the eligibility criteria that were applied to study subjects. Eligibility criteria should be described in sufficient detail to make the study's findings reproducible. Well-defined and explicit eligibility criteria are important because, without them, we cannot know which to patients the study applies.
Selection *(Item 3)* Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	This item asks reviewers whether study subjects are representative of the population in which the study's findings will be applied. Studies on tiny, unique demographic subgroups may not apply to broader populations. For example, studies that focus on autistic TGNB subpopulations may not always be relevant to allistic TGNB adolescents.
All eligible participants enrolled *(Item 4)* Were all eligible participants that met the prespecified entry criteria enrolled?	This item asks reviewers whether the investigators developed eligibility criteria before they began recruiting subjects, and whether all eligible subjects, or a representative sample (ie, a random sample) of subjects was included. This item is intended to help reviewers identify studies in which included subjects are a cherry-picked subset of all eligible subjects, in whom the treatment effects may be different.
Sample size *(Item 5)* Was the sample size sufficiently large to provide confidence in the findings?	This item asks reviewers to assess whether study authors adequately and clearly justified their reasons for selecting or recruiting the number of individuals included in the study. Reviewers were asked to look for a samples size calculation, and if so, to assess whether the study was powered to detect a clinically meaningful difference.

Table I.4. Explanations for ROB items included in the NIH/NHLBI tool for longitudinal, pre-post descriptive studies [45]

Domain *(Item no)* Question	Description
	It is uncommon for non-experimental studies to include a power/sample size calculation in the methods section. Most observational and descriptive studies include all eligible subjects, so authors frequently neglect the question of power on the rationale that they can do nothing about it if their study is underpowered. However, this question is highly relevant for readers of studies that show no significant difference. An underpowered study that shows no difference is interpreted differently from a well-powered study that shows no difference.
Intervention clearly described *(Item 6)* Was the test/service/intervention clearly described and delivered consistently across the study population?	This item asks reviewers whether the intervention is adequately and clearly defined, and whether study authors gave any indication that it was consistently administered to study subjects. The purpose of this item is to determine the likelihood that study outcomes resulted from the administration of study interventions. If participants received outside (ie, non-study) interventions, study results could be biased.
Outcome measures clearly described, valid, and reliable *(Item 7)* Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	This item asks reviewers to assess whether study outcomes were defined in sufficient detail, and whether appropriate and reliable tools for measuring outcomes were used. Some outcome measures are more objective, accurate, and reliable than others, such as measuring death, or lab levels. These examples would get a "yes." Other measures that are more subjective, such as self-reports, would get a "no" answer. This question is important influences the reader's confidence in the validity of study results.
Blinding of outcome assessors *(Item 8)* Were the people assessing the outcomes blinded to the participants' exposures/interventions?	This item asks reviewers to evaluate if study outcomes assessors were blinded to the exposures/interventions. Often there is insufficient detail provided for reviewers to make this assessment, in which case they would respond that it is "unclear." Blinding is critical for a study's internal validity because unblinded investigators are more likely to assess outcomes differentially in different treatment groups. The risk of bias is higher if outcomes are also subjective.
Follow-up rate *(Item 9)* Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	This item asks reviewers to assess the amount of attrition (ie, "loss-to-follow-up") in a longitudinal study. Studies have repeatedly shown that reasons for attrition tend to be systematically associated with exposures and outcomes, which means that studies with higher rates of attrition are more likely to produce biased results. An acceptable rate of follow-up rate is usually ≥ 80% of

Return to TOC

Table I.4. Explanations for ROB items included in the NIH/NHLBI tool for longitudinal, pre-post descriptive studies [45]

Domain *(Item no)* Question	**Description**
	participants whose interventions or exposures were measured at baseline.
Statistical analysis *(Item 10)* Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided P values for the pre-to-post changes?	This item asks reviewers if formal statistical tests were used to assess the significance of the changes in the outcome measures between the before and after time periods. The reported study results should present values for statistical tests, such as P values or 95% confidence intervals (CIs), to document the statistical significance (or lack thereof) for any observed outcome changes.
Multiple outcome measures *(Item 11)* Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	This item asks reviewers to evaluate whether outcome measures for each person were measured more than once in the study follow-up period. Multiple measurements with the same result increase confidence that the outcomes were accurately measured.
Group-level interventions and individual-level outcome efforts *(Item 12)* If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	This item asks reviewers to assess whether statistical analyses accounted for any group-level effects, such as when interventions were provided at the clinic level in cases where the clinics may differ in the intensity of the interventions. Group-level interventions are usually not relevant for clinical interventions in which the interventions are applied at the individual patient level. In those cases, the questions were coded as "N/A" in the assessment tool.

Return to TOC

I.4.0 RESULTS OF EVIDENCE SYNTHESIS

I.4.1 Search Results

I.4.1.1 Ovid Medline search results

All Ovid Medline searches yielded a total of N = 1,731 records. After deduplication, there were N = 769 (44.4%) unique citations in Ovid Medline that underwent title/ abstract screening. Before screening, we noted that no single major MeSH heading was widely used to index retrieved citations, and that indexing seemed to be relatively heterogenous compared to other medical topics. As shown in **Figure I.2**, the most common major MeSH terms were *Transgender Persons*, *Gender Dysphoria*, *Transsexualism*, and *Gender Identity*, which occurred in 335 (43.5%), 159 (20.7%), 156 (20.3%), and 127 (16.5%), respectively.

Figure I.2. Top ten indexed major MeSH headings in all first- and second- corpus Ovid Medline results

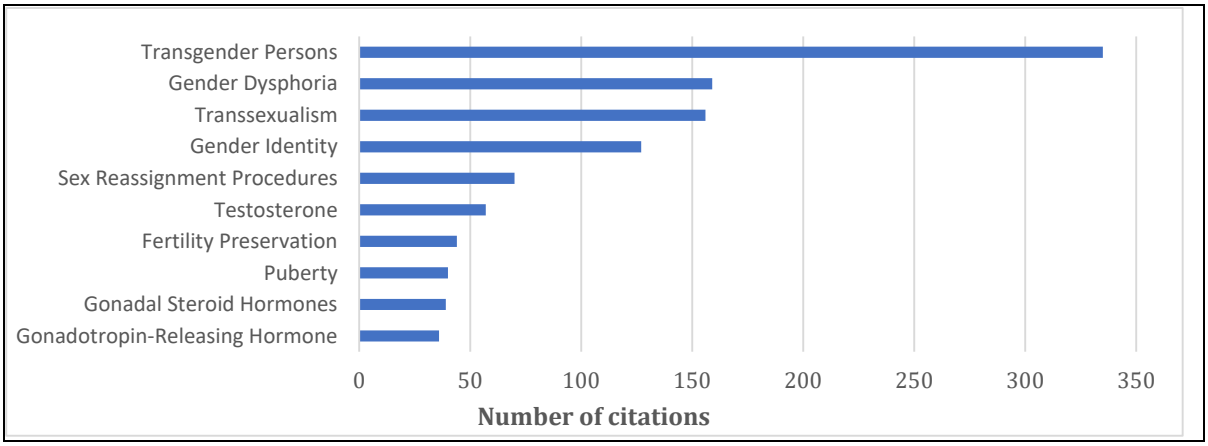


Figure abbreviations: MeSH, medical subject headings, structured vocabulary keyword terms used to index bibliographic records in Medline

I.4.1.2 Embase search results

An analysis of major keyword headings from Embase was not done since Embase does not use a major-topic indicator for their indexed keywords.

I.4.1.3 PRISMA

As shown in the PRISMA diagram in **Figure I.3**, a total of N = 4980 citations were identified. These included 1731 Ovid Medline and 3062 Embase citations that were uploaded to Covidence. Outside of Covidence, we identified another 171 citations from reference lists of included studies, 12 citations from clinical trial registries, and 4 citations recommended by experts in the field. In total, after removing duplicates, N = 1425 studies were eligible to be screened for relevance in the title/abstract (TIAB) screening stage.

Figure I.3. PRISMA flow chart for study selection

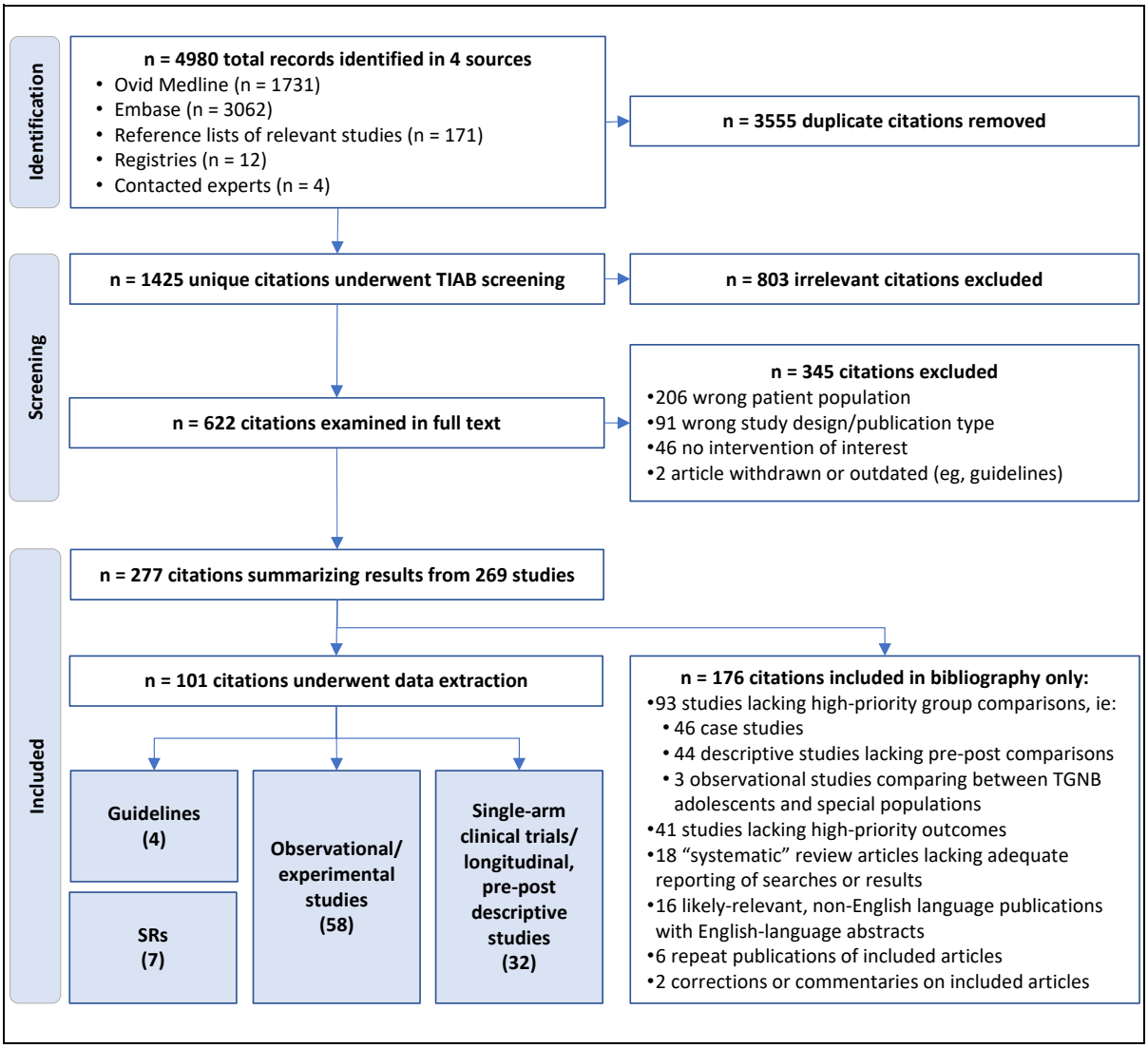


Figure abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; TIAB, title and abstract; SR, systematic review; TGNB, transgender, nonbinary, or gender diverse

During TIAB screening, 803 irrelevant citations were excluded, leaving 622 (43.6%) that underwent full-text review. Of these, 345 (55.4%) citations were excluded, leaving 277 separate publications that represented 269 unique studies. These included 101 citations that underwent data extraction as described in the sections that follow, and 176 citations that were included in the bibliography only.

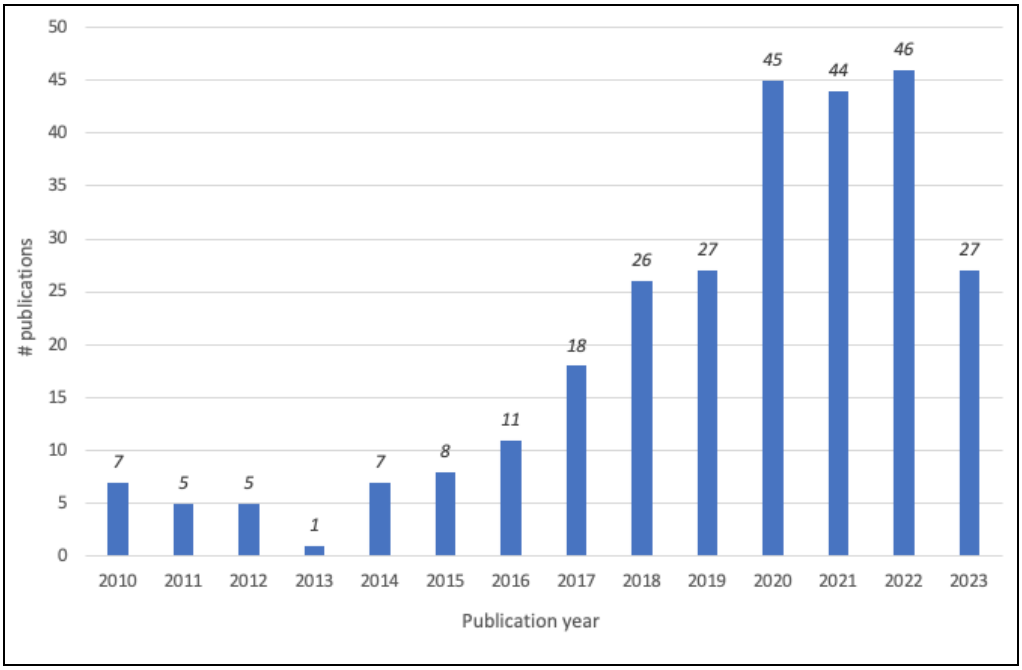
Appendix I.C contains a list of all studies examined in full-text review that were **excluded** from eligibility, along with reasons for exclusion.

Return to TOC

I.4.1.4 Publication year

The publication year of N=277 included studies is summarized in **Figure I.4**. Most of the studies (88%) were published in 2016 or later; the largest number of studies (N=46) was published in 2022. As of the end date of our searches (June 5, 2023), there were already N=27 studies published in 2023.

Figure I.4. Number of included publications per year, 2010-2023 (N = 277)



I.4.2 Guidelines

I.4.2.1 Included guidelines

A total of 5 guidelines was identified in bibliographic database searches that were eligible for inclusion in the bibliography, including 1 non-English (German-language) guideline that is included in the bibliography only. The remaining included guidelines comprised 3 guidelines that made drug-therapy-related recommendations for treatment of GD in pediatric TGNB patients and 1 guideline with recommendations pertinent to people who menstruate. **Appendix I.D** includes summary tables of information extracted from these English-language guidelines.

I.4.2.2 Guideline recommendations

I.4.2.2.1 Overview of reviewed guidelines

- We identified 4 clinical practice guidelines or position statements that met our inclusion criteria for data extraction (see **Table I.1** and Section I.3.3.1 for criteria).
- Reviewed guidelines were published by the following organizations: the World Professional Association for Transgender Health (WPATH; 2022),[39] the Endocrine Society (ES; 2017),[42] the

Return to TOC

European Society for Sexual Medicine (ESSM; 2020),[41] and the American College of Obstetricians and Gynecologists (ACOG; 2022).[40]

I.4.2.2.2 Key guideline hormonal therapy recommendations

- **Guidelines providing hormone therapy recommendations do not recommend starting hormonal therapies in pre-pubertal children**.[39,41,42] The WPATH, ES, and ESSM provided hormonal therapy recommendations for adolescents,[39,41,42] defined by the WPATH guideline as youth who reached puberty (ie, at least sexual maturity of Tanner stage ≥ 2) and are less than 18 years old (or age of majority).[39] ACOG guideline recommendations for menstrual suppression are non-specific to age.[40]
- Generally, hormonal therapies for TGNB adolescents desiring treatment include puberty-suppression agents (eg, gonadotropin-hormone releasing [GnRH] analogs) and cross-sex hormone therapies (CSHT; eg, estradiol or testosterone).[39,41,42]
- Evidence tables for reviewed guidelines are provided in **Appendix I.D. Table I.D.1** describes guideline development methodology, including criteria used for level of evidence (LOE) ratings. **Table I.D.2** shows recommended eligibility criteria for use of hormone or hormone-blocking GAHT for TGNB adolescents, recommended hormonal therapy by drug class or specific medication, and recommendations for starting or stopping hormonal treatments. **Table I.D.3** provides an overview of hormonal treatment monitoring parameters addressed by guidelines.

I.4.2.2.3 Considerations for interpretation of guideline recommendations

- Most guidelines are broad,[39,41,42] addressing many aspects of TGNB care outside the scope of this report, such as provider training or background, non-pharmacologic treatments for pre-pubescent children, surgical treatment, and counseling recommendations (eg, regarding benefits or risks of medications). The guideline evidence tables in this report focus on guideline development methods and pharmacologic hormone or hormone-blocking therapy recommendations for minors. Please refer to the guidelines for details about other important aspects of TGNB care across the lifespan.
- According to WPATH (page S7), "The goal of gender-affirming care is to partner with TGD [transgender and gender diverse] people to holistically address their social, mental, and medical health needs and well-being while respectfully affirming their gender identity."[39] Medically necessary care should be provided to TGNB people; medical necessity is defined by WPATH using criteria by the American Medical Association (page S16-S17):

  > "'Health care services that a physician and/or healthcare professional, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are: (a) in accordance with generally accepted standards of medical practice; (b) clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury, or disease; and (c) not primarily for the convenience of the patient, physician, or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnosis results as to the diagnosis or treatment of that patient's illness, injury or disease.' The treating HCP [healthcare professional] asserts and documents that a proposed treatment is medically necessary for the treatment of the condition."[39]

- Both the WPATH and ES guidelines recommended adolescents meet specific criteria to receive hormonal therapy (see eligibility criteria in the left column of **Table I.D.2**). An important criterion to start hormonal therapy is collecting informed consent (or assent) from the adolescent and guardian(s) (in most cases).[39,42]
    - To provide informed consent/assent, adolescents must be informed of the possible risks and benefits of hormonal therapies, including the reversibility of therapies and possible fertility risks.[39,41,42] Guidelines consider the effects of puberty suppression with GnRH analogs to be "fully reversible" whereas CSHT is "partially reversible."[39,42]
    - Adolescents should be capable of providing informed consent/assent to initiate hormonal therapies.[39,41,42] WPATH and ESSM guidelines do not specify an age at which all adolescents can consent to hormonal therapy, but the consenting adolescent must have the "capacity" for consent.[39,41] See the WPATH guideline for suggestions on how to assess an adolescent's capacity to consent to treatment.
    - Similar to WPATH and ESSM guidelines, the ES requires adolescents to consent to hormonal therapy once they have sufficient capacity. Unlike the other guidelines, the ES specifies an age at which most adolescents can consent to GAHT. According to the ES, most adolescents have sufficient capacity to consent to CSHT by age 16; however, there are compelling reasons to start earlier than 16, which may be possible for some adolescents.[42]
- ES and ESSM guidelines did not provide separate recommendations for TGNB sub-populations (eg, non-binary),[41,42] whereas the WPATH developed separate recommendations for tailoring hormonal therapy and other care to other gender-diverse populations (ie, non-binary, Eunuch, people who are TGNB and intersex),[d] asserting that hormonal therapies should be accessible to all gender-diverse people (not only people identifying as male or female) who would benefit from gender-affirming treatments.[39]
- Guidelines providing hormonal therapy recommendations for TGNB adolescents are generally in agreement about recommended therapies and treatment approach (see **Table I.D.2**). GAHT given to TGNB adolescents may include agents for suppression of endogenous puberty (eg, GnRH analogs), and CSHT with feminizing sex hormones (eg, 17-β-estradiol) or masculinizing sex hormones (eg, testosterone). To receive therapy, youth should meet eligibility criteria (see left column of **Table I.D.2**) and not have any contraindications to treatment. The approach to therapy depends on an individual's pubertal developmental stage (eg, early puberty vs near-complete endogenous puberty completion) and treatment goals.[39,41,42] Medication interventions are not intended to be implemented using an all-or-nothing approach: treatments should be tailored to the individual.[39]
    - Puberty suppression may begin as soon as early puberty (Tanner stage 2). Guidelines recommend puberty suppression with GnRH analogs.[39,41,42]
    - For youth presenting in early puberty (eg, Tanner stage 2), CSHT typically follows a period of monotherapy with puberty suppression agents in youth meeting eligibility criteria. CSHT *may* start as early as Tanner stage 2 in adolescents meeting additional guideline eligibility criteria (see left column of guideline evidence **Table I.D.2**).[39,41] WPATH describes "When considering the timing and initiation of gender-affirming [ie, cross-sex] hormones, providers should compare the

[d] *Recommendations for how to adapt hormonal therapies to people with specific gender diverse identities/expression were not extracted from the 2022 WPATH guideline; please see this guideline for additional information regarding the use of hormonal therapy in these populations.*

potential physical and psychological benefits and risks of starting treatment with the potential risks and benefits of delaying treatment" (page S66).[39]

- Eligible TGNB youth assigned female at birth desiring masculinizing therapy are typically treated with testosterone therapy.[39,41,42]
- Eligible TGNB youth assigned male at birth desiring feminizing therapy are typically treated with estrogen therapy, and possibly, anti-androgen therapy (eg, spironolactone or GnRH analogs)[39,41,42].

- Generally, CSHT in adolescents is started at low doses and gradually titrated to a maintenance dose that achieves physiologic sex hormone levels similar to cisgender peers.[39,41,42] For youth presenting for care after completion or near completion of puberty, more rapid CSHT dose escalation can be considered. When levels can be measured, serum sex hormone levels should be monitored during therapy.[39,42] Refer to the WPATH (2022) and ES (2017) guidelines for suggested CSHT puberty induction dosing regimens in youth.
- Recommendations for specific medications by guidelines do not account for availability of that medication in the United States.
- Generally, guidelines recommend that healthcare professionals providing gender-affirming care to TGNB youth have sufficient general and gender-specific training to deliver care effectively.[39,41,42] Access to experts should not be a barrier to care. Multidisciplinary care is often necessary for assessment of youth seeking GAHT.[39]

I.4.3 Systematic Reviews

A total of 38 reviews met our criteria for population and interventions as well as our broad criteria for "systematic" review (ie, those that describe a systematic search in 1 or more bibliographic database or that were described by authors as "systematic"). Of these, 31 (81.6%) were subsequently determined to be of low priority for data extraction for the reasons listed below. These were assigned to the bibliography only.

- 10 reviews lacked a description of either the search strategy, search results, or both.
- 8 were based on searches conducted in only a single bibliographic database.
- 7 lacked high-priority outcomes.
- 4 were likely-relevant but published in a language other than English.
- 2 were duplicate publications of reviews counted elsewhere.

I.4.3.1 High-priority systematic reviews

Detailed summaries of findings from the N=7 reviews that underwent data extraction are included in **Appendix I.E**. **Table I.5** summarizes some key characteristics of these reviews. While 2 reviews primarily addressed GnRH analogs, all included primary studies of patients who had received subsequent CSHT. The number of primary studies in each review ranged from 9 to 91, but when considering only primary studies of TGNB adolescents, the range was 4 to 24.

As summarized in **Table I.5**, most of the extracted reviews addressed a majority of our high-priority outcomes. Psychosocial outcomes, a key indicator of treatment efficacy, were addressed by all 7 extracted reviews.[46-52] Body changes, a key goal of therapy for many TGNB patients, and bone health, an

Table I.5. Characteristics of 7 systematic reviews addressing high-priority outcomes associated with gender-affirming hormone therapy (GAHT) in adolescents

First author *(Year)* Purpose	Primary studies Patients	Treatments addressed	Outcomes addressed	Funding source
Baker (2021)[46] To examine the effects of CSHT on mental health and psychosocial outcomes in TGNB adults and adolescent and the effect of **GnRH analogs** for puberty suppression in TGNB adolescents	**Primary studies**: Out of 20 primary studies, 3 addressed adolescents in 4 publications **Patients**: Includes longitudinal experience from N=143 adolescents.	In pediatric patients, **GnRH analogs** for puberty suppression with or without subsequent **CSHT** (anti-androgens [including GnRH analogs], estrogens, progestins, and testosterone) In adult or mixed pediatric/adult populations, CSHT	**Mental health** (anxiety, death by suicide, depression) and **psychosocial outcomes** (QOL)	World Professional Association for Transgender Health
Chew (2018) [47] To examine the impact of **GAHT** on physical and mental health of TGNB adolescents and young adults	**Primary studies**: 11 out of 13 primary studies included only patient groups with mean ages <18 years, including 1 study that did not mention the age of participants but referred to them collectively as "adolescents;" 1 study's transgender male participants met this criterion, but not it's trans female participants. One study included patients with a mean age >18; we did not extract results from this study. **Patients**: Includes longitudinal experience from N=649 adolescents *plus* short-term or cross-sectional experience from N=178 more.	Unspecified **GnRH analogs** for puberty suppression with or without subsequent **CSHT** (anti-androgens, estrogens, progestins, or testosterone) and **CSHT**	**Body changes** (endogenous hormone levels, height, growth velocity, lean and fat body mass); **Bone health** (BMD); **psychosocial outcomes** (executive functioning, mental rotation, global functioning, anger, behavioral and emotional problems gender and body dysphoria); and **mental health outcomes** (anxiety, depression)	Royal Children's Hospital Foundation, Melbourne Children's Clinician Scientist Fellowship Scheme, Apex Foundation for Research into intellectual Disability, and William Collie Trust at University of Melbourne

Return to TOC

Table I.5. Characteristics of 7 systematic reviews addressing high-priority outcomes associated with gender-affirming hormone therapy (GAHT) in adolescents

First author *(Year)* Purpose	Primary studies Patients	Treatments addressed	Outcomes addressed	Funding source
D'hoore (2022)[48] To identify recent information from larger cohorts on modern GAHT regimens in adult and adolescent TGNB patients	**Primary studies**: Out of 91 primary studies, 21 addressed adolescents, 1 addressed both adolescents and adults, and 69 addressed adults only. **Patients**: Includes experience from more than N=4052 patients.	Unspecified **GnRH analogs** for puberty suppression, **CSHT** (antiandrogens [including GnRH analogs], testosterones and estrogens), progestins, spironolactone	**Mental health**, **psychosocial outcomes** (body image); **body changes** (body composition); **cardiovascular** and **metabolic outcomes** (insulin resistance, cardiovascular and thromboembolic safety); **bone health**; **cancer risk**	Not reported
Ludvigsson (2023)[49] To examine the effect of puberty suppression and CSHT on body changes, bone health, mental health, psychosocial outcomes, and metabolic changes in pediatric TGNB patients	**Primary studies**: 24 primary studies were included out of 36 retrieved studies. **Patients**: Includes experience from N=6552 TGNB adolescents.	Unspecified **GnRH analogs** in young adolescents with or without subsequent **CSHT** in older adolescents	**Mental health** (anxiety, depression, acute distress, suicidality, self-harm, psychotropic medication use, mental health service utilization); **Psychosocial outcomes** (global functioning, anger, cognitive function, executive function, QOL); **Body changes** (height, height velocity weight, BMI, subperiosteal width, endocortical diameter, lean body mass); **Bone** (BMD); **Cardiovascular risk factors and metabolic changes** (BMI, BP, SBP, DBP, liver enzymes, creatinine, glucose, HbA1c, insulin, cholesterol, triglycerides, HOMA, hematocrit, thrombosis); **Other outcomes** (medication use, mental health utilization)	Swedish Agency for Health Technology Assessment and Assessment of Social Services
Mahfouda (2019)[50] To examine the effects of medical (GnRH analogs and CSHT) and surgical interventions on mental health,	**Primary studies**: N=12 studies that examined GAHT (plus N=5 studies examining surgical interventions)	**GnRH analogs** for puberty suppression in young adolescents with or without subsequent **CSHT** in older adolescents and **CSHT.**	**Psychosocial outcomes** (gender dysphoria, global functioning, cognitive effects); **cardiovascular risk factors** (hematological effects, cholesterol); **bone health** (BMD, bone turnover markers); **body changes** (lean mass, fat mass, BMI, waist-to-hip ratio, body/facial	University of Western Australia, Perth Children's Hospital Fund, Raine Medical Foundation, Australian National

Return to TOC

Table I.5. Characteristics of 7 systematic reviews addressing high-priority outcomes associated with gender-affirming hormone therapy (GAHT) in adolescents

First author *(Year)* Purpose	Primary studies Patients	Treatments addressed	Outcomes addressed	Funding source
psychosocial outcomes, cardiovascular and metabolic effects, bone health, and body changes in TGNB adolescents	**Patients**: Includes longitudinal experience of N=778 TGNB patients and N=41 cisgender patients.		hair changes, breast development, testicular volume)	Health and Medical Research Council
Ramos (2021)[51] To examine the effects of GnRH analogs for puberty suppression (with or without subsequent CSHT) on mental health, psychosocial function, body changes, and liver and kidney function in TGNB youths with "gender incongruity"	**Primary studies**: Out of 11 primary studies, 3 addressed adolescents in 4 publications **Patients**: Includes longitudinal experience from N=143 adolescents.	**GnRH analogs** (including triptorelin and other unspecified agents) for puberty suppression in young adolescents with or without subsequent **CSHT** (testosterone ester, 17estradiol, or other unspecified agents)	**Mental health** (suicide, general mental health); **psychosocial outcomes** (GD and body image); **body changes** (fat mass, lean mass, waist-to-hip ratio); **bone health** (BMD, BMAD, bone turnover markers)	Authors reported that there was no funding for this work.
Rew (2021)[52] To examine the impact of **GnRH analogs** with or without CSHT on mental and psychosocial outcomes, body changes, bone health, metabolic changes, and other safety outcomes in TGNB youths	**Primary studies**: 9 primary studies **Patients**: Includes longitudinal experience from N=702 TGNB patients.	**GnRH analogs** (triptorelin, leuprorelin, and other unspecified agents) with or without subsequent **CSHT** (testosterone, estradiol)	**Mental health** (anxiety, depression, suicide ideation, affect); **psychosocial outcomes** (anger, emotional and behavioral problems, IQ, social life); **body changes** (feminization/masculinization, testicular volume, menstrual outcomes, lean mass, fat mass, growth/height velocity); **bone health** (BMD, bone turnover markers); **metabolic changes** (liver function, creatinine); and other safety outcomes	Authors reported that there was no funding for this work.

Return to TOC

important safety outcome, were addressed by 6 reviews.[47-52] Mental health outcomes, our last key efficacy indicator, were addressed by 5 reviews.[46,48,49,51,52] Cardiovascular and metabolic outcomes were addressed in 4 reviews.[48-50,52] Cancer was only addressed in 2 reviews[47,48]; neither review found any studies examining cancer risk in TGNB adolescents.

I.4.3.2 Systematic review risks of bias (ROB)

A summary of the ROB for SRs that underwent data extraction is given in in **Table I.6**. A complete summary of all ROB details is given in **Appendix I.E**.

The recent SR by Ludvigsson (2023),[49] was an outlier in terms of several key methods. Ludvigsson and co-authors were the only reviewers to exclude one-third of all relevant studies from consideration for inclusion in their review. They justified this choice by stating that they were only excluding studies with the highest risk of study-level bias, but this choice is a violation of best practices for systematic reviewers. ROB assessment is a highly subjective process, which makes this choice highly susceptible to investigator bias. In addition, it is well-known that the many tools available for assessing study-level bias are highly variable in terms of how they group the studies into high-and low-risk categories. Thus, even in the absence of any investigator manipulation of their results, authors that use different ROB tools on the same set of studies and then exclude some studies from inclusion based on the resultant ROB findings will end up including different subsets of the same studies, and consequently coming to different conclusions. Consequently, the best practice is to assess ROB using the tool selected by the investigators *a priori*, and then rather than excluding studies with a high ROB, assessing the impact of study-level differences in ROB on their findings.

Ludvigsson and colleagues were also the only review authors who did not include a summary of findings in the individual primary studies. Rather, they reported what outcomes were assessed by reviewers, and then reported only their conclusions about the body of evidence as a whole. This was a highly irregular choice; best practices are for systematic reviewers to include a summary of study-level findings on which they based their conclusions.

Ludvigsson and colleagues were also the only review authors who did not base their conclusions about key outcomes on all of their *included* studies. Instead, they based their conclusions on only a subset of the included studies. Taken together, these irregularities suggest that the conclusions drawn by Ludvigsson might best be considered unhelpful.

Nonetheless, Ludvigsson and colleagues found the largest number of primary studies (N=36) out of all SRs included in this report. As mentioned previously, the authors excluded 12 primary studies that they considered to have a high ROB and reported their findings based only on a subset.[53] Consequently, we checked the excluded references to ensure that any relevant studies excluded by Ludvigsson were included in our report, a practice that is supported by best practices. **Table I.7** lists N=11 excluded studies along with their disposition in this review; a twelfth excluded study was not provided in the authors' list.[54]

The 11 studies listed in **Table I.7** included 8 relevant studies that we included in evidence tables, 2 likely-relevant studies that we included in the bibliography only, and 1 irrelevant study that we excluded during title/abstract screening.

Table I.6. Summary of AMSTAR-2 ROB domains[43] for 7 SRs examining relevant/included outcomes associated with GD therapy in TGNB children/adolescents

AMSTAR-2 Item	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
1. Well-specified research question	Yes	Yes	Yes	Yes	No	Partial yes	Yes
2. Pre-specified protocol	***Yes***	***Yes***	***No***	***Yes***	***No***	***No***	***No***
3. Study design restrictions	No	No	No	No	No	No	Yes
4. Comprehensive search strategy	***No***	***Partial yes***	***No***	***Partial yes***	***Partial yes***	***Partial yes***	***No***
5. Duplicate study selection	Yes	Yes	Yes	Yes	No	No	No
6. Duplicate data extraction	Yes	Yes	No	Unclear	No	Unclear	No
7. Excluded studies list	***No***	***No***	***No***	***No***	***No***	***No***	***No***
8. Described included studies	Yes	Partial yes	No	No	Partial yes	No	Partial yes
9. Assessed study-level ROB	***Yes***	***Unclear***	***No***	***Yes***	***No***	***Yes***	***Yes***
10. Assessed primary study funding	No	No	No	No	No	No	No
11. Appropriate synthesis method	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***
12. Assessed ROB impact	Yes	Yes	No	No	No	No	No
13. Discussed ROB impact	***Yes***	***Yes***	***No***	***No***	***No***	***No***	***No***
14. Discussed heterogeneity	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15. Assessed small-study effects	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***	***N/A***
16. Review authors conflicts	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table I.7. Disposition of N=11 likely-relevant primary studies excluded from one recent SR that searched 13 different databases

Author (year)	Disposition in this review
Achille (2020)[55]	Cohort study found in bibliographic database searches and cited in other SRs; included in evidence tables for between-TGNB group and longitudinal, pre-post comparisons.
Allen (2019)[56]	Descriptive study not found in bibliographic database searches, but cited in other SRs; included in evidence tables for longitudinal, pre-post comparisons.
de Vries (2011)[57]	Descriptive study found in bibliographic database searches and cited in other SRs; included in evidence tables for longitudinal, pre-post and between-TGNB group comparisons.
Ghelani (2020)[58]	Descriptive study found in bibliographic database searches; included in evidence tables for longitudinal, pre-post comparisons.

Return to TOC

Table I.7. Disposition of N=11 likely-relevant primary studies excluded from one recent SR that searched 13 different databases

Author (year)	Disposition in this review
Hannema (2017)[59]	Descriptive study found in bibliographic database searches and cited in other SRs; included in evidence tables for longitudinal, pre-post comparisons.
Jensen (2019)[60]	Cohort study found in bibliographic database searches; included in evidence tables for between-TGNB group comparisons.
Karalexi (2020)[61]	SR not found in bibliographic database searches; included in bibliography only due to an inadequate search strategy (ie, a single database).
López de Lara (2020)[62]	Non-English descriptive study found in bibliographic database searches.
Millington (2020)[63]	Cohort study found in bibliographic database searches; excluded from consideration during title/abstract screening due to the absence of relevant treatments.
Neyman (2019)[64]	Descriptive study found in bibliographic database searches; included in evidence tables for longitudinal, pre-post comparisons.
Zucker (2011)[65]	Cross-sectional study not found in bibliographic database searches but cited in other SRs; included in evidence tables for between-TGNB-group comparisons.

Table abbreviations: SR, systematic review; TGNB, transgender, nonbinary, or gender-diverse

I.4.4 Bibliography of Included Publications

The bibliography of all included studies–that is, guidelines, systematic reviews, and experimental, observational, and descriptive studies that passed the search screening, the title and abstract screening, and the full-text screening–is in **Appendix I.F**.

I.4.5 Included Relevant Clinical Studies

I.4.5.1 Characteristics of relevant clinical studies

We found relevant, English-language clinical studies about populations from all over the world, including the US, Canada, the United Kingdom, Europe, Australia, Brazil, and the middle east (eg, Israel, Turkey). A summary of the characteristics of included studies is given below, by geographic region, and the basic characteristics of each study can be found in **Appendix I.G.** In all, there were N=134 primary clinical studies reporting findings in TGNB populations all over the world, including the experience of more than N=28,056 pediatric TGNB patients.

I.4.5.2 Relevant clinical studies from US populations

By far, the largest numbers of unique studies, clinical sites, and subjects, including the largest number of TGNB youths, were from the United States. **Table I.8** includes a summary of the numbers of clinical studies, sites, and subjects for these studies. These included a total of N = 118 studies examining

outcomes in at least 62 discrete samples of TGNB adolescents. The total number of subjects included was nearly 65,000, of which at least 18,561 were TGNB youths.

When considering geographic regions among the US studies, the largest subsets of studies (25) and unique patient samples (13) were conducted among the nationally-representative or multi-state subset of studies. This subset included observations from nearly 60,000 subjects, including at least 13,995 TGNB children and adolescents.

In the studies conducted among individual US states or territories, there were 93 unique studies conducted among 49 unique sites across 21 states and the District of Columbia (DC). Collectively, these studies included more than N = 5,081 subjects, including more than N = 4,367 pediatric TGNB children and adolescents. Notably, although New York and California both had largest number of individual practice sites in any state (ie, 6 and 7 sites, respectively), neither of them contributed as many individual publications as came from the 4 sites in the state of Massachusetts (15 studies). The key characteristics of the 118 US studies we found, grouped by geographic area and site, are found in **Appendix I.G**.

Table I.8. Summary of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US

State/Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
Multi-state/ National	**13 (listed below)**	**25**	**≥ 59,551**	**≥ 14,143**
	1. National internet survey			≥ 3235
	2. National internet survey			156
	3. US Youth Risk Behavior Survey			≥ 3494
	4. Children's Hospital Association's Pediatric Health and Information System			≥ 264
	5. Military Healthcare Data Repository			≥ 952
	6. Cystic Fibrosis care center survey			30
	7. Trans Youth Project in 23 states and Canada			317
	8. A dataset from PEDSnet (a pediatric learning health system network), comprising data from 7 PEDSnet participating institutions			4172
	[redacted]			≥ 391
	[redacted]			22

Return to TOC

Table I.8. Summary of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US

State/Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
	[redacted]			116
	12. STRONG cohort			958
	13. [redacted]			36
Unspecified/ Inconclusive locations	**2 (listed below)**	**2**	**54**	**54**
	[redacted]			1
	2. A regional, referral-based adolescent specialty clinic for dependent children of military service members			53
Arizona	**1 (listed below)**	**1**	**260**	**≥ 13**
[redacted]	[redacted]			≥ 13
California	**7 (listed below)**	**9**	**≥ 885**	**≥ 783**
[redacted]	[redacted]			≥ 66
	[redacted]			14
[redacted]	[redacted]			417
[redacted]	[redacted]			106
[redacted]	[redacted]			119
[redacted]	[redacted]			1
[redacted]	[redacted]			60
Colorado	**2 (listed below)**	**4**	**≥ 363**	**≥ 255**
[redacted]	[redacted]			≥ 35
	[redacted]			220
Connecticut	**2 (listed below)**	**2**	**31**	**31**
[redacted]	[redacted]			8
[redacted]	[redacted]			23
Delaware	**1 (listed below)**	**3**	**≥ 133**	**≥ 133**

Return to TOC

Table I.8. Summary of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US

State/Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
[redacted]	[redacted]			≥ 133
Georgia	**1 (listed below)**	**1**	**60**	**60**
[redacted]	[redacted]			60
Illinois	**1 (listed below)**	**5**	**≥ 105**	**≥ 105**
[redacted]	[redacted]			≥ 105
Indiana	**1 (listed below)**	**1**	**13**	**13**
[redacted]	[redacted]			13
Iowa	**1 (listed below)**	**1**	**1**	**1**
[redacted]	[redacted]			1
Massachusetts	**4 (listed below)**	**15**	**≥ 1153**	**≥ 1129**
[redacted]	[redacted]			≥ 1124
	[redacted]			3
	[redacted]			1
[redacted]	[redacted]			1
Michigan	**1 (listed below)**	**1**	**30**	**30**
[redacted]	[redacted]			30
Minnesota	**1 (listed below)**	**1**	**2**	**2**
[redacted]	[redacted]			2
Missouri	**2 (listed below)**	**4**	**≥ 114**	**≥ 114**
[redacted]	[redacted]			47
[redacted]	[redacted]			≥ 67
New York	**6 (listed below)**	**7**	**195**	**193**
[redacted]	[redacted]			2
[redacted]	[redacted]			1
	[redacted]			1
[redacted]	[redacted]			139

Return to TOC

Table I.8. Summary of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US

State/Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
[redacted]	[redacted]			1
[redacted]	[redacted]			50
Ohio	**2 (listed below)**	**10**	**735**	**690**
[redacted]	[redacted]			611
[redacted]	[redacted]			79
Oklahoma	**2 (listed below)**	**3**	**222**	**119**
[redacted]	[redacted]			1
[redacted]	[redacted]			118
Oregon	**1 (listed below)**	**1**	**80**	**80**
[redacted]	[redacted]			80
Pennsylvania	**2 (listed below)**	**6**	**151**	**71**
[redacted]	[redacted]			64
[redacted]	[redacted]			7
Rhode Island	**1 (listed below)**	**1**	**5**	**5**
[redacted]	[redacted]			5
Texas	**4 (listed below)**	**7**	**≥ 371**	**≥ 371**
[redacted]	[redacted]			192
[redacted]	[redacted]			≥ 148
	[redacted]			30
[redacted]	[redacted]			1
Washington	**1 (listed below)**	**5**	**104**	**104**
[redacted]	[redacted]			104
Washington DC	**1 (listed below)**	**3**	**68**	**68**
	[redacted]			68
Total	***62***	***118***	***≥ 64,656***	***≥ 18,561***

Return to TOC

I.4.5.3 Relevant clinical studies from Dutch populations

Studies from the Netherlands are those with the longest duration of follow-up, including at least 4 studies of more than 40 years duration,[66-69] one of which counted N = 1360 TGNB children/adolescents and more than N = 6,793 subjects overall, as summarized in **Table I.9** and **Appendix I.G**.[67]

Table I.9. Summary of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands

Site	Number of studies	All subjects	Pediatric TGNB subjects
[redacted]	**36**	**≥ 8831**	**≥ 1766**
[redacted]	*6*	*≤ 8831*	*≤ 1766*
[redacted]	*30*	*Nested in but unaffiliated with ACOG*	
[redacted]	**4**	**≥ 143**	**≥ 143**
[redacted]	**3**	**≥ 36**	**≥ 14**
Total	***43***	***≥ 9010***	***≥ 1923***

[redacted]

The treatment and study of TGNB patients in the Netherlands stretches back to 1972. Most such care and investigation were done at [redacted] In 2002, [redacted] established a gender identity clinic for children and adolescents, called [redacted] which incidentally centralized records of all TGNB patients seen at the [redacted] since 1972. Youth diagnosed with gender dysphoria in other mental health or medical settings are able to start or continue medical treatment at [redacted] treats TGNB youth from all over the world.

Studies on TGNB patients seen at [redacted] have been conducted on an ongoing basis. However, a study of the entire [redacted] TGNB patient population was not published until [redacted] This study comprised persons with some form of GD/TGNB diagnosis and at least 1 visit to [redacted] patients in this cohort are referred to as the [redacted] Cohort of Gender Dysphoria (ACOG). This study counted 6793 gender dysphoric/TGNB visiting patients, of which [redacted] A more recent study [redacted] updates the ACOG's number from [redacted] to [redacted]

In 2018, [redacted] merged with [redacted] and was renamed the [redacted] Of the two medical centers [redacted] the former [redacted] remains the locus of gender dysphoria referral, diagnosis, and

Return to TOC

treatment, and is now called [redacted] Most, but not all, [redacted] studies published after this period use "[redacted]

[redacted] University in [redacted] the Netherlands, has developed its own gender identity treatment and research program. The [redacted] was established in 1998, with the [redacted] Clinic serving as the intake point for young, gender dysphoric patients. A dedicated gender clinic was established [redacted] Research has been conducted on TGNB youths seen at this clinic, in collaboration [redacted] and separately.

I.4.5.4 Relevant clinical studies from Canada, Australia, the United Kingdom, and Europe

We present here in **Table I.10** the 59 relevant, English-language studies from Canada, Australia, New Zealand, the UK, and Europe. For more information, please see **Appendix I.G**.

Table I.10. Summary of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe

Country/ Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
Multinational	**2**	**2**	**3087**	**3087**
[redacted]				316
[redacted]				2771
Australia	**3**	**6**	**418**	**408**
[redacted]				10
[redacted]				39
[redacted]				355
Belgium	**1**	**1**	**27**	**27**
[redacted]				27
Canada	**11**	**16**	**1063**	**843**

Return to TOC

Table I.10. Summary of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe

Country/ Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
Multi-site	[redacted]			35
	[redacted]			174
Alberta	[redacted]			33
British Columbia	[redacted]			84
	[redacted]			21
	[redacted]			21
Ontario	[redacted]			1
	[redacted]			172
	[redacted]			300
	[redacted]			1
Quebec	[redacted]			1
Finland	**2**	**2**	**176**	**176**
[redacted]	[redacted]			124
[redacted]	[redacted]			52
France	**2**	**2**	**5**	**5**
[redacted]	[redacted]			1
[redacted]	[redacted]			4
Germany	**4**	**6**	**425**	**214**
[redacted]	[redacted]			82
[redacted]	[redacted]			22
[redacted]	[redacted]			75

Return to TOC

Table I.10. Summary of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe

Country/ Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
[redacted]	[redacted]			35
Italy	**2**	**2**	**127**	**127**
[redacted]	[redacted]			125
[redacted]	[redacted]			2
Poland	**1**	**1**	**166**	**166**
[redacted]	[redacted]			166
Slovenia	**1**	**1**	**1**	**1**
[redacted]	[redacted]			1
Spain	**5**	**7**	**378**	**125**
[redacted]	[redacted]			1
[redacted]	[redacted]			80
[redacted]	[redacted]			23
[redacted]	[redacted]			20
[redacted]	[redacted]			1
Switzerland	**2**	**2**	**56**	**56**
[redacted]	[redacted]			1
[redacted]	[redacted]			80
United Kingdom	**7**	**12**	**5715**	**2242**
Multisite	[redacted]			668
	[redacted]			360
	[redacted]			980
England	[redacted]			95

Return to TOC

Table I.10. Summary of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe

Country/ Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
[redacted]	[redacted]	[redacted]	[redacted]	12
[redacted]	[redacted]	[redacted]	[redacted]	36
Scotland	[redacted]	[redacted]	[redacted]	91
Total	***43***	***59***	***11,644***	***7476***

I.4.5.5 Relevant clinical studies published in other populations

Table I.11 describes the remaining published, English-language studies captured in our searches and meeting inclusion criteria. They are from Brazil, Israel, and Turkey. Their details are in **Appendix I.G**.

Table I.11. Summary of N = 9 relevant, English-language clinical studies conducted in other pediatric TGNB populations

Country/ Geographic Area	Number of sites, samples, or unique populations	Number of studies/ publications	All subjects	Pediatric TGNB subjects
Brazil	**3**	**3**	**659**	**44**
[redacted]	[redacted]	[redacted]	[redacted]	1
[redacted]	[redacted]	[redacted]	[redacted]	28
[redacted]	[redacted]	[redacted]	[redacted]	15
Israel	**1**	**3**	**106**	**106**
[redacted]	[redacted]	[redacted]	[redacted]	106
Turkey	**3**	**3**	**36**	**36**
[redacted]	[redacted]	[redacted]	[redacted]	4
[redacted]	[redacted]	[redacted]	[redacted]	30
[redacted]	[redacted]	[redacted]	[redacted]	2
Total	***7***	***9***	***801***	***96***

Return to TOC

I.4.5.6 Risk of bias analyses

Tables I.12 through I.**16** summarize the risk of bias for all studies with an observational comparison (ie, TGNB vs TGNB or TGNB vs cisgender peer) that underwent data extraction. The Newcastle-Ottawa Scales for cohort and case-control studies, and an adapted version for cross-sectional studies, were used as described in Section I.3.3.5.3. Cohort, cross-sectional, and case-control studies are listed separately due to differences in the risk of bias analysis. They are further separated by comparison type (ie, TGNB vs TGNB or TGNB vs cisgender peer). The ROB details are in **Appendix I.I.**

Table I.17 summarizes the risk of bias for studies with a descriptive, longitudinal, pre-post comparison. The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group was used (see description in Section I.3.3.6.3). We found some limitations with this tool for assessing the studies:

- Question 5 asked whether the sample size was large enough, but in these types of studies, a power calculation is not normally done. For this question, we answered "unclear" on many of the studies, however; this is only relevant if no difference was found. When a finding is statistically significant (ie, p-value <0.05), then we can rest assured that the study was adequately powered to detect a difference of the magnitude observed. However, when a finding is statistically nonsignificant, then the question of whether or not the study was adequately powered to detect a clinically-meaningful difference becomes relevant.
- Question 8 asked about assessor blinding. Due to the fact that the pre-post comparisons that we were extracting all had to have an intervention of interest, it was usually not feasible for the assessors to be blinded, as all of the participants had taken an intervention of interest. The ROB details are in **Appendix I.I.**

Table I.12. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs TGNB cohort studies

Cohort Study First Author (year)	Selection ☆☆☆☆ max	Comparability ☆☆ max	Outcome ☆☆☆ max	Total Stars
Achille (2020)[55]	☆☆☆☆	☆	☆☆	7/9
Allen (2019)[56]	☆☆	☆	☆☆	5/9
Arnoldussen (2022)[71]	☆☆☆☆	☆	☆☆	7/9
Becker-Hebly (2021)[72]	☆☆☆		☆☆	5/9
Boogers (2022)[66]	☆☆☆☆	☆	☆☆☆	8/9
Carmichael (2021)[73]	☆☆☆☆	☆	☆☆	7/9
Cantu (2020)[74]	☆☆☆		☆	4/9
Chen (2023)[75]	☆☆☆☆	☆☆	☆☆	8/9
Chiniara (2018)[76]	☆☆☆☆		☆☆	6/9
Costa (2015)[77]	☆☆☆☆		☆	5/9
de Vries (2010)[78]	☆☆☆		☆☆	5/9
de Vries (2011)[57]	☆☆☆☆	☆		5/9

Table I.12. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs TGNB cohort studies

Cohort Study First Author (year)	Selection ☆☆☆☆ max	Comparability ☆☆ max	Outcome ☆☆☆ max	Total Stars
de Vries (2014)[79]	☆☆☆☆	☆	☆	6/9
Eitel (2023)[80]	☆☆☆☆		☆☆	6/9
Grimstad (2021)[81]	☆☆☆☆		☆☆☆	7/9
Khatchadourian (2014)[82]	☆☆☆		☆☆☆	6/9
Klaver (2018)[83]	☆☆☆☆	☆	☆☆	7/9
Laurenzano (2021)[84]	☆☆☆☆		☆☆	6/9
Lee (2020)[85]	☆☆☆☆	☆☆	☆☆	8/9
Martinez-Martin (2023)[86]	☆☆☆☆	☆☆	☆☆	8/9
Marwa (2022)[87]	☆☆☆☆	☆	☆☆☆	8/9
Millington (2019)[88]	☆☆☆☆		☆☆☆	7/9
Millington (2021)[89]	☆☆☆☆	☆	☆☆	7/9
Millington (2022)[90]	☆☆☆☆	☆	☆☆☆	8/9
Mullins (2021)[91]	☆☆☆☆		☆☆☆	7/9
Navabi (2021)[92]	☆☆☆	☆	☆☆☆	7/9
Olson-Kennedy (2021)[93]	☆☆☆☆	☆☆	☆☆☆	9/9
Schagen (2018)	☆☆☆		☆☆	5/9
Schagen (2020)[94]	☆☆	☆☆	☆☆	6/9
Schulmeister (2022)[95]	☆☆☆	☆	☆☆☆	7/9
Tordoff (2022)[96]	☆☆☆☆	☆	☆	6/9
Valentine (2021)[97]	☆☆	☆	☆	4/9
Valentine (2022)[98]	☆☆☆	☆☆	☆☆	7/9
Vlot (2017)[99]	☆☆☆	☆	☆☆☆	7/9

Low risk of bias (higher quality): 7-9 stars; Fair risk of bias: 5-6 stars; High risk of bias: 1-4 stars.

***Selection Criteria composed of questions about**: Representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and outcome temporality requirements. **Comparability criteria composed of question about**: comparability of exposure/comparator cohorts-controlling for most important factors (age, sex) and additional factors. **Outcome criteria composed of questions about**: method of outcome assessment, duration of follow-up, attrition.*

Table I.13. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs TGNB cross-sectional studies

Cross-sectional Studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Outcome ☆ max	Total Stars
Arnoldussen (2020)[100]	☆☆☆	☆		4/6
Avila (2019)[101]	☆☆☆			3/6

Table I.13. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs TGNB cross-sectional studies

Cross-sectional Studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Outcome ☆ max	Total Stars
Bauer (2021)[102]	☆☆☆		☆	4/6
Becker (2018)[103]	☆☆	☆		3/6
Chen (2021)[104]	☆☆☆			3/6
Conn (2023)[105]	☆☆	☆☆		4/6
de Vries (2011)[106]	☆☆☆	☆	☆	5/6
de Vries (2016)[107]	☆☆	☆☆		4/6
de Graaf (2022)[108]	☆☆	☆☆		4/6
Durwood (2017)[109]	☆☆			2/6
Grannis (2021)[110]	☆☆☆	☆		4/6
Green (2022)[111]	☆☆	☆☆		4/6
Karakilic Ozturan (2023)[112]	☆☆☆	☆	☆	5/6
Mirabella (2022)[113]	☆☆☆	☆		4/6
Morningstar (2023)[114]	☆☆☆	☆	☆	5/6
Nahata (2017)[115]	☆☆☆			3/6
Olsavsky (2023)[116]	☆☆☆	☆☆		5/6
Segev-Becker (2020)[117]	☆☆☆	☆		4/6
Sorbara (2020)[118]	☆☆☆	☆☆		5/6
Staphorius (2015)[119]	☆☆	☆		3/6
Tollit (2023)[120]	☆☆☆		☆	4/6
Turban (2020)[121]	☆☆	☆☆		4/6
Turban (2022)[122]	☆☆	☆☆		4/6
van der Grift (2020)[123]	☆☆	☆☆		4/6
van der Miesen (2020)[124]	☆☆	☆		3/6
Vehmas (2022)[125]	☆☆☆		☆	4/6
Vrouenraets (2021)[126]	☆☆☆			3/6
Willemsen (2023)[127]	☆☆☆	☆	☆	5/6
Zucker (2010)[65]	☆☆☆	☆☆	☆	6/6

Low risk of bias (higher quality): 5-6 stars, Fair risk of bias: 3-4 stars, High risk of bias: 1-2 stars.

Selection Criteria composed of questions about: *Representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and outcome temporality requirements.* ***Comparability criteria composed of question about:*** *comparability of exposure/comparator cohorts-controlling for most important factors (age, sex) and additional factors.* ***Outcome criteria composed of questions about****: method of outcome assessment, duration of follow-up, attrition. The outcome temporality requirement, duration of follow-up, and attrition questions were excluded.*

Table I.14. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs TGNB case-control studies

Case-control studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Exposure ☆ max	Total Stars
Maru (2021)[128]	☆☆☆		☆	4/6

Low risk of bias (higher quality): 5-6 stars, Fair risk of bias: 3-4 stars, High risk of bias: 1-2 stars.

Selection Criteria composed of questions about: *Adequacy of the case definition, representativeness of the cases, selection of controls, and definition of controls.* ***Comparability criteria composed of question about:*** *Comparability of cohorts on the basis of design or analysis.* ***Outcome criteria composed of questions about:*** *Assessment of exposure, same method of ascertainment for cases and controls, and non-response rates.*

Table I.15. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs Peer cohort studies

Cohort Studies First Author (year)	Selection ☆☆☆☆ max	Comparability ☆☆ max	Outcome ☆☆☆ max	Total Stars
Beking (2020)[129]	☆☆☆☆	☆	☆☆☆	8/9
Burke (2016)[130]	☆☆☆☆	☆☆	☆☆☆	9/9
Costa (2015)[77]	☆☆☆		☆	4/9
López de Lara (2020)[62]	☆☆☆☆	☆	☆☆	7/9
Millington (2022)[90]	☆☆☆	☆	☆☆	6/9
Nokoff (2020)[131]	☆☆☆	☆	☆☆	6/9
Schulmeister (2022)[95]	☆☆	☆	☆☆☆	6/9
Valentine (2021)[97]	☆☆☆☆	☆	☆☆	7/9

Low risk of bias (higher quality): 7-9 stars, Fair risk of bias: 5-6 stars, High risk of bias 1-4 stars.

Selection Criteria composed of questions about: *Representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and outcome temporality requirements.* ***Comparability criteria composed of questions about:*** *comparability of exposure/comparator cohorts-controlling for most important factors (age, sex) and additional factors.* ***Outcome criteria composed of questions about:*** *method of outcome assessment, duration of follow-up, attrition.*

Table I.16. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs Peer cross-sectional studies

Cross-sectional Studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Outcome ☆ max	Total Stars
Alvares (2022)[132]	☆	☆		2/6
Burke (2015)[133]	☆☆☆	☆	☆	5/6
Durwood (2017)[109]		☆		1/6
Nokoff (2021)[134]	☆	☆☆	☆	4/6
Staphorius (2015)[119]	☆☆☆	☆	☆	5/6

Table I.16. Newcastle-Ottawa Quality Assessment Scale ROB data for TGNB vs Peer cross-sectional studies

Cross-sectional Studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Outcome ☆ max	Total Stars
Valentine (2022)[98]	☆☆☆	☆☆	☆	6/6
Van der Miesen (2020)[124]	☆			1/6

Low risk of bias (higher quality): 5-6 stars, Fair risk of bias: 3-4 stars, High risk of bias: 1-2 stars.

Selection Criteria composed of questions about: *Representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and outcome temporality requirements.* ***Comparability criteria composed of questions about:*** *comparability of exposure/comparator cohorts-controlling for most important factors (age, sex) and additional factors.* ***Outcome criteria composed of questions about:*** *method of outcome assessment, duration of follow-up, and attrition. Outcome temporality requirement, duration of follow-up, and attrition questions are excluded.*

Table I.17. NIH Quality Assessment Tool ROB data for Pre-Post studies

Pre-post study Author (Year)	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group												Quality (Total "Yes" answers)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	
Achille (2020)[55]	Y	Y	U	Y	U	N	Y	N	N	Y	U	N/A	5/11
Allen (2019)[56]	Y	Y	U	Y	U	N	Y	N	Y	Y	N	N/A	6/11
Arnoldussen (2022)[135]	Y	Y	N	Y	U	N	Y	N	Y	Y	N	N/A	6/11
Alvares (2022)[132]	Y	Y	Y	N	N	N	U	N	Y	U	N	N/A	4/11
Becker-Hebly (2021)[72]	Y	Y	U	Y	U	N	Y	N	U	Y	N	N/A	5/11
Beking (2020)[129]	Y	U	U	N	U	Y	Y	U	Y	Y	N	N/A	5/11
Boogers (2022)[66]	Y	Y	U	Y	U	Y	Y	N	N	Y	N	N/A	6/11
Cantu (2020)[74]	Y	Y	Y	N	N	N	Y	N	Y	Y	N	N/A	6/11
Carmichael (2021)[73]	Y	Y	Y	Y	U	Y	Y	N	U	Y	N	N/A	7/11
Chen (2023)[75]	Y	Y	Y	U	U	U	Y	N	Y	Y	N	N/A	6/11
Costa (2015)[77]	Y	Y	Y	Y	U	U	Y	N	Y	Y	N	N/A	7/11
De Vries (2010)[78]	Y	N	N	N	U	Y	Y	N	N	Y	N	N/A	4/11

2013.0Q1: Was the study question or objective clearly stated?, Q2: Were eligibility/selection criteria for the study population prespecified and clearly described?, Q3: Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest?, Q4: Were all eligible participants that met the prespecified entry criteria enrolled?, Q5: Was the sample size sufficiently large to provide confidence in the findings?, Q6: Was the test/service/intervention clearly described and delivered consistently across the study population?, Q7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?, Q8: Were the people assessing the outcomes blinded to the participants' exposures/interventions?, Q9: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?, Q10: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? Q11: Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?, Q12: If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Good: Met 8+ criteria, Fair: Met 5-7 criteria, Poor: met < 4 criteria.

Y = Yes, N = No, U = Unclear, N/A = not applicable, NIH = National Institutes of Health

Return to TOC

Table I.17. NIH Quality Assessment Tool ROB data for Pre-Post studies

Pre-post study Author (Year)	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group												Quality (Total "Yes" answers)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	
De Vries (2011)[57]	Y	Y	U	N	U	U	Y	N	Y	Y	N	N/A	5/11
De Vries (2014)[79]	Y	Y	U	N	U	U	Y	N	Y	Y	N	N/A	5/11
Ghelani (2020)[58]	Y	N	Y	Y	U	Y	Y	Y	Y	Y	N	N/A	8/11
Hannema (2017)[59]	Y	Y	U	U	N	Y	Y	N	N	Y	N	N/A	5/11
Jarin (2017)[136]	Y	Y	Y	Y	U	Y	Y	U	Y	Y	N	N/A	8/11
Joseph (2019)[137]	Y	N	U	Y	U	Y	Y	U	N	Y	N	N/A	5/11
Kaltiala (2020)[138]	Y	Y	Y	Y	U	N	Y	N	Y	Y	N	N/A	7/11
Klaver (2018)[83]	Y	Y	Y	Y	U	Y	Y	N	N	Y	Y	N/A	8/11
Klaver (2020)[139]	Y	Y	U	U	U	Y	Y	N	Y	Y	N	N/A	6/11
Klink (2015)[140]	Y	Y	Y	Y	U	Y	Y	N	N	Y	N	N/A	7/11
Kuper (2020)[141]	Y	Y	N	Y	U	Y	Y	N	N	Y	N	N/A	6/11
Lavender (2023)[142]	Y	Y	N	Y	Y	N	Y	N	N	Y	N	N/A	6/11

2013.0Q1: Was the study question or objective clearly stated?, Q2: Were eligibility/selection criteria for the study population prespecified and clearly described?, Q3: Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest?, Q4: Were all eligible participants that met the prespecified entry criteria enrolled?, Q5: Was the sample size sufficiently large to provide confidence in the findings?, Q6: Was the test/service/intervention clearly described and delivered consistently across the study population?, Q7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?, Q8: Were the people assessing the outcomes blinded to the participants' exposures/interventions?, Q9: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?, Q10: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? Q11: Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?, Q12: If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Good: Met 8+ criteria, Fair: Met 5-7 criteria, Poor: met < 4 criteria.

Y = Yes, N = No, U = Unclear, N/A = not applicable, NIH = National Institutes of Health

Table I.17. NIH Quality Assessment Tool ROB data for Pre-Post studies

Pre-post study Author (Year)	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group												Quality (Total "Yes" answers)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	
Laurenzano (2021)[84]	Y	Y	Y	U	U	Y	Y	N	Y	Y	U	N/A	7/11
López de Lara (2020)[62]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
Millington (2022)[90]	Y	N	U	U	U	Y	Y	N	N	Y	N	N/A	4/11
Millington (2021)[89]	Y	N	Y	Y	U	N	U	U	U	Y	N	N/A	4/11
Navabi (2021)[92]	Y	Y	Y	U	U	Y	Y	N	N	Y	N	N/A	6/11
Neyman (2019)[64]	Y	Y	U	Y	N	Y	Y	N	Y	N	Y	N/A	7/11
Olson-Kennedy (2021)[93]	Y	Y	Y	Y	U	U	Y	N	Y	Y	U	N/A	7/11
Olson-Kennedy (2018)[143]	Y	Y	Y	Y	N	U	Y	N	N	Y	U	N/A	6/11
Perl (2020)[144]	Y	Y	N	Y	U	Y	Y	N	Y	Y	N	N/A	7/11
Perl (2021)[145]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
Roy (2023)[146]	Y	N	N	U	N	Y	Y	N	Y	U	N	N/A	4/11
Schagen (2018)[147]	Y	Y	Y	Y	U	Y	Y	N	U	Y	N	N/A	7/11

2013.0Q1: Was the study question or objective clearly stated?, Q2: Were eligibility/selection criteria for the study population prespecified and clearly described?, Q3: Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest?, Q4: Were all eligible participants that met the prespecified entry criteria enrolled?, Q5: Was the sample size sufficiently large to provide confidence in the findings?, Q6: Was the test/service/intervention clearly described and delivered consistently across the study population?, Q7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?, Q8: Were the people assessing the outcomes blinded to the participants' exposures/interventions?, Q9: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?, Q10: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? Q11: Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?, Q12: If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Good: Met 8+ criteria, Fair: Met 5-7 criteria, Poor: met < 4 criteria.

Y = Yes, N = No, U = Unclear, N/A = not applicable, NIH = National Institutes of Health

Return to TOC

Table I.17. NIH Quality Assessment Tool ROB data for Pre-Post studies

Pre-post study Author (Year)	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group												Quality (Total "Yes" answers)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	
Schagen (2016)[148]	Y	Y	Y	Y	U	Y	Y	N	U	Y	N	N/A	7/11
Schagen (2020)[94]	Y	N	U	U	U	Y	Y	U	U	Y	N	N/A	4/11
Stoffers (2019)[149]	Y	Y	Y	Y	U	Y	Y	U	N	Y	N	N/A	7/11
Tack (2017)[150]	Y	Y	U	U	U	Y	Y	U	N	Y	N	N/A	5/11
Tordoff (2022)[96]	Y	Y	Y	N	U	Y	Y	N	N	Y	Y	N/A	7/11
Valentine (2021)[97]	Y	Y	N	N	U	Y	Y	U	N	Y	N	N/A	5/11
Van der Loos (2021)[69]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
Vlot (2017)[99]	Y	Y	U	N	U	Y	Y	U	N	Y	N	N/A	5/11
Willemsen (2023)[127]	Y	Y	Y	Y	U	U	N	N	Y	N	N	N/A	5/11

2013.0Q1: Was the study question or objective clearly stated?, Q2: Were eligibility/selection criteria for the study population prespecified and clearly described?, Q3: Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest?, Q4: Were all eligible participants that met the prespecified entry criteria enrolled?, Q5: Was the sample size sufficiently large to provide confidence in the findings?, Q6: Was the test/service/intervention clearly described and delivered consistently across the study population?, Q7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?, Q8: Were the people assessing the outcomes blinded to the participants' exposures/interventions?, Q9: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?, Q10: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? Q11: Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?, Q12: If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Good: Met 8+ criteria, Fair: Met 5-7 criteria, Poor: met < 4 criteria.

Y = Yes, N = No, U = Unclear, N/A = not applicable, NIH = National Institutes of Health

Return to TOC

I.4.6 Experimental Studies

The term "experimental study" can refer to several different types of study designs. In addition to the archetypal design that we are all familiar with (ie, the prospective, randomized or non-randomized, blinded or unblinded, crossover- or parallel-group, interventional studies with 2 or more comparison groups), the category can also include either single-arm clinical trials or experimental case studies.[151]

According to Gehlbach's taxonomy, which we used to facilitate study eligibility assessment and to organize our team's data extraction tasks, experimental trials must include at least 2 treatment groups, and treatments must be assigned by the study investigators.[32] This definition is most consistent with the archetypal experimental study design. However, this taxonomy groups single-arm clinical trials and experimental case studies with descriptive studies, and treats them as non-inferential studies.[32] However, we must be clear that *longitudinal, pre-post descriptive studies, which include single-arm clinical trials, are considered to be inferential in nature by many experts* other than Gehlbach, and *may also be considered experimental studies*, especially when the interventions of interest are still deemed to be experimental. Such single-arm, experimental trials serve as the basis of US FDA market approval for many drugs that lack effective alternative interventions, including pediatric cancer treatments,[152] and even a recently-approved, novel gene therapy for the treatment of spinal muscular atrophy (SMA). The latter drug was FDA-approved using data from only 2 single-arm clinical trials including the experience of N = 36 patients in total.[153] Certainly, the amount of evidence available for treating pediatric GD patients with GAHT far exceeds the quantity that supported the use of SMA gene therapy upon FDA approval.

The question of whether hormonal treatments for pediatric gender dysphoria are still considered to be *experimental* is the subject of some debate. Most experts, including WPATH and USPATH, argue that the treatments are no longer experimental; rather they say, the treatments are well-established with decades of clinical research supporting their use, and they are safe and effective options for pediatric GD patients.[39,154] Nonetheless, others argue that the treatments are still experimental,[155-158] a designation that they may posit invalidates the treatments' use in children. It should be noted that the *experimental status of any drug does not preclude its use in children*, particularly for conditions like GD, which have no other effective interventions. In fact, *if pediatric patients were routinely excluded from receiving experimental treatments, we would never have non-experimental treatments to offer them in any disease state*.

In one recent SR by Ludvigsson and colleagues,[49] based on what may be an arbitrary subset of the evidence, authors concluded that the treatments should still be considered experimental.[49] If so, we may regard any prospective study in which patients were treated and data were collected according to a protocol as an experimental study for the purposes of this report. Thus, in the subsections that follow, we provide a list of relevant experimental studies as those that meet one or more of the criteria listed in **Table I.18**. As these definitions are hierarchical, with the first definitions being most restrictive and the last being least so, studies that meet any of the definitions for experimental studies will be listed in the first appropriate subsection.

Table I.18. Four competing criteria for classifying experimental studies

No	Definition
1.	Gehlbach's taxonomy defines experimental studies as any study in which 2 or more treatment groups are compared, and in which study investigators assigned patients to receive the treatments of interest.
2.	Authors' statements can be used to identify experimental studies as any in which investigators describe their studies using terms such as "experimental," "pseudo-experimental," "quasi-experimental," or "clinical trial."
3.	Trial registries, such as clinicaltrials.gov,[159] can be used to identify experimental studies or clinical trials.
4.	Experimental treatments: This definition classifies single- or multiple-arm studies as experimental if they are conducted prospectively, and if patients were treated and data were collected according to an a priori protocol (eg, most of the Dutch studies).

Findings from most experimental studies meeting each of these 4 criteria are summarized in evidence tables that are grouped according to high-priority comparison types, listed in **Table I.19**, rather than according to study design. Thus, experimental studies (along with observational and descriptive studies) may have findings reported in more than one place.

Table I.19. High-priority comparison types used for extracting findings from experimental studies

Group comparison types	Study designs
Between-TGNB group comparisons	Experimental studies that compare 2 or more groups of TGNB patients (eg, treated versus untreated TGNB patients) are found in these evidence tables (**Appendix I.J**).
TGNB/cisgender peer group comparisons	Experimental studies that compare 1 or more group of TGNB patients to 1 or more groups of cisgender patients (eg, brain imaging studies of TGNB patients, cisgender males, and cisgender females who were exposed to pheromones) are included in these evidence tables (**Appendix I.K**).
Longitudinal, pre-post, within-group comparisons	Single- or multiple-arm experimental studies that examine within-group changes over time (eg, an examination of changes over time in a single group of pediatric TGNB patients who were given GnRH analogs for puberty suppression) are included in these evidence tables (**Appendix I.L**).

Experimental case studies, and other descriptive studies that lacked longitudinal, within-group comparisons, did not undergo data extraction due to time and scope limitations. These studies that lacked high-priority comparisons are listed in the bibliography only.

I.4.6.1 Experimental studies as defined by Gehlbach's taxonomy

Searches yielded only 1 study that met our eligibility criteria for population, intervention, and comparator, and that was regarded as an experimental study according to Gehlbach's taxonomy (which uses the most restrictive criteria; **Table I.20**).[129] The study is summarized in **Appendix I.K**, **Table I.K.3**, and **Appendix I.L**, **Table I.L.3**.

Table I.20. Comparison types reported in experimental studies as defined by Gehlbach's taxonomy

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Beking (2020)[129]	Authors used a quasi-experimental design in which Dutch, transgender boys and cisgender girls and boys underwent laboratory assays (salivary testosterone levels), face-matching tests, and fMRI imaging in sessions conducted before and after the transgender boys had received exogenous testosterone.		X	X

Table abbreviations: TGNB, transgender, nonbinary, gender-diverse; TGNB/TGNB, between-TGNB comparisons; TGNB/Peer, TGNB versus cisgender peer group comparisons

I.4.6.2 Experimental studies as defined by authors

Searches yielded only 2 studies that met our eligibility criteria for population, intervention, and comparator and that were described by study authors as either experimental or as clinical trials (**Table I.21**).[119,132] Alvares is listed in **Appendix I.K**, **Table I.K.3**, and **Appendix I.L**, **Table I.L.3**, and Staphorsius is listed in **Appendix I.J**, **Table I.J.2**, and **Appendix I.K**, **Table I.K.2**.

Table I.21. Comparison types reported in experimental studies as defined by study authors

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Alvares (2022)[132]	Authors described having used an experimental protocol to conduct cardiopulmonary assessment in transgender women who started treatments as adolescents, and cisgender men and women who did not. They also underwent laboratory assays (hemoglobin, hematocrit, and levels of FSH, LH, estradiol, and testosterone), physical activity assessments, anthropometric and body composition measurement, and muscle strength tests.		X	X
Staphorsius (2015)[119]	Authors described having used an experimental design to examine executive functioning in adolescents with GD who were given cognitive tasks to perform as they underwent fMRI imaging.	X	X	

Table abbreviations: TGNB, transgender, nonbinary, gender-diverse; TGNB/TGNB, between-TGNB comparisons; TGNB/Peer, TGNB versus cisgender peer group comparisons

Return to TOC

I.4.6.3 Experimental studies according to trial registries

I.4.6.3.1 US Clinical Trials Register

A search of ClinicalTrials.gov conducted on September 6, 2023 yielded 7 studies conducted in TGNB patients that were described as clinical trials. Abstracts of each were examined, and all 7 were excluded from this report as irrelevant because they included only adult subjects (wrong population). Thus, no experimental studies were found in the US clinical trial registry.

I.4.6.3.2 International Standard Randomized Controlled Trial Register

Four studies from the same geographic location (Netherlands, Amsterdam, Vrije) each reported that they were registered as clinical trials in the International Standard Randomized Controlled Trial Register (ISRCT) and were assigned an ISRCT number (ISRCTN), which they shared. These are listed in **Table I.22**.

Table I.22. Comparison types reported in experimental studies as defined by ISRCT registration

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Schagen (2016)[148]	Authors examined changes in growth, body composition, and endogenous hormone levels in N = 116 TGNB adolescents who were treated with GnRH analogs for 1 year (ISRCTN 81574253).			X
Hannema (2017)[59]	Authors examined changes in endogenous hormone levels, anthropometric measures, bone, blood pressure measures among N = 28 transgender girls treated with estradiol (ISRCTN 81574253).			X
Schagen (2018)[147]	Authors examined changes in endogenous hormones during puberty suppression and CSHT in adolescents with GD (ISRCTN 81574253).	X		X
Schagen (2020)[94]	Authors examined bone changes over time in N = 121 TGNB patients who started treatment at different pubertal stages (ISRCTN 81574253).[160]	X		X

Table abbreviations: ISRCT, International Standard Randomized Controlled Trial Register (ISRCT); TGNB, transgender, nonbinary, gender-diverse; TGNB/TGNB, between-TGNB comparisons; TGNB/Peer, TGNB versus cisgender peer group comparisons

I.4.6.4 Prospective studies of treatments for pediatric gender dysphoria

In addition to the 7 studies listed above, searches yielded 29 additional prospective studies that may be considered to be experimental studies under the premise that the treatments are still considered experimental in children. These are listed in **Table I.23**.

Table I.23. Comparison types reported in experimental studies as defined by prospective study design, assuming that treatments are regarded as "experimental"

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Achille (2020)[55]	Authors examined mental health outcomes in N = 50 TGNB adolescents.	X		X
Arnoldussen (2022)[71]	Authors examined educational achievement after puberty suppression with GnRH analogs and GAHT in N = 72 TGNB adolescents.	X		
Bauer (2021)[102]	Authors examined characteristics and mental health needs between N = 174 TGNB patients.	X		
Becker (2018)[103]	Authors examined the effect of hormones and GnRH analogs on body image outcomes in TNGB adolescents (N = 82) and adults (N = 112).	X		
Becker-Hebly (2021)[72]	Authors examined the effect of unspecified GnRH analogs and CSHT on psychosocial functioning in treated versus untreated TGNB youth.	X		X
Burke (2015)[133]	Authors examined effects of testosterone on fMRI outcomes in N = 36 TGNB youth (17 AFAB and 19 AMAB children) vs N = 39 age- and sex-matched cisgender controls.		X	
Burke (2016)[130]	Authors examined the effects of testosterone on fMRI outcomes in TGNB adolescents vs age- and sex-matched controls.		X	
Carmichael (2021)[73]	Authors examined short-term (ie, 1-3 years) bone and psychosocial outcomes in N = 44 TGNB youths (including 25 AMAB and 19 AFAB children) ages 12-15 years who received GnRH analog monotherapy	X		X
Chen (2021)[104]	Authors examined mental health outcomes in N = 95 TGNB youth initiating treatment with GnRH analogs or GAH.	X		
Chen (2023)[75]	Authors examined mental health and psychosocial outcomes in TGNB adolescents after 2 years of CSHT and mental health outcomes between early- and late-treated adolescents.	X		X

Table abbreviations: TGNB, transgender, nonbinary, or gender-diverse; TGNB/TGNB, comparisons between 2 or more TGNB patient groups; TGNB/Peer, comparisons between 1 or more TGNB group and 1 or more cisgender peer groups; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy, including puberty suppression and/or cross-sex hormone therapy; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imaging; AFAB, assigned female at birth; AMAB, assigned male at birth; WPATH, World Professional Association for Transgender Health

Return to TOC

Table I.23. Comparison types reported in experimental studies as defined by prospective study design, assuming that treatments are regarded as "experimental"

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Costa (2015)[77]	Authors examined mental health changes in N = 201 TGNB adolescents, including a comparison between transgender males vs transgender females treated with unspecified GnRH analogs according to the WPATH guideline. They also looked at changes over time within groups.	X	X	X
de Vries (2010)[78] Thesis (C7)	Authors examined treatment satisfaction, social functioning, sexual functioning, and quality of life in N = 27 transgender males who initiated treatment as adolescents.	X		X
de Vries (2011)[57]	Authors examined mental health outcomes in N = 70 TGNB patients treated with GnRH analogs	X		X
de Vries (2014)[79]	Authors examined psychosocial functioning after GnRH analogs, CSHT, and surgery among TGNB adolescents.	X		X
Durwood (2017)[109]	Authors examined mental health and self-worth outcomes between TGNB treatment groups and between TGNB adolescents versus controls (ie, siblings and community controls).	X	X	
Ghelani (2020)[58]	Authors examined body composition changes in N = 36 TGNB adolescents receiving triptorelin for puberty suppression.			X
Grannis (2021)[110]	Authors examined depression and anxiety severity in N = 42 treated vs untreated transgender boys.	X		
Kuper (2020)[161]	Authors examined changes in body dissatisfaction and mental health (anxiety/depression) among N = 148 TGNB adolescents receiving puberty suppression and/or CSHT.			X
Lee (2020)[85]	Authors examined changes in bone between N = 63 TGNB patients treated with GnRH analogs.	X		

Table abbreviations: TGNB, transgender, nonbinary, or gender-diverse; TGNB/TGNB, comparisons between 2 or more TGNB patient groups; TGNB/Peer, comparisons between 1 or more TGNB group and 1 or more cisgender peer groups; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy, including puberty suppression and/or cross-sex hormone therapy; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imaging; AFAB, assigned female at birth; AMAB, assigned male at birth; WPATH, World Professional Association for Transgender Health

Table I.23. Comparison types reported in experimental studies as defined by prospective study design, assuming that treatments are regarded as "experimental"

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
Lopez de Lara (2020)[62]	Authors examined psychosocial outcomes in 23 TGNB patients who attend a pediatric endocrinology clinic before and after one-year of cross hormonal therapy (CHT).		X	X
Millington (2021)[89]	Authors examined growth, body composition, and cholesterol changes in N = 269 TGNB adolescents (83 AMAB and 186 AFAB children) receiving CSHT.	X		X
Millington (2022)[90]	Authors examined changes in kidney function measures in N = 286 TGNB adolescents (194 AFAB and 92 AMAB children) receiving GAHT.	X	X	X
Morningstar (2013)[114]	Authors examined neural responses to peer and caregiver voices between N = 44 CSHT-treated or untreated transgender boys.	X		
Nokoff (2020)[131]	Authors examined insulin and DEXA outcomes between N = 35 TGNB patients versus N = 108 cisgender peers.	X		
Nokoff (2021)[134]	Authors examined insulin sensitivity and glycemic control outcomes between N = 17 TGNB youths versus N = 31 cisgender peers.	X		
Olsen-Kennedy (2019)[162]	In this protocol, authors describe that they plan to examine growth and bone density in N = 90 TGNB adolescents starting puberty suppression, and N = 301 patients starting CSHT. No high-priority results were included, so it was included only in the bibliography.			
Roy (2023)[146]	Authors examined red blood cells in N = 15 transgender boys receiving testosterone therapy			X
Schulmeister (2022)[95]	Authors examined height velocity (ie, growth) in TGNB patients who initiated GnRH analog puberty suppression at the various Tanner stages.	X	X	
Tordoff (2022)[96]	Authors examined mental health outcomes (depression/anxiety) in N = 104 TGNB	X		X

Table abbreviations: TGNB, transgender, nonbinary, or gender-diverse; TGNB/TGNB, comparisons between 2 or more TGNB patient groups; TGNB/Peer, comparisons between 1 or more TGNB group and 1 or more cisgender peer groups; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy, including puberty suppression and/or cross-sex hormone therapy; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imaging; AFAB, assigned female at birth; AMAB, assigned male at birth; WPATH, World Professional Association for Transgender Health

Table I.23. Comparison types reported in experimental studies as defined by prospective study design, assuming that treatments are regarded as "experimental"

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/Peer Appendix I.K	Pre-post Appendix I.L
	adolescents and young adults receiving puberty suppression, CSHT, or both.			
Vrouenraets (2021)[126]	Authors examined medical competence and related outcomes in N = 74 TGNB adolescents	X		

Table abbreviations: TGNB, transgender, nonbinary, or gender-diverse; TGNB/TGNB, comparisons between 2 or more TGNB patient groups; TGNB/Peer, comparisons between 1 or more TGNB group and 1 or more cisgender peer groups; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy, including puberty suppression and/or cross-sex hormone therapy; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imaging; AFAB, assigned female at birth; AMAB, assigned male at birth; WPATH, World Professional Association for Transgender Health

I.4.7 Observational Studies

A total of 83 studies that were primarily observational (though some had descriptive components) met eligibility criteria, including 1 that was a repeat publication of another included study, 3 studies without high-priority group comparisons of interest, and 22 studies that lacked any high-priority outcomes of interest: these were all relegated to the bibliography only. Thus, 57 observational studies had at least one high-priority outcome of interest, made high-priority group comparisons, and underwent data extraction. These were divided into categories according to the types of comparisons made, listed below (studies could have comparisons in both categories; **Table I.24**):

A. Between-TGNB-group comparisons: 50 studies
B. TGNB vs cisgender peer comparisons: 12 studies

Outcomes of interest included the following:

- Mental health (eg, depression, anxiety, suicidality)
- Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
- Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
- Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
- Bone health (eg, bone density, bone turnover measures)
- Cardiovascular risk factors (eg, thrombotic changes, insulin sensitivity, blood pressure, obesity)
- Cancer

I.4.7.1 TGNB patients compared to other TGNB subgroups

Overall, we identified 50 observational studies with comparisons between TGNB youth and other TGNB subgroups with at least one outcome of interest (**Table I.24**; see **Appendix I.J**). Of these, 9 studies also had longitudinal, pre-post descriptive comparisons of interest. Their detailed findings are in **Appendix I.L**.

None of the reviewed TGNB vs TGNB observational studies had cancer-related outcomes, but the remaining outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 25
- Psychosocial functioning: 22
- Body changes: 15
- Body image: 9
- Bone health: 7
- Cardiovascular risk factors: 10

Table I.24. Comparison types reported in observational studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Achille (2020)[55]	Authors examined mental health outcomes in N = 50 TGNB adolescents.	X		X
Alvares (2022)[132]	Authors compared cardiopulmonary capacity and muscle strength (ie, determinants of physical performance) in Brazilian transgender women versus cisgender men and women, none of whom were athletes.		X	X
Arnoldussen (2020)[100]	Authors examined the association between birth-assigned sex and psychosocial functioning in N = 1072 TGNB adolescents, including 404 AFAB and 668 AMAB children.	X		
Arnoldussen (2022)[71]	Authors examined educational achievement after puberty suppression with GnRH analogs and GAHT in N = 72 TGNB adolescents.	X		
Avila (2019)[101]	Authors compared EDE-Q (eating disorder scale) scores between treated and untreated TGNB subjects	X		
Bauer (2021)[102]	Authors examined characteristics and mental health needs between N = 174 TGNB patients.	X		
Becker (2018)[103]	Authors examined the effect of hormones and GnRH analogs on body image outcomes in TNGB adolescents (N = 82) and adults (N = 112).	X		
Becker-Hebly (2021)[72]	Authors examined the effect of unspecified GnRH analogs and CSHT on psychosocial functioning in treated versus untreated TGNB youth.	X		X
Boogers (2022)[66]	Authors compared dosages, growth, bone age, IGF-1 levels, and more outcomes between N = 161 trans females with different hormone treatments and dosages.	X		X
Burke (2015)[133]	Authors examined effects of testosterone on fMRI outcomes in N = 36 TGNB youth (17 AFAB and 19 AMAB children) vs N = 39 age- and sex-matched cisgender controls.		X	
Burke (2016)[130]	Authors examined the effects of testosterone on fMRI outcomes in TGNB adolescents vs age- and sex-matched controls.		X	
Chen (2021)[104]	Authors examined mental health outcomes in N = 95 TGNB youth initiating treatment with GnRH analogs or GAH.	X		
Chiniara (2018)[76]	Authors examined baseline mental health in N = 79 TGNB AFAB vs AMAB children	X		
Conn (2023)[105]	Authors examined risk factors for mental health outcomes in N = 315 TGNB adolescents from the Trans Youth Care Study.	X		

Table I.24. Comparison types reported in observational studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Costa (2015)[77]	Authors examined mental health changes in N = 201 TGNB adolescents, including a comparison between transgender males vs transgender females treated with unspecified GnRH analogs according to the WPATH guideline. They also looked at changes over time within groups.	X	X	X
De Graaf (2022)[108]	Authors examined mental health characteristics of TGNB patients who were referred (ie, for GnRH analog treatment) versus non-referred across 3 clinics	X		
de Vries (2014)[79]	Authors examined psychosocial functioning after GnRH analogs, CSHT, and surgery among TGNB adolescents.	X		X
de Vries (2016)[107]	Authors examined mental health characteristics of TGNB patients who were referred (ie, for GnRH analog treatment) versus non-referred across 2 clinics	X		
De Vries (2011)[106]	A cross-sectional study examining mental health diagnoses among AFAB vs AMAB TGNB adolescents, and between treated vs untreated TGNB patients	X		
Durwood (2017)[109]	Authors examined mental health and self-worth outcomes between TGNB treatment groups and between TGNB adolescents versus controls (ie, siblings and community controls).	X	X	
Eitel (2023)[80]	Authors compared hormone levels and puberty suppression outcomes between N = 48 transgender youths (16 AFAB and 32 AMAB children) receiving Lupron vs Eligard	X		
Grannis (2021)[110]	Authors examined depression and anxiety severity in N = 42 treated vs untreated transgender boys.	X		
Green (2022)[111]	Authors compared demographic and mental health characteristics between N = 5753 adolescents and young adults who self-reported receiving GAHT versus not, including N = 3235 adolescents ages 13-17 years	X		
Grimstad (2021)[81]	Authors compared menstrual suppression outcomes in N = 232 transgender boys in different GnRH analogs and hormone treatment groups. Also makes case-control-type comparisons examining risk factors for breakthrough bleeding in transgender males.	X		
Karakilic Ozturan (2023)[112]	Authors examined body changes and endogenous hormone levels in TGNB adolescents	X		

Return to TOC

Table I.24. Comparison types reported in observational studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Khatchadourian (2014)[82]	Authors compared demographic characteristics, adverse effects, GnRH analog/CSHT initiation, Tanner stages, and psychiatric comorbidities between N = 84 MTF and FTM transgender youth.	X		
Lee (2020)[85]	Authors examined changes in bone between N = 63 TGNB patients treated with GnRH analogs.	X		
Martinez-Martin (2023)[86]	Authors compared blood pressure outcomes in N = 302 young transgender patients receiving different hormone therapies, including treatment groups with mean ages < 18 years.	X		
Maru (2021)[128]	Authors examined risk factors for type I DM, including age at presentation, and hormone therapy.	X		
Marwa (2022)[87]	Authors examined differences in bone density in N = 119 TGNB patients based on natal sex, including N = 46 AMAB and N = 73 AFAB children	X		
Millington (2019)[88]	Authors examined the risk of hyperkalemia associated with spironolactone in N = 85 transfeminine or nonbinary adolescents	X		
Mirabella (2022)[113]	Authors examined gender identity changes between AMAB vs AFAB TGNB subjects, and between trans binary vs nonbinary TGNB subjects.	X		
Morningstar (2023)[114]	Authors examined neural responses to peer and caregiver voices between N = 44 CSHT-treated or untreated transgender boys.	X		
Mullins (2021)[91]	Authors examined thrombosis risk factors and outcomes in N = 611 TGNB adolescents initiating GAHT. [No thrombosis events were observed and too few observations had any of the relevant outcomes for inferential comparisons.]	X		
Nahata (2017)[115]	Authors examined mental health and psychosocial outcomes between transgender males and transgender females	X		
Navabi (2021)[92]	Authors examined baseline and follow-up changes in bone mass, body composition, vitamin D, and puberty suppression outcomes between N = 172 transgender male vs female youths who received GnRH analogs. Also looked at changes from baseline within each group.	X		X

Return to TOC

Table I.24. Comparison types reported in observational studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Nokoff (2020)[131]	Authors examined insulin and DEXA outcomes between N = 35 TGNB patients versus N = 108 cisgender peers.		X	
Nokoff (2021)[134]	Authors examined insulin sensitivity and glycemic control outcomes between N = 17 TGNB youths versus N = 31 cisgender peers.		X	
Olsavsky (2023)[116]	Authors examined associations between treatments and mental health outcomes among N = 75 TGNB adolescents	X		
Olson-Kennedy (2021)[93]	Authors compared puberty suppression outcomes in N = 66 TGNB subjects receiving two forms of histrelin (Vantas vs SupprelinLA). Also examined within-group outcomes.	X		X
Schagen (2020)[94]	Authors compared bone changes over time for TGNB subjects at different pubertal stages. Also examined changes over time in N = 121 TGNB patients. The study was registered with the International Standard Randomized Controlled Trial Number register (ISRCTN 81574253).	X		X
Schulmeister (2022)[95]	Authors examined height velocity (ie, growth) in TGNB patients who initiated GnRH analog puberty suppression at the various Tanner stages.	X	X	
Segev-Becker (2020)[117]	Authors examined mental health and behavioral outcomes in N = 106 transgender boys vs girls	X		
Sorbara (2020)[118]	Authors examined mental health problems in older- versus younger-presenting TGNB adolescents	X		
Staphorius (2015)[119]	Authors analyzed of the impact of GAHT on executive function in N = 40 TGNB adolescents	X	X	
Tollit (2023)[120]	Authors examined characteristics of AFAB vs AMAB TGNB adolescents, including mental health and psychosocial parameters	X		
Tordoff (2022)[96]	Authors examined mental health outcomes (depression/anxiety) in N = 104 TGNB adolescents and young adults receiving puberty suppression, CSHT, or both.	X		X
Turban (2020)[121]	Authors conducted a secondary analysis of the 2015 US Transgender Survey, (N = 27,715 TGNB respondents), restricted to those who wanted puberty suppression hormones (n = 3494). They examined associations between adolescent and adult mental health outcomes, including measures of suicidality.	X		

Return to TOC

Table I.24. Comparison types reported in observational studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Turban (2022)[122]	Authors conducted a secondary analysis of the 2015 US Transgender Survey (N = 27,715 TGNB respondents), restricted to those who desired GAHT (n = 21.598). They examined associations between access to GAHT during early adolescence (age 14–15), late adolescence (age 16–17), or adulthood (age > 18) and adult mental health outcomes, with participants who desired but never accessed GAHT as the reference group.	X		
Valentine (2021)[97]	Authors examined cardiometabolic parameters in N = 44 transgender adolescents receiving testosterone versus N = 82 cisgender females. The study also compares outcomes between transgender treatment groups.		X	X
Valentine (2022)[98]	Authors compared cardiometabolic parameters between N = 4172 TGNB adolescents, (N = 2766 AFAB and N = 1407 AMAB) versus N = 16648 controls (N = 11130 AFAB and N = 5518 AMAB), and between TGNB adolescents receiving different treatments	X	X	
Van de Grift (2020)[123]	Authors compared surgical outcomes between 3 TGNB groups: (a) youths who received early puberty suppression, (b) youths who received late puberty suppression, and (c) TGNB adults who did not receive puberty suppression.	X		
Van der Loos (2021)[69]	Authors compared bone outcomes in N = 322 TGNB adolescents compared to cisgender controls and a pre-post descriptive study reporting on bone changes over time			X
Van der Miesen (2020)[124]	Authors compared mental health outcomes in treated versus untreated TGNB adolescents; also compares mental health outcomes between TGNB adolescents and cisgender peers	X	X	
Vehmas (2022)[125]	Authors examined characteristics of N = 124 pediatric TGNB patients presenting for treatment.	X		
Vrouenraets (2021)[126]	Authors examined medical competence and related outcomes in N = 74 TGNB adolescents	X		
Zucker (2010)[65]	Authors examined correlates of puberty suppressive treatment	X		

I.4.7.2 TGNB compared to cisgender peers

Overall, we identified 12 observational studies with comparisons between TGNB youth and cisgender peer groups with at least one outcome of interest (see **Table I.24**; see **Appendix I.K**) Of these, 3 also had a longitudinal, pre-post descriptive component. Their detailed findings are in **Appendix I.L**.

None of the reviewed TGNB vs peer observational studies had cancer-related, body image, or bone health outcomes, but the remaining outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 2
- Body changes: 6
- Psychosocial functioning: 4
- Cardiovascular risk factors: 5

I.4.7.3 Summary of observational studies

Table I.24 contains all observational studies that underwent data extraction, including TGNB vs TGNB and TGNB versus cisgender peer comparisons, and where data can be found for each study. Some observational studies also have pre-post comparisons and have data included in **Appendix I.L**.

I.4.7.4 Outcomes addressed with comparisons of TGNB adolescents to other TGNB subgroups

See **Appendix I.J** for evidence tables regarding study details and findings, organized by outcome of interest. Note that some studies evaluated more than one outcome of interest and are represented in more than one table. Some studies also have TGNB vs cisgender peer data or pre-post comparison within the study, and may be included in Appendixes I.K and I.L. ROB assessment is provided in Section I.4.5.6.

Some limited take-aways based on the findings from included observational studies with TGNB patients compared to other TGNB subgroups, organized by outcome of interest:

- **Mental health:**
  - Generally, rates of depression and suicidal thoughts/self-harm tended to be lower among hormonally treated transgender youth compared to untreated transgender individuals.
  - Starting hormone therapy earlier tended to have a neutral to positive effect on mental health outcomes.
  - Transgender youth exhibit a relatively high prevalence of mental health comorbidities, including anxiety, depression, and/or suicidality.
  - Transmasculine adolescents tend to report more severe symptoms of depression and anxiety compared to transfeminine adolescents.
- **Psychosocial Functioning:**
  - Generally, psychosocial functioning tended to be comparable between natal males and natal females

Return to TOC

- In general, when compared to untreated TGNB adolescents, TGNB youth who used hormone therapy tended to see a decrease in problem scores and an increase in functioning and quality of life scores.

- **Body changes:**
  - Typically, transgender females and transgender males had comparable body compositions.
- **Body image:**
  - In general, natal females reported a greater degree of gender dysphoria compared to natal males
  - Compared to untreated transgender individuals, those who received hormonal treatment tended to have improvements in body image satisfaction
- **Bone health:**
  - Transgender females tend to have lower levels of bone mineral density compared to transgender males
- **Cardiovascular risk factors:**
  - As a rule, some cardiovascular risk factors increase for transgender patients when they start CSHT. However, these risk factors tend to be within the reference range for transgender patients compared to that of the affirmed sex.

I.4.7.5 Outcomes addressed with comparisons of TGNB patients to their cisgender peers

See **Appendix I.K** for evidence tables regarding study details and findings, organized by outcome of interest. Note that some studies evaluated more than one outcome of interest and are represented in more than one table. Some studies also have TGNB vs TGNB data or pre-post comparison within the study and may be included in **Appendixes I.J** and I.**L**.

Due to fewer studies, with varied outcomes, there are few generalizations to make for the TGNB vs. cisgender peer studies.

I.4.8 Descriptive Studies

A total of 144 descriptive studies met eligibility criteria, including 35 case reports (2 of which were not in English), 14 case series (1 of which was not in English), 4 other non-English studies with abstracts in English that warranted inclusion, 1 commentary on another included study, 2 repeat publications of included studies, 12 studies that lacked any high-priority outcomes of interest, and 44 studies that lacked high priority comparisons. These were all relegated to the bibliography only (see **Appendix I.F**). The remainder, 32 studies, had a high-priority comparison and at least one high-priority outcome of interest and thus had their data extracted. The non-English and lacking studies can be found only in the Bibliography of Included Studies, **Appendix I.F**.

See **Appendix I.L** for evidence tables regarding details and findings of the descriptive studies that had their data extracted in full, organized by outcome of interest. Note that some studies evaluated more than one outcome of interest and are represented in more than one table.

Outcomes of interest included the following:

- Mental health (eg, depression, anxiety, suicidality)
- Psychosocial functioning (eg, executive function, brain activity, education, quality of life)
- Body image (eg, body dysphoria/gender dysphoria, body satisfaction)
- Body changes (eg, changes in height, fat/lean/body mass changes, development of secondary sex characteristics such as breast development or deepening voice, menstruation)
- Bone health (eg, bone density, bone turnover measures)
- Cardiovascular risk factors (eg, thrombotic changes, insulin sensitivity, blood pressure, obesity)
- Cancer

I.4.8.1 Longitudinal, pre-post comparisons

None of the reviewed descriptive studies had cancer-related outcomes, but the remaining outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 11
- Psychosocial functioning: 11
- Body image: 5
- Body changes: 22
- Bone health: 7
- Cardiovascular risk factors: 14

I.4.8.2 Summary of longitudinal, pre-post descriptive studies

Table I.25 below contains all included descriptive studies with high-priority, pre-post comparisons and where extracted data can be found (see **Appendix I.L**). Some descriptive studies also had observational comparisons; the observational comparisons are summarized above in Section I.4.7, and their extracted data can be found in **Appendixes I.J** and I.**K**.

Overall, we identified 39 descriptive studies with longitudinal pre-post comparisons, 31 of which had at least one high priority outcome of interest (**Table I.25**). Thirteen of these longitudinal pre-post studies also had an observational component (see **Appendix I.L**).

Table I.25. Comparison types reported in descriptive studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Allen (2019)[56]	Authors examined mental health and suicidality outcomes among N = 47 TGNB adolescents who received GnRH analogs followed by CSHT vs CSHT only.	X		X
Arnoldussen (2022)[135]	Authors examined changes in psychosocial outcomes in TGNB adolescents before (while on hormonal treatments only) vs after gender-affirming surgery.			X

Table I.25. Comparison types reported in descriptive studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Cantu (2020)[74]	Authors examined changes in anxiety and depression in treated and untreated TGNB youth. Also compares differences in changes over time between TGNB groups.	X		X
Carmichael (2021)[73]	Authors examined short-term (ie, 1-3 years) bone and psychosocial outcomes in N = 44 TGNB youths (including 25 AMAB and 19 AFAB children) ages 12-15 years who received GnRH analog monotherapy	X		X
Chen (2023)[75]	Authors examined mental health and psychosocial outcomes in TGNB adolescents after 2 years of CSHT and mental health outcomes between early- and late-treated adolescents.	X		X
de Vries (2010)[78] Thesis (C7)	Authors examined treatment satisfaction, social functioning, sexual functioning, and quality of life in N = 27 transgender males who initiated treatment as adolescents.	X		X
de Vries (2011)[57]	Authors examined mental health outcomes in N = 70 TGNB patients treated with GnRH analogs	X		X
Ghelani (2020)[58]	Authors examined body composition changes in N = 36 TGNB adolescents receiving triptorelin for puberty suppression.			X
Hannema (2017)[59]	Authors examined changes in endogenous hormone levels, anthropometric measures, bone, blood pressure measures among N = 28 transgender girls treated with estradiol			X
Jarin (2017)[136]	Authors examined cardiovascular and metabolic changes associated with CSHT in N = 116 adolescents with gender dysphoria			X
Joseph (2019)[137]	Authors examined bone outcomes in N = 31 TGNB adolescents treated with GnRH analogs			X
Kaltiala (2020)[138]	Authors examined psychosocial functioning in N = 52 TGNB adolescents before and after 1-year of CSHT			X
Klaver (2018)[83]	Authors examined body composition changes over time in N = 192 transgender patients who received unspecified GnRH analogs and CSHT	X		X
Klaver (2020)[139]	Authors compared changes in cardiovascular risk factors between TGNB subjects who received surgical vs GnRH analog gonadal suppression, and between transwomen and transmen. Also examined within-group changes over time.			X
Klink (2015)[140]	Authors examined patient characteristics and bone outcomes over time in N = 34 GnRH analog and CSHT-treated adolescents with GD			X
Kuper (2020)[141]	Authors examined changes in body dissatisfaction and mental health (anxiety/depression) among N = 148			X

Return to TOC

Table I.25. Comparison types reported in descriptive studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
	TGNB adolescents receiving puberty suppression and/or CSHT.			
Laurenzano (2021)[84]	Authors examined endogenous hormone levels, menstrual outcomes, and body changes in N = 119 transmasculine and gender-diverse adolescents treated with subcutaneous testosterone	X		X
Lavender (2023)[142]	Authors examined changes in mental health and suicidality for N = 38 TGNB youths after initiating unspecified GnRH analogs and CSHT.			X
Lopez de Lara (2020) [62]	Authors examined psychosocial outcomes in 23 TGNB patients who attend a pediatric endocrinology clinic before and after one-year of cross hormonal therapy (CHT).		X	X
Millington (2021)[89]	Authors examined growth, body composition, and cholesterol changes in N = 269 TGNB adolescents (83 AMAB and 186 AFAB children) receiving CSHT.	X		X
Millington (2022)[90]	Authors examined changes in kidney function measures in N = 286 TGNB adolescents (194 AFAB and 92 AMAB children) receiving GAHT.	X	X	X
Neyman (2019)[64]	Authors reported on clinical and laboratory characteristics of N = 13 transfeminine patients treated with the antiandrogen bicalutamide as an androgen blocker after insurance denials of claims for GnRH analogs			X
Olson-Kennedy (2018)[143]	Authors examined cardiovascular and metabolic outcomes over time in N = 101 transmasculine and transfeminine adolescents			X
Perl (2020)[144]	Authors examined blood pressure outcomes in N = 15 transgender males receiving puberty-suppressing GnRH analogs, N = 9 of which went on to receive CSHT with testosterone			X
Perl (2021)[145]	Authors examined blood pressure, weight, and hormone levels in N = 19 adolescents who received GnRH analogs for puberty suppression, N = 15 of which also went on to receive CSHT with estradiol			X
Roy (2023)[146]	Authors examined red blood cells in N = 15 transgender boys receiving testosterone therapy			X
Schagen (2016)[148]	Authors examined growth, body composition, and endogenous hormone levels in N = 116 TGNB adolescents who received GnRH analogs for 1 year			X
Schagen (2018)[147]	Authors examined changes in endogenous hormones during puberty suppression and CSHT in adolescents with GD.	X		X
Stoffers (2019)[149]	Authors examined body changes, growth, cardiovascular risk factors, and metabolic outcomes in testosterone-treated adolescents with GD			X

Table I.25. Comparison types reported in descriptive studies that underwent full data extraction

Author (year)	Description	TGNB/TGNB Appendix I.J	TGNB/peer Appendix I.K	Pre-post Appendix I.L
Tack (2017)[150]	Authors examined growth, cardiovascular risk factors, and metabolic changes in N = 27 transgender female adolescents taking estrogen with an antiandrogen not available in the US (cyproterone)			X
Vlot (2017)[99]	Authors examined bone changes over time with puberty suppression and CSHT in N = 70 TGNB adolescents	X		X
Willemsen (2023)[127]	Authors examined height and weight outcomes in N = 146 TGNB adolescents who initiated GnRH analogs before age 16 years.	X		X

I.4.8.3 Outcomes addressed with longitudinal, pre-post comparisons

See **Appendix I.L** for evidence tables regarding descriptive study details and findings, organized by outcome of interest. Below are some limited takeaways based on the findings from included pre-post descriptive studies of within-TGNB population comparisons, organized by outcome of interest:

- Mental health:
  - Generally, rates of suicidal thoughts/self-harm tended to be lower when followed up after treatment
  - Scores for anxiety and depressive symptoms tended to either have no change, or decrease while on treatment
  - Scores for gender dysphoria tended to decline after treatment
- Psychosocial functioning:
  - Generally, there was an increase in scores for psychosocial functioning, and a decrease in behavioral and emotional problem scores after treatment
- Body image:
  - In general, there was a decrease in body dissatisfaction scores in patients after treatment
- Body changes:
  - Body composition tended to change (fat distribution, lean body mass) towards the affirmed sex with CSH treatment
- Bone health:
  - There were changes in bone mineral density, usually with a drop in z-scores, often leveling out over time. This was more apparent in transgender girls.
- Cardiovascular risk factors:
  - Cardiovascular risk factors tended to increase for transgender patients when they started therapy, but still often stayed within normal range. However, many of these risk factors often plateaued or returned to normal after more time on therapy. Transgender boys tended to have more changes to their cardiovascular health.

I.5.0 OBJECTIVE 4: PERSISTENCE, DESISTANCE, AND REGRETS

Persistence, desistance, and regret were not among our high-priority outcome categories for this review. However, these concepts were pointedly of interest to the legislature, per Utah SB 16,[14] so we examined the evidence in the retrieved studies. We found 32 studies that addressed persistence, desistance, and/or regret. Findings from these studies that relate to rates of persistence and desistance are summarized in **Table I.26**.

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
Barnard (2019)[163]	N=11 TGNB presented at an academic fertility clinic for fertility preservation. Of these, • 2 (18%) paused GAHT for fertility preservation.
Brik (2020)[164]	N=143 TGNB adolescents were seen at a clinic in the Netherlands and started GnRH analog therapy between November 2010 and January 2018. There were n=105 trans boys (median age 16.1 years) and n=38 trans girls (median age 15.0 years). Of this group, • After a median duration of 0.8 years on GnRH analogs, n=125 started GAHT • 5 had not yet started GAHT because they were not yet eligible due to their age at the time of data collection, 6 had been referred to a gender clinic elsewhere • Of those who started GnRH analogs, 9 (6%) discontinued: ○ 5 (3.5%) no longer wished to pursue gender-affirming treatment. ○ 4 (2.3%) discontinued, but then later restarted GAHT.
Butler (2022)[165]	N=1151 TGNB children were referred to 1 of 2 British gender identity clinics in 2008-2021; N=1089 were followed until 2022. Of these, • 999 (91.7%) persisted with their initial gender identity variant. • 32 (2.9%) reverted to their birth gender and never started GAHT. • 58 (5.3%) reverted to their birth gender after initiating GAHT.
Carmichael (2021)[73]	N=44 TGNB youth on GnRH analog monotherapy at a gender clinic in Brazil. Bone data was assessed. Of these, • 1 (2.3%) chose not to start CSHT.
Clark (2020)[166]	N= 21 trans youth (aged 14-18) and their parents, residing in British Columbia, Canada, were interviewed about the decision-making process related to initiating GAHT between August 2016 and February 2017. Of these youth, • 0 (0%) expressed regret about the decision to start hormone therapy, though some wished the process had unfolded differently. In particular, those who wished the process had unfolded differently were those who had been denied

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
	puberty blockers and who had developed unwanted secondary sex characteristics while waiting for care.
Cohen (2023)[167]	N=68 out of 130 TGNB children requesting GAHT or surgery in a US, national hospital-based gender identity clinic were interviewed over time to assess patterns of change in requests for GAHT or surgery. Of these, • 20 (29%) experienced a shift in their treatment requests related to gender identity: ○ 4 (5.9%) withdrew their request before starting treatment. ○ 2 (2.9%) withdrew their requests after starting treatment. ○ 14 (20.6%), withdrew their request and then subsequently re-requested treatment.
Cohen-Kettenis (2011)[168]	N=1 transgender male followed up over 22 years. He was treated with GnRH analogs at 13 years of age, was eligible for androgen treatment at age 17 years, and had gender reassignment surgeries at 20 and 22 years. At follow-ups, he expressed a lack of regret about undergoing his treatment.
De Vries (2010) (Chapter 7)[78]	N=27 TGNB youths presented to a Dutch gender identity clinic, underwent GAHT and gender reassignment surgery, and were followed up at a mean age of 20 years. Of these, • 0 (0%) expressed feelings of regret with either GAHT or surgery.
De Vries (2014)[79]	N=55 TGNB adults at a Dutch gender identity clinic had initiated puberty suppression during adolescence and undergone assessments at 3 times: (1) before the start of puberty suppression (mean age 13.6 years), (2) when CSHT was introduced (mean age 16.7 years), and (3) at least 1 year after gender reassignment surgery (mean age 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated. Of these, • 55 (100%) of young adults were generally satisfied with their physical appearance. • 0 (0%) regretted treatment.
Expösito-Campos (2022)[169]	N=1 transgender female (age 16 years) presented at a Spanish gender identity clinic with severe GD in 2014. She was prescribed GAHT with cyproterone and estradiol. In 2016, she legally changed her name to a feminine-affirming name. Vaginoplasty was delayed for unrelated reasons, but after starting a sexual relationship with a male partner, she desisted from pursuing surgery in 2017 and discontinued cyproterone. In 2018, she discontinued hormonal treatment completely, saying that she "does not need [hormones] to be a woman." At the time of publication, she continues to persist in her transfeminine gender identity.

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
Hannema (2017)[59]	N=28 TGNB girls at a Dutch gender identity clinic were treated with oral estrogen for 1+ year. Tanner stage, anthropometry, laboratory parameters, bone age, and body composition were evaluated. Of this group, • 0 (0%) discontinued estrogen treatment
Jensen (2019)[60]	N=83 patients at a pediatric gender clinic who were receiving GAHT before March of 2016. 17 out of 83 patients were taking GnRH analogs. Of these, • 10 (59%) of patients discontinued use of GnRH analogs, most commonly due to a loss of insurance coverage.
Laurenzano (2021)[84]	N= 119 TNGB youth at a California hospital started GAHT between 2012 and 2020 with subcutaneous testosterone at ages 13-19 years and were evaluated for side effects, dosage, and response to treatment. Of the 119 youth, • 3 (2.5 %) stopped GAHT altogether due to desire to end masculinizing therapy. • 2 (1.7%) stopped because they were satisfied with the effects they had achieved. • 1 (0.8%) stopped within 6 months of starting after reassessing their gender identity and concerns about a potential impact on fertility.
Karakilic Ozturan (2023)[112]	N=30 TGNB adolescents referred for GD to a clinic in Turkey had their charts reviewed for clinical findings. Of these, • 1 (3.3%) had their GD resolve and did not continue with CSHT after GnRH analogs. • 1 (3.3%) developed depression due to body dissatisfaction related to cosmetic appearance after a gender-affirming surgery and treatments were discontinued.

Khatchadourian (2014)[82]	N=84 TNGB adolescents (median age 16.9 years) seen in a British Columbia hospital were included in a chart review study from 1998 through 2011. Of these,
	• 1 (1.2%) patient with undecided gender was prescribed GnRH analogs but discontinued after 13 months and chose not to pursue transition.
	• 63 (75%) were treated with CSHT during the observation period.
	  ○ 0 (0%) of the 63 discontinued treatment permanently.
	  ○ 3 (4.8%) temporarily paused treatment and later restarted.
	  ▪ 2 due to concomitant psychiatric comorbidities
	  ▪ 1 due to distress over androgenic alopecia

Kuper (2020)[141]	N=148 TGNB participants (mean age 14.9 years) were receiving GAHT in a program in Texas. Participants completed surveys assessing various mental health outcomes at baseline and 1 year (11-18 months) after initial assessment. Of this group, • 0 (0%) participants discontinued feminizing or masculinizing hormone therapy during study period
Masic (2022)[170]	N=439 TGNB youths who presented to a British gender identity clinic in 2017-2018 were followed until November 2020. Of these,

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
	• 30 (6.8%) discontinued GAHT or chose not to start it for the following reasons: ○ 13 (3.0%) stopped/did not start for unknown reasons. ○ 5 (1.1%) stopped/did not start for health reasons. ○ 4 (0.9%) paused to preserve fertility. ○ 4 (0.9%) transferred to a private provider. ○ 3 (0.7%) stopped/did not start because they felt unsure about starting GAHT. ○ 1 (0.2%) stopped/did not start for mental health reasons.
McCallion (2021)[171]	N=91 TGNB patients (median age 14.6 years) were referred to a pediatric endocrinology clinic for GD, of whom 79 (87%) started treatment with GnRH analogs. Of those who started GnRH analogs, • 6 (8%) discontinued GnRH analogs after a median of 6 months. • 41 (51.9%) started CSHT. • 1 (1.3%) discontinued CSHT.
Nieder (2021)[172]	N=75 TGNB adolescents ages 11-21 years who presented to a German gender identity service were assessed for satisfaction of care, social support, reasons for regret and termination of transition related care and (dis)satisfaction with transition-related medical interventions. Of these, • 0 (0%) adolescents regretted undergoing treatment at follow-up • 13 (17.3%) participants had suspended or terminated their care at the clinic-reasons related to mental health issues were most often listed, followed by reasons unrelated to direct treatment experience (eg, long distance to clinic) ○ 9 (12%) had not started medical interventions ○ 3 (4%) were taking GAHT ○ 1 (1.3%) was at the stage for gender-affirming surgery
Nos (2022)[173]	N=434 TGNB patients (mean age 15.4) presented with GD at a US military healthcare system. Of these, • 70 (16.1%) were prescribed GnRH analogs. • "Few" discontinued treatment.
O'Bryan (2018)[174]	N=139 TNGB youths enrolled in a registry at a rural gender identity clinic. Of these, • 121 (87.7%) had socially transitioned. • 123 (89.1%) had begun medically transitioning. • 20 (14.4%) had undergone a gender-affirming surgical procedure. • 1 (0.7%) reverted to their birth-assigned sex after starting CSHT. • 1 (0.7%) stopped GnRH analogs and subsequently resumed them.

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
	• 1 (0.7%) continued to take GnRH analogs while exploring an emerging gender identity. • 1 (0.7%) desisted after taking GnRH analogs.

Olson (2022)[175]	N=317 TNGB children (mean age 8.1 years) participating in the longitudinal Trans Youth Project were followed for 5 years after an initial social transition. Of these,
	• 298 (94.0%) still identified as a binary transgender youth.
	  ○ 23 (7.3%) had retransitioned at least once.
	  ○ 4 (1.3%) had retransitioned to another identity before returning to their binary transgender identity.
	• 11 (3.5%) identified as nonbinary.
	• 8 (2.5%) identified as cisgender 5 years after their initial social transition.
	  ○ A cisgender identity 5 years after the social transition was more likely in patients whose social transition occurred before age 6 years.

Pullen Sansfaçon (2019)[176]	N=35 Canadian TGNB youths ages 9-17 years who participated in semi-structured interviews through clinics where they had received or were waiting for GAHT. Of these, • 0 (0%) of youth regretted their choice to undergo the interventions even though some described unwanted medication side-effects and others said they had questioned their transition trajectory at certain moments in the past.
Schagen (2016)[148]	N=116 TGNB youth seen in a Dutch clinic were treated with triptorelin. Physical examination took place every 3 months and blood samples were drawn at 0, 3, and 6 months and every 6 months after. After 12 months of treatment, of this group, • 0 (0%) of the subjects discontinued GnRH analogs.

Segev Becker (2020)[117]	N=106 TGNB youth at an Israeli gender clinic (median age at referral 15.5 years) from March 2013 through December 2018 were retrospectively assessed for psychiatric comorbidities, behavioral characteristics, fertility preservation and treatment. Of the pubertal group (n=96),
	• 77 (80%) began on GnRH analog treatment (mean [SD] age of 15.6 [1.6] years) during the observation period.
	  ○ 61 (83%) of the patients who began on GnRH analog treatment were started on GAHT either concurrently or later, at a mean (SD) age of 16.5 (1.3) years
	  ○ At the time of study analysis, some chose not to pursue treatment with GAHT.
	  ▪ 12 (16%) lacked a complete GD diagnosis by a health care provider
	  ▪ 3 (3.9%) lacked parental consent
	  ▪ 1 (1.3%) was delaying treatment for the purpose of fertility preservation
	  ▪ 3 (3.9%) had other reasons for not pursuing GAHT at that time

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
	• 2 (2%) of the 96 patients in the pubertal group expressed regret. 2 transgender females who had been on GnRH analogs and low-dose estrogen for 3 months chose not to continue transition and discontinued treatment. One of those had autistic spectrum disorder, and the other identified as a homosexual male and was lost to follow-up.
Singh (2021)[177]	N=139 birth assigned males were assessed at a gender identity service in Canada around the mean age of 7.49 years at the mean year of 2002. In childhood, 88 (63.3%) of the boys met the criteria for gender identity disorder; the remaining 51 (36.7%) were subthreshold for the criteria. Gender identity/dysphoria was assessed via multiple methods. At follow-up, when patients were a mean age of 20.58, after an interval of mean 12.88 years, of the 139 participants, • 17 (12.2%) were classified as persisters • 122 (87.8%) were classified as desisters Of the 88 participants who met the full diagnostic criteria for GID in childhood, • 12 (13.6%) were classified as persisters • 76 (86.4%) were classified as desisters

Tollit (2023)[120]	N=359 TGNB patients (median age at presentation, 14.3 years) who had had an appointment with a large Australian pediatric gender service from Jan 2001-Dec 2016 and had either a self-reported gender which differed from what was presumed for them at birth or sought guidance regarding gender identity/expression had their charts reviewed for data. Of the 359 patients, 234 received medical interventions. Of the 234 patients,
	• 54/234 (23%) were treated with GnRH analogs.
	  ○ 1 (1.9%) patient stopped without progressing to CSHT during the study period
	• 48/234 (20.5%) were treated with CSHT
	  ○ 1 (2.1%) patient stopped GAH unexpectedly during the study period

Turban (2018)[178]	N=1 TGNB girl who presented to a multidisciplinary clinic at the age of 15. She received a puberty blocker (histrelin GnRH analog implant.) At age 16, she started estrogen therapy at a small dose, with a plan to escalate to adult dosing over a prolonged period of time. Four months later, the patient adopted nonbinary pronouns they, them and their and did not wish to increase the dose of estrogen any further, nor did they wish to stop estrogen. The patient then decided they did not identify as a boy or girl and chose to discontinue estrogen therapy and remove their puberty blocker with the understanding that they would go through male puberty. They continued to be followed and continues to identify as gender nonbinary. The patient sometimes expresses a desire to have no secondary sex characteristics but overall are happy with their decisions.
van der Loos (2022)[68]	N= 720 TGNB adolescents seen at a Dutch gender identity clinic (from the ACOG data set), from 1972 to 2018, of whom 220 (31%) were assigned male at birth and 500 (69%) were assigned female at birth. At the start of GnRH analog treatment, the

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

Table I.26. Included studies that addressed issues related to persistence and desistance with GAHT in pediatric GD patients

Author (year)	Findings
	median age was 14.1 years for people assigned male at birth and 16·0 years for people assigned female at birth. Median age at end of data collection was 20.2 years for people assigned male at birth and 19.2 years for those assigned female at birth. Of the 720 adolescents: • 704 (98%) people who had started GAHT in adolescence continued to use GAHT at follow-up.
van der Loos (2023)[70]	N=1766 TGNB children and adolescents seen at a Dutch clinic from 1972 to 2018 for gender dysphoria . Of possibly eligible adolescents who had their first visit before age 10 years, nearly half started GnRH analogs vs around two-thirds who had their first visit at or after age 10 years. The proportion starting GnRH analogs rose only for those first visiting before age 10. Of those that started GnRH analogs, • 1.4% stopped GnRH analogs, mostly because of remission of gender dysphoria
Vrouenraets (2022)[179]	N= 8 TGNB adolescents who proceeded with GAMT after PS ("continuers") and N=6 adolescents who discontinued PS ("discontinuers") participated in structured interviews about their experience. All patients were seen at a Dutch gender identity clinic. • All informants considered inhibition of development of secondary sex characteristics an important function of PS. • Most continuers saw PS as the first step of GAMT. Nevertheless, some were glad that the effects were reversible even if they didn't expect to change their minds. • Some discontinuers did experience PS as an expanded diagnostic phase. • One continuer used the time on PS to get used to living in the affirmed gender role, and several parents found the time helpful to adapt to their child's new gender role. • PS provided clinicians more time for diagnostic assessment.
Wiepjes(2018)[67]	N=6793 TGNB people who visited a single Dutch gender identity clinic from 1972 to 2015. From this group: • 0.6 % of transwomen and 0.3% of transmen who underwent gonadectomy who started HT after the age of 18 had regret. • No cases of regret were observed among the 1360 individuals who were first seen before the age of 18 years. 1.9% of adolescents who started PS (n=812) stopped PS and did not start HT

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy; CSHT, cross-sex hormone therapy; US, United States; GD, gender dysphoria;

I.6.0 CONCLUSIONS

The conventional wisdom among non-experts has long been that there are limited data on the use of GAHT in pediatric patients with GD. However, results from our exhaustive literature searches have led us to the opposite conclusion.

We found more than 277 individual, full-text citations that met eligibility for study design, population, and treatments of interest, including N=230 primary clinical studies reporting on the patient-level experience of at least N=28,056 pediatric GD patients all over the world. We provide in this report extracted findings and ROB assessments for N=89 English-language clinical studies that included high-priority comparisons and outcomes (listed below). Another 127 English-language clinical observational studies, descriptive studies, and case studies that did not undergo data extraction are also provided in a bibliography. Due to the extremely limited time available for this work, we were forced to deprioritize studies that lacked our high-priority comparison types (n=93) and outcomes (n=41).

- High-priority comparison types: Between TGNB-group; TGNB versus cisgender peer group; and TGNB within-group, before-after (pre-post) comparisons
- High-priority outcomes: Mental health and psychosocial changes; body changes; body image; bone health; cardiovascular risk factors and metabolic changes; and cancer.

We were not contracted to include a synthesis of the evidence that we found: only to assess ROB and provide evidence tables summarizing safety and efficacy findings. However, after having spent many months searching for, reading, and evaluating the available literature, it was impossible for us to avoid drawing some high-level conclusions. Namely, **the consensus of the evidence supports that the treatments are effective in terms of mental health, psychosocial outcomes, and the induction of body changes consistent with the affirmed gender in pediatric GD patients. The evidence also supports that the treatments are safe in terms of changes to bone density, cardiovascular risk factors, metabolic changes, and cancer**. With regards to these safety outcomes, reviewed studies show that any patient-level changes are minimal, and that despite any small improvements or decrements in individual disease risk factors, the average patient's values remain within the bounds of normal, non-pathological ranges for human populations. For example, transgender women typically realize adult BMD levels that, while lower than their pre-treatment potential, remain in the normal range for healthy cisgender women.

With respect to guidelines, we used the IOM's definition, which enabled us to ignore a vast body of opinion-based position statements and editorials from interested groups across the political spectrum. We considered only publications focused on optimizing patient care that came from a recognized medical authority, and that provided graded recommendations based on a systematic review of the available evidence. We found 5 guidelines that met these criteria, in addition to also meeting our population and intervention criteria. We extracted data from 4 guidelines; the fifth was not in English and is included in the bibliography only.

Reviewed guidelines generally recommend use of puberty suppressing drugs in GD patients during ***early puberty (but not earlier)*** and using CSHT in older adolescents. They also address some key considerations that are outside the scope of this report, but that are nonetheless important, such as provider training recommendations, non-pharmacologic treatments for pre-pubescent children,

counseling recommendations, and surgical treatments. (The latter are typically only recommended in adulthood, especially genital surgeries.) The consensus of guideline recommendations acknowledges the validity of medically treating pediatric GD patients after puberty.

With regards to any misgivings that stakeholders may have about allowing pediatric patients to receive pharmacologic (and frequently surgical) treatments over concerns about future regret, we found (based on the N=32 studies that addressed it) that there is virtually no regret associated with receiving the treatments, even in the very small percentages of patients who ultimately discontinued them. Reasons for discontinuing GAHT are varied, but changed minds about gender identities is only a very minor proportion overall.

We found 39 reviews that described themselves as "systematic" or that included search terms for ≥1 bibliographic database, but we only extracted data from the 7 reviews that conducted systematic, reproducible searches in 2 or more databases, reported search results and findings, and addressed our high-priority outcomes. Most reviewed SRs supported the conclusion that GAHT in pediatric GD patients is generally effective in terms of mental health, psychosocial outcomes, and/or producing the desired body changes; they also supported the conclusion that the treatments are generally safe in terms of cardiovascular risk factors, metabolic changes, bone health, and/or cancer. One SR notably concluded that the treatments should be regarded as experimental,[49] but this conclusion was based on what evidence remained after excluding a third of the eligible, retrieved studies, which violates best practices for systematic review authors.[30,43]

Notably, our searches yielded a larger number of primary studies than any of the systematic reviews that underwent data extraction. Ludvigsson (2023) found the largest number of studies (36) in their search of 13 databases using eligibility criteria that broadly included all study designs, including case studies.[49] Thanks to the skills of our evidence retrieval experts, we found more than 200 studies (including case studies) and extracted data from 89 primary experimental studies, observational studies, and longitudinal, pre-post studies of high-priority outcomes.

Based on the reviewed evidence included in this report, **it is our expert opinion that policies to prevent access to and use of GAHT for treatment of GD in pediatric patients cannot be justified based on the quantity or quality of medical science findings or concerns about potential regret in the future, and that high-quality guidelines are available to guide qualified providers in treating pediatric patients who meet diagnostic criteria**.

I.7.0 LIMITATIONS

- We performed no formal synthesis. Conclusions are those of DRRC authors who reviewed the individual studies.
- Data extraction was not performed in duplicate; but a pharmacist author double-checked all extracted data performed by other authors.
- We may have overlooked some studies due to our abbreviated timeline, but given that we have found a more exhaustive set of studies than any included systematic review or guideline, our report is likely the most comprehensive to date.
- We would have liked to extract data from clinical case studies and other descriptive studies. However, due to time constraints, the best we can do is provide those studies in the bibliography.

PART I REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-5-TR).* 5th ed. American Psychiatric Association; 2022. doi:10.1176/appi.books.9780890425763 Last Updated 2022. Accessed February 27, 2023. Available at https://www.appi.org/Products/DSM-Library/Diagnostic-and-Statistical-Manual-of-Mental-Di-(1)

2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders - Revised (DSM-III-R).* American Psychiatric Association; 1980. doi:10.1176/appi.books.9780890420188.dsm-iii-r Accessed February 27, 2023. Available at https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890420188.dsm-iii-r

3. Koh J. [The history of the concept of gender identity disorder]. *Seishin Shinkeigaku Zasshi*. 2012;114(6):673-680. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22844818

4. 43 BCE-17 AD or 18 AD Ovid. *Ovid metamorphoses*. Tarrant RJ, ed. Oxford University Press; 2004.

5. Kaufman E. What We Owe Children Contemplating a Gender Transition. *Wall Street Journal*. August 23, 2022. Accessed February 27, 2023. Available at https://www.wsj.com/articles/trans-gender-transition-medical-surgery-hormones-affirm-therapy-conversion-academy-pediatrics-aap-11661289032

6. Bazelon E. The Battle over Gender Therapy. *New York Times Magazine*. June 15, 2022. Accessed February 27, 2023. Available at https://www.nytimes.com/2022/06/15/magazine/gender-therapy.html

7. American Academy of Pediatrics. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. *Pediatrics*. 2018;142(4)doi:10.1542/peds.2018-2162 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30224363

8. Almeida J, Johnson RM, Corliss HL, Molnar BE, Azrael D. Emotional distress among LGBT youth: the influence of perceived discrimination based on sexual orientation. *J Youth Adolesc*. 2009;38(7):1001-1014. doi:10.1007/s10964-009-9397-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19636742

9. Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. doi:10.1300/J082v51n03_04 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/17135115

10. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014;39:65-73. doi:10.1016/j.psyneuen.2013.09.029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24275005

11. Haas AP, Eliason M, Mays VM, et al. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51.

Return to TOC

doi:10.1080/00918369.2011.534038 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21213174

12. Maguen S, Shipherd JC. Suicide risk among transgender individuals. *Psychology and Sexuality*. 2010;1(1):34-43. doi:10.1080/19419891003634430 Accessed February 27, 2023. Available at https://www.researchgate.net/publication/233355000_Suicide_risk_among_transgender_individuals

13. Grossman AH, D'Augelli AR. Transgender youth and life-threatening behaviors. *Suicide Life Threat Behav*. 2007;37(5):527-537. doi:10.1521/suli.2007.37.5.527 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/17967119

14. Transgender Medical Treatments and Procedures, S.B. 16, 65th Leg., Gen. Sess. (Utah 2023). Accessed February 27, 2023. Available at https://le.utah.gov/~2023/bills/static/SB0016.html

15. Sands L. Utah banned gender-affirming care for trans kids. What does that mean? *Washington Post*. February 1, 2023. Accessed February 27, 2023. Available at https://www.washingtonpost.com/nation/2023/02/01/utah-gender-affirming-care-ban/

16. Meerwijk EL, Sevelius JM. Transgender Population Size in the United States: a Meta-Regression of Population-Based Probability Samples. *Am J Public Health*. 2017;107(2):e1-e8. doi:10.2105/AJPH.2016.303578 https://www.ncbi.nlm.nih.gov/pubmed/28075632

17. Kidd KM, Sequeira GM, Douglas C, et al. Prevalence of Gender-Diverse Youth in an Urban School District. *Pediatrics*. 2021;147(6)doi:10.1542/peds.2020-049823 https://www.ncbi.nlm.nih.gov/pubmed/34006616

18. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166(9):1021-1026. doi:10.1001/archinte.166.9.1021 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/16682577

19. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc*. 2012;87(10):982-990. doi:10.1016/j.mayocp.2012.04.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22877654

20. Allen HC, Garbe MC, Lees J, et al. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. *J Okla State Med Assoc*. 2018;111(8):776-783. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31379392

21. Pasquali SK, Hall M, Slonim AD, et al. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circ Cardiovasc Qual Outcomes*. 2008;1(2):74-83. doi:10.1161/CIRCOUTCOMES.108.787176 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20031793

22. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med*. 2007;161(3):282-290. doi:10.1001/archpedi.161.3.282 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/17339510

23. Giurin MS, Trojniak MP, Arbo A, et al. Safety of Off-Label Pharmacological Treatment in Pediatric Neuropsychiatric Disorders: A Global Perspective From an Observational Study at an Italian Third

Level Children's Hospital. *Front Pharmacol*. 2022;13:837692. doi:10.3389/fphar.2022.837692 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35496268

24. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 2020;323(9):844-853. doi:10.1001/jama.2020.1166 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32125404

25. Section 505A of the Food and Drug Administration Modernization Act (FDAMA), Pub. L. No. 105-115, 111 Stat. 2305 (1997). Accessed April 18, 2023. Available at https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-modernization-act-fdama-1997

26. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A). Fact sheet. FDA.gov. March 1, 2022. Accessed April 18, 2023. Available at https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently

27. IBM Micromedex. MicromedexSolutions.com; 2023. Last Updated April 2023. Accessed April 18, 2023. Available at https://www.micromedexsolutions.com

28. Lexicomp Online. Lexicomp.com; 2023. Last Updated April 2023. Accessed April 18, 2023. Available at https://online.lexi.com

29. US Food and Drug Administration. Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 18, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

30. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71 Accessed July 12, 2022. Available at https://www.ncbi.nlm.nih.gov/pubmed/33782057

31. Institute of Medicine (IOM). *Clinical Practice Guidelines We Can Trust*. The National Academies Press; 2011:300. Accessed May 23, 2023. Available at https://www.ncbi.nlm.nih.gov/books/NBK209539/

32. Gehlbach SH. *Interpreting the Medical Literature*. 5th ed., McGraw-Hill, Medical Pub. Division; 2006:293.

33. Canadian Agency for Drugs and Technologies in Health (CADTH). Search filter for Guidelines - Broad - MEDLINE, Embase, PsycInfo. SearchFilters.CADTH.ca; 2021. Last Updated December 9, 2021. Accessed May 24, 2023. Available at https://searchfilters.cadth.ca/link/26

34. Canadian Agency for Drugs and Technologies in Health (CADTH). Search filter for Observational Studies - MEDLINE, Embase, PsycInfo. SearchFilters.CADTH.ca; 2021. Last Updated December 16, 2021. Accessed May 24, 2023. Available at https://searchfilters.cadth.ca/link/36

35. Canadian Agency for Drugs and Technologies in Health (CADTH). Search filter for Qualitative Studies - MEDLINE. SearchFilters.CADTH.ca; 2020. Last Updated February 2020. Accessed May 24, 2023. Available at https://searchfilters.cadth.ca/link/40

36. Canadian Agency for Drugs and Technologies in Health (CADTH). Search filter for Qualitative Add-On Option - Surveys and Questionnaires - MEDLINE. SearchFilters.CADTH.ca; 2017. Last Updated September 18, 2017. Accessed May 24, 2023. Available at https://searchfilters.cadth.ca/link/42

37. University of Texas Houston School of Public Health. Search filters for Various Databases - Ovid Medline - Systematic reviews or meta-analyses. LibGuides.sph.uth.tmc.edu; 2014. Last Updated July 12, 2021. Accessed May 24, 2023. Available at https://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters

38. Canadian Agency for Drugs and Technologies in Health (CADTH). Search filter for NOT Animal Studies - Standard - MEDLINE, Embase. SearchFilters.CADTH.ca; 2012. Last Updated November 2012. Accessed July 3, 2023. Available at https://searchfilters.cadth.ca/link/6

39. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health*. 2022;23(Suppl 1):S1-S259. doi:10.1080/26895269.2022.2100644 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36238954

40. American College of Obstetricians, Gynecologists' Committee on Clinical Consensus-Gynecology. General Approaches to Medical Management of Menstrual Suppression: ACOG Clinical Consensus No. 3. *Obstet Gynecol*. 2022;140(3):528-541. doi:10.1097/AOG.0000000000004899 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36356248

41. T'Sjoen G, Arcelus J, De Vries ALC, et al. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction". *J Sex Med*. 2020;17(4):570-584. doi:10.1016/j.jsxm.2020.01.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32111534

42. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658 Accessed May 18, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945902

43. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. doi:10.1136/bmj.j4008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28935701

44. Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa Hospital Research Institute; 2021: 7 pages. Last Updated 2021. Accessed July 3, 2023. Available at https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

45. National Institutes of Health National Heart Lung and Blood Institute. Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group. NHLBI.NIH.gov. 2021. Last Updated July. Accessed July 6, 2023. Available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

46. Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. *J Endocr Soc*. 2021;5(4):bvab011. doi:10.1210/jendso/bvab011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644622

47. Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. *Pediatrics*. 2018;141(4)doi:10.1542/peds.2017-3742 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29514975

48. D'hoore L, T'Sjoen G. Gender-affirming hormone therapy: An updated literature review with an eye on the future. *J Intern Med*. 2022;291(5):574-592. doi:10.1111/joim.13441 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34982475

49. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*. 2023, 10.1111/apa.16791:ePub ahead of print. doi:10.1111/apa.16791 Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/apa.16791?download=true

50. Mahfouda S, Moore JK, Siafarikas A, et al. Gender-affirming hormones and surgery in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2019;7(6):484-498. doi:10.1016/S2213-8587(18)30305-X Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30528161

51. Ramos GGF, Mengai ACS, Daltro CAT, Cutrim PT, Zlotnik E, Beck APA. Systematic Review: Puberty suppression with GnRH analogues in adolescents with gender incongruity. *J Endocrinol Invest*. 2021;44(6):1151-1158. doi:10.1007/s40618-020-01449-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33111215

52. Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child Adolesc Ment Health*. 2021;26(1):3-14. doi:10.1111/camh.12437 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33320999

53. Egger M, Higgins JPT, Smith GD. *Systematic Reviews in Health Research: Meta-Analysis in Context*. 3rd ed., 10.1002/9781119099369BMJ Books; 2022:576.

54. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. Appendix 2. Studies excluded due to high risk of bias (supplementary material). *A systematic review of hormone treatment for children with gender dysphoria and recommendations for research*. Swedish Agency for Health Technology Assessment and Assessment of Social Services; 2023:2. Accessed September 7, 2023. Available at https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-2-exkluderade-studier-med-hog-risk-for-bias.pdf

55. Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol*. 2020;2020(1):8. doi:10.1186/s13633-020-00078-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32368216

56. Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. *Clinical Practice in Pediatric Psychology*. 2019;7(3):302-311. doi:10.1037/cpp0000288 Accessed September 15, 2023. Available at https://psycnet.apa.org/record/2019-52280-009

57. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;8(8):2276-2283. doi:10.1111/j.1743-6109.2010.01943.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20646177

58. Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. *J Pediatr Endocrinol Metab*. 2020;33(1):107-112. doi:10.1515/jpem-2019-0045 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31834861

59. Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. *J Clin Endocrinol Metab*. 2017;102(7):2356-2363. doi:10.1210/jc.2017-00373 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28419243

60. Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. *Transgend Health*. 2019;4(1):300-303. doi:10.1089/trgh.2018.0061 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31663037

61. Karalexi MA, Georgakis MK, Dimitriou NG, et al. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2020;119:104721. doi:10.1016/j.psyneuen.2020.104721 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32512250

62. Lopez de Lara D, Perez Rodriguez O, Cuellar Flores I, et al. [Psychosocial assessment in transgender adolescents]. *An Pediatr (Engl Ed)*. 2020;93(1):41-48. doi:10.1016/j.anpedi.2020.01.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32144041

63. Millington K, Schulmeister C, Finlayson C, et al. Physiological and Metabolic Characteristics of a Cohort of Transgender and Gender-Diverse Youth in the United States. *J Adolesc Health*. 2020;67(3):376-383. doi:10.1016/j.jadohealth.2020.03.028 https://www.ncbi.nlm.nih.gov/pubmed/32417098

64. Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an Androgen Blocker With Secondary Effect of Promoting Feminization in Male-to-Female Transgender Adolescents. *J Adolesc Health*. 2019;64(4):544-546. doi:10.1016/j.jadohealth.2018.10.296 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30612811

65. Zucker KJ, Bradley SJ, Owen-Anderson A, Singh D, Blanchard R, Bain J. Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study. *Journal of Gay & Lesbian Mental Health*. 2010;15(1):58-82. doi:10.1080/19359705.2011.530574

Accessed June 12, 2023. Available at https://www.tandfonline.com/doi/abs/10.1080/19359705.2011.530574

66. Boogers LS, Wiepjes CM, Klink DT, et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. *J Clin Endocrinol Metab*. 2022;107(9):e3805-e3815. doi:10.1210/clinem/dgac349 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35666195

67. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *J Sex Med*. 2018;15(4):582-590. doi:10.1016/j.jsxm.2018.01.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463477

68. van der Loos M, Hannema SE, Klink DT, den Heijer M, Wiepjes CM. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health*. 2022;6(12):869-875. doi:10.1016/S2352-4642(22)00254-1 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36273487

69. van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *J Bone Miner Res*. 2021;36(5):931-941. doi:10.1002/jbmr.4262 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33507568

70. van der Loos M, Klink DT, Hannema SE, et al. Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol. *J Sex Med*. 2023;20(3):398-409. doi:10.1093/jsxmed/qdac029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36763938

71. Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry*. 2022;27(4):1069-1076. doi:10.1177/13591045221091652 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35638479

72. Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service. *Eur Child Adolesc Psychiatry*. 2021;30(11):1755-1767. doi:10.1007/s00787-020-01640-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32990772

73. Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS One*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33529227

74. Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. *Transgend Health*.

2020;5(3):196-200. doi:10.1089/trgh.2019.0077 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644311

75. Chen D, Berona J, Chan YM, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *N Engl J Med*. 2023;388(3):240-250. doi:10.1056/NEJMoa2206297 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36652355

76. Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of Adolescents Referred to a Gender Clinic: Are Youth Seen Now Different from Those in Initial Reports? *Horm Res Paediatr*. 2018;89(6):434-441. doi:10.1159/000489608 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29920505

77. Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *J Sex Med*. 2015;12(11):2206-2214. doi:10.1111/jsm.13034 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26556015

78. de Vries ALC. Puberty Suppression Followed by Cross-sex Hormones and Gender Reassignment Surgery: A Prospective Follow-up of Gender Dysphoric Adolescents into Adulthood. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:91-106:chap 7. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

79. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25201798

80. Eitel KB, Hodax JK, DiVall S, Kidd KM, Salehi P, Sequeira GM. Leuprolide Acetate for Puberty Suppression in Transgender and Gender Diverse Youth: A Comparison of Subcutaneous Eligard Versus Intramuscular Lupron. *J Adolesc Health*. 2023;72(2):307-311. doi:10.1016/j.jadohealth.2022.09.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36404242

81. Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. *J Pediatr Adolesc Gynecol*. 2021;34(5):706-716. doi:10.1016/j.jpag.2021.04.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33910088

82. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Pediatr*. 2014;164(4):906-911. doi:10.1016/j.jpeds.2013.10.068 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24315505

83. Klaver M, de Mutsert R, Wiepjes CM, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. *J Sex Med*. 2018;15(2):251-260. doi:10.1016/j.jsxm.2017.12.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29425666

84. Laurenzano SE, Newfield RS, Lee E, Marinkovic M. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents

and Young Adults: A Single Center's 8-Year Experience. *Transgend Health*. 2021;6(6):343-352. doi:10.1089/trgh.2020.0103 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34988290

85. Lee JY, Finlayson C, Olson-Kennedy J, et al. Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study. *J Endocr Soc*. 2020;4(9):bvaa065. doi:10.1210/jendso/bvaa065 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32832823

86. Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. *Hypertens Res*. 2023;46(1):219-225. doi:10.1038/s41440-022-01067-z Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36229533

87. Marwa A, Misra M, Lopez X. Determinants of Bone Mineral Density in Transgender Youth. *Transgend Health*. 2022;7(3):213-218. doi:10.1089/trgh.2020.0111 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36643057

88. Millington K, Liu E, Chan YM. The Utility of Potassium Monitoring in Gender-Diverse Adolescents Taking Spironolactone. *J Endocr Soc*. 2019;3(5):1031-1038. doi:10.1210/js.2019-00030 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31065620

89. Millington K, Finlayson C, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Association of High-Density Lipoprotein Cholesterol With Sex Steroid Treatment in Transgender and Gender-Diverse Youth. *JAMA Pediatr*. 2021;175(5):520-521. doi:10.1001/jamapediatrics.2020.5620 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33587098

90. Millington K, Barrera E, Daga A, et al. The effect of gender-affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: implications for estimating GFR. *Pediatr Nephrol*. 2022;37(9):2141-2150. doi:10.1007/s00467-022-05445-0 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35083530

91. Mullins ES, Geer R, Metcalf M, et al. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. *Pediatrics*. 2021;147(4)doi:10.1542/peds.2020-023549 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33753543

92. Navabi B, Tang K, Khatchadourian K, Lawson ML. Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2020-039339 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34497118

93. Olson-Kennedy J, Streeter LH, Garofalo R, Chan YM, Rosenthal SM. Histrelin Implants for Suppression of Puberty in Youth with Gender Dysphoria: A Comparison of 50 mcg/Day (Vantas) and 65 mcg/Day (SupprelinLA). *Transgend Health*. 2021;6(1):36-42. doi:10.1089/trgh.2020.0055 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644320

94. Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *J Clin Endocrinol Metab*. 2020;105(12):e4252-4263. doi:10.1210/clinem/dgaa604 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32909025

95. Schulmeister C, Millington K, Kaufman M, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. *J Adolesc Health*. 2022;70(1):108-113. doi:10.1016/j.jadohealth.2021.06.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34315674

96. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. *JAMA Netw Open*. 2022;5(2):e220978. doi:10.1001/jamanetworkopen.2022.0978 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35212746

97. Valentine A, Nokoff N, Bonny A, et al. Cardiometabolic Parameters Among Transgender Adolescent Males on Testosterone Therapy and Body Mass Index-Matched Cisgender Females. *Transgend Health*. 2021;6(6):369-373. doi:10.1089/trgh.2020.0052 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993308

98. Valentine A, Davis S, Furniss A, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. *J Clin Endocrinol Metab*. 2022;107(10):e4004-e4014. doi:10.1210/clinem/dgac469 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35945152

99. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*. 2017;95:11-19. doi:10.1016/j.bone.2016.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27845262

100. Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? *Eur Child Adolesc Psychiatry*. 2020;29(6):803-811. doi:10.1007/s00787-019-01394-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305255/pdf/787_2019_Article_1394.pdf

101. Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. *J Adolesc Health*. 2019;65(6):815-817. doi:10.1016/j.jadohealth.2019.06.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31500946

102. Bauer GR, Pacaud D, Couch R, et al. Transgender Youth Referred to Clinics for Gender-Affirming Medical Care in Canada. *Pediatrics*. 2021;148(5)doi:10.1542/peds.2020-047266 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34620727

103. Becker I, Auer M, Barkmann C, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. *Arch Sex Behav*. 2018;47(8):2335-2347. doi:10.1007/s10508-018-1278-4 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30088234

104. Chen D, Abrams M, Clark L, et al. Psychosocial Characteristics of Transgender Youth Seeking Gender-Affirming Medical Treatment: Baseline Findings From the Trans Youth Care Study. *J Adolesc Health*. 2021;68(6):1104-1111. doi:10.1016/j.jadohealth.2020.07.033 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32839079

105. Conn BM, Chen D, Olson-Kennedy J, et al. High Internalized Transphobia and Low Gender Identity Pride Are Associated With Depression Symptoms Among Transgender and Gender-Diverse Youth. *J Adolesc Health*. 2023;72(6):877-884. doi:10.1016/j.jadohealth.2023.02.036 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00146-5/pdf

106. de Vries AL, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011;52(11):1195-1202. doi:10.1111/j.1469-7610.2011.02426.x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21671938

107. de Vries AL, Steensma TD, Cohen-Kettenis PT, VanderLaan DP, Zucker KJ. Poor peer relations predict parent- and self-reported behavioral and emotional problems of adolescents with gender dysphoria: a cross-national, cross-clinic comparative analysis. *Eur Child Adolesc Psychiatry*. 2016;25(6):579-588. doi:10.1007/s00787-015-0764-7 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26373289

108. de Graaf NM, Steensma TD, Carmichael P, et al. Suicidality in clinic-referred transgender adolescents. *Eur Child Adolesc Psychiatry*. 2022;31(1):67-83. doi:10.1007/s00787-020-01663-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33165650

109. Durwood L, McLaughlin KA, Olson KR. Mental Health and Self-Worth in Socially Transitioned Transgender Youth. *J Am Acad Child Adolesc Psychiatry*. 2017;56(2):116-123 e112. doi:10.1016/j.jaac.2016.10.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28117057

110. Grannis C, Leibowitz SF, Gahn S, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology*. 2021;132:105358. doi:10.1016/j.psyneuen.2021.105358 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34333318

111. Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolesc Health*. 2022;70(4):643-649. doi:10.1016/j.jadohealth.2021.10.036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34920935

112. Karakilic Ozturan E, Ozturk AP, Bas F, et al. Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey. *J Clin Res Pediatr Endocrinol*. 2023, 10.4274/jcrpe.galenos.2023.2023-1-13doi:10.4274/jcrpe.galenos.2023.2023-1-13 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36987788

113. Mirabella M, Piras I, Fortunato A, et al. Gender Identity and Non-Binary Presentations in Adolescents Attending Two Specialized Services in Italy. *J Sex Med*. 2022;19(6):1035-1048. doi:10.1016/j.jsxm.2022.03.215 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/19/6/1035/6961405?redirectedFrom=fulltext

114. Morningstar M, Thomas P, Anderson AM, et al. Exogenous testosterone administration is associated with differential neural response to unfamiliar peer's and own caregiver's voice in

transgender adolescents. *Dev Cogn Neurosci*. 2023;59:101194. doi:10.1016/j.dcn.2022.101194 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36634500

115. Nahata L, Quinn GP, Caltabellotta NM, Tishelman AC. Mental Health Concerns and Insurance Denials Among Transgender Adolescents. *LGBT health*. 2017;4(3):188-193. doi:10.1089/lgbt.2016.0151 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L621194440&from=export

116. Olsavsky AL, Grannis C, Bricker J, et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. *J Adolesc Health*. 2023;72(6):860-868. doi:10.1016/j.jadohealth.2023.01.031 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00097-6/pdf

117. Segev-Becker A, Israeli G, Elkon-Tamir E, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. *Endocr Pract*. 2020;26(4):423-428. doi:10.4158/EP-2019-0418 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32045294

118. Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental Health and Timing of Gender-Affirming Care. *Pediatrics*. 2020;146(4)doi:10.1542/peds.2019-3600 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_20193600.pdf

119. Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;56:190-199. doi:10.1016/j.psyneuen.2015.03.007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25837854

120. Tollit MA, May T, Maloof T, et al. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. *International journal of transgender health*. 2023;24(1):59-69. doi:10.1080/26895269.2021.1939221 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9879187/pdf/WIJT_24_1939221.pdf

121. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1725 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974216

122. Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLoS One*. 2022;17(1):e0261039. doi:10.1371/journal.pone.0261039 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35020719

123. van de Grift TC, van Gelder ZJ, Mullender MG, Steensma TD, de Vries ALC, Bouman MB. Timing of Puberty Suppression and Surgical Options for Transgender Youth. *Pediatrics*. 2020;146(5)doi:10.1542/peds.2019-3653 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106340

124. Van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *J Adolesc Health*. 2020;66(6):699-704.

doi:10.1016/j.jadohealth.2019.12.018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32273193

125. Vehmas N, Holopainen E, Suomalainen L, Savolainen-Peltonen H. Somatic Health and Psychosocial Background Among Finnish Adolescents with Gender Dysphoria Seeking Hormonal Interventions. *Transgend Health*. 2022;7(6):505-513. doi:10.1089/trgh.2021.0084 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644116

126. Vrouenraets LJJJ, de Vries ALC, de Vries MC, van der Miesen AIR, Hein IM. Assessing Medical Decision-Making Competence in Transgender Youth. *Pediatrics*. 2021;148(6)doi:10.1542/peds.2020-049643 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_2020049643.pdf

127. Willemsen LA, Boogers LS, Wiepjes CM, et al. Just as Tall on Testosterone; a Neutral to Positive Effect on Adult Height of GnRHa and Testosterone in Trans Boys. *The Journal of clinical endocrinology and metabolism*. 2023;108(2):414-421. doi:10.1210/clinem/dgac571 Accessed September 15, 2023. Available at https://watermark.silverchair.com/dgac571.pdf

128. Maru J, Millington K, Carswell J. Greater Than Expected Prevalence of Type 1 Diabetes Mellitus Found in an Urban Gender Program. *Transgend Health*. 2021;6(1):57-60. doi:10.1089/trgh.2020.0027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644323

129. Beking T, Burke SM, Geuze RH, et al. Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. *Psychoneuroendocrinology*. 2020;111:104461. doi:10.1016/j.psyneuen.2019.104461 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31630051

130. Burke SM, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Klink DT, Bakker J. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. *J Psychiatry Neurosci*. 2016;41(6):395-404. doi:10.1503/jpn.150147 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27070350

131. Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. *J Clin Endocrinol Metab*. 2020;105(3):e704-714. doi:10.1210/clinem/dgz029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31544944

132. Alvares LAM, Santos MR, Souza FR, et al. Cardiopulmonary capacity and muscle strength in transgender women on long-term gender-affirming hormone therapy: a cross-sectional study. *Br J Sports Med*. 2022;56(22):1292-1298. doi:10.1136/bjsports-2021-105400 Accessed September 15, 2023. Available at https://bjsm.bmj.com/content/bjsports/56/22/1292.full.pdf

133. Burke SM, Bakker J. The Role of Pubertal Hormones in the Development of Gender Identity: fMRI Studies. In: Bourguignon J-P, Carel J-C, Christen Y, eds. *Research and Perspectives in Endocrine Interactions*. Springer Cham; 2015:29-43:chap 3. Accessed May 17, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L601349832&from=export

134. Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists. *Transgend Health*. 2021;6(2):111-119. doi:10.1089/trgh.2020.0029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33937527

135. Arnoldussen M, van der Miesen AIR, Elzinga WS, et al. Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT health*. 2022;9(4):238-246. doi:10.1089/lgbt.2020.0494 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/pdf/10.1089/lgbt.2020.0494?download=true

136. Jarin J, Pine-Twaddell E, Trotman G, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. *Pediatrics*. 2017;139(5)doi:10.1542/peds.2016-3173 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28557738

137. Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab*. 2019;32(10):1077-1081. doi:10.1515/jpem-2019-0046 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31472062

138. Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nord J Psychiatry*. 2020;74(3):213-219. doi:10.1080/08039488.2019.1691260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31762394

139. Klaver M, de Mutsert R, van der Loos M, et al. Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. *Pediatrics*. 2020;145(3)doi:10.1542/peds.2019-0741 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32102929

140. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;100(2):E270-275. doi:10.1210/jc.2014-2439 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25427144

141. Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*. 2020;145(4)doi:10.1542/peds.2019-3006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32220906

142. Lavender R, Shaw S, Maninger JK, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. *LGBT Health*. 2023, 10.1089/lgbt.2022.0201doi:10.1089/lgbt.2022.0201 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36989498

143. Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. *J Adolesc Health*. 2018;62(4):397-401. doi:10.1016/j.jadohealth.2017.08.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29056436

144. Perl L, Segev-Becker A, Israeli G, Elkon-Tamir E, Oren A. Blood Pressure Dynamics After Pubertal Suppression with Gonadotropin-Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents: A Pilot Study. *LGBT Health*. 2020;7(6):340-344. doi:10.1089/lgbt.2020.0026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32735503

145. Perl L, Elkon-Tamir E, Segev-Becker A, Israeli G, Brener A, Oren A. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab*. 2021;34(6):741-745. doi:10.1515/jpem-2021-0172 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33823098

146. Roy MK, Wilkerson RB, Alexander K, Nokoff NJ, Cree-Green M, D'Alessandro A. Longitudinal metabolic study of red blood cells from patients undergoing gender-affirming testosterone therapy. *Blood Adv*. 2023;7(16):4269-4277. doi:10.1182/bloodadvances.2022008061 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36001490

147. Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. *J Sex Med*. 2018;15(9):1357-1363. doi:10.1016/j.jsxm.2018.07.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30224022

148. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. *J Sex Med*. 2016;13(7):1125-1132. doi:10.1016/j.jsxm.2016.05.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27318023

149. Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J Sex Med*. 2019;16(9):1459-1468. doi:10.1016/j.jsxm.2019.06.014 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31405768

150. Tack LJW, Heyse R, Craen M, et al. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. *J Sex Med*. 2017;14(5):747-757. doi:10.1016/j.jsxm.2017.03.251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28499525

151. Evans SR. Clinical trial structures. *J Exp Stroke Transl Med*. 2010;3(1):8-18. doi:10.6030/1939-067x-3.1.8 https://www.ncbi.nlm.nih.gov/pubmed/21423788

152. Agrawal S, Arora S, Amiri-Kordestani L, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. *JAMA Oncol*. 2023;9(2):266-272. doi:10.1001/jamaoncol.2022.5985 https://www.ncbi.nlm.nih.gov/pubmed/36580315

153. ZOLGENSMA (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion. Prescribing information. Novartis Gene Therapies; 2023. Accessed September 25, 2023. Available at https://www.zolgensma-hcp.com/

154. USPATH and WPATH Confirm Gender-Affirming Health Care is Not Experimental; Condemns Legislation Asserting Otherwise. Position statement. www.WPATH.org. March 22, 2023. Accessed September 25, 2023. Available at https://www.wpath.org/policies

155. Czopek M. Is all gender-affirming care for children "experimental"? Experts say no. Politifact.com. 2023. Last Updated January 17. Accessed September 25, 2023. Available at https://www.politifact.com/factchecks/2023/jan/17/instagram-posts/is-all-gender-affirming-care-for-children-experime/

156. Santoro H. Gender-affirming care for trans youth: Separating medical facts from misinformation. CBSnews.com. 2023. Last Updated June 28. Accessed September 25, 2023. Available at https://www.cbsnews.com/news/trans-youth-gender-affirming-health-care-misinformation/

157. Twohey M, Jewett C. They Paused Puberty, but Is There a Cost? *The New York Times*. November 14, 2022. Accessed September 25, 2023. Available at https://www.nytimes.com/2022/11/14/health/puberty-blockers-transgender.html

158. Siddique H. High court ruling on puberty blockers 'based on partisan evidence'. *The Guardian*. June 23, 2021. Accessed September 25, 2023. Available at https://www.theguardian.com/society/2021/jun/23/high-court-ruling-on-puberty-blockers-based-on-partisan-evidence

159. National Library of Medicine (NLM). ClinicalTrials.gov. ClinicalTrials.gov; 2000. Last Updated September 23, 2023. Accessed September 23, 2023. Available at https://clinicaltrials.gov

160. BioMed Central Ltd. Brain development, brain functioning, growth and metabolic aspects in the clinical management of transsexual adolescents. ISRCTN81574253. www.isrctn.com; 2000. Last Updated June 8, 2021. Accessed September 25, 2023. Available at https://www.isrctn.com/ISRCTN81574253

161. Kuper LE, Adams N, Mustanski BS. Exploring Cross-Sectional Predictors of Suicide Ideation, Attempt, and Risk in a Large Online Sample of Transgender and Gender Nonconforming Youth and Young Adults. *LGBT Health*. 2018;5(7):391-400. doi:10.1089/lgbt.2017.0259 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30280981

162. Olson-Kennedy J, Chan Y-M, Garofalo R, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. *JMIR research protocols*. 2019;8(7):e14434. doi:10.2196/14434 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31290407

163. Barnard EP, Dhar CP, Rothenberg SS, et al. Fertility Preservation Outcomes in Adolescent and Young Adult Feminizing Transgender Patients. *Pediatrics*. 2019;144(3)doi:10.1542/peds.2018-3943 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31383814

164. Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav*. 2020;49(7):2611-2618. doi:10.1007/s10508-020-01660-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32152785

165. Butler G, Adu-Gyamfi K, Clarkson K, et al. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child*.

2022;107(11):1018-1022. doi:10.1136/archdischild-2022-324302 Accessed September 15, 2023. Available at https://adc.bmj.com/content/107/11/1018

166. Clark BA, Marshall SK, Saewyc EM. Hormone therapy decision-making processes: Transgender youth and parents. *J Adolesc*. 2020;79:136-147. doi:10.1016/j.adolescence.2019.12.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31972534

167. Cohen A, Gomez-Lobo V, Willing L, et al. Shifts in Gender-Related Medical Requests by Transgender and Gender-Diverse Adolescents. *J Adolesc Health*. 2023;72(3):428-436. doi:10.1016/j.jadohealth.2022.10.020 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36529618

168. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011;40(4):843-847. doi:10.1007/s10508-011-9758-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21503817

169. Expösito-Campos P, Gomez-Balaguer M, Hurtado-Murillo F, Garcia-Moreno RM, Morillas-Arino C. Medical detransition following transgender identity reaffirmation: two case reports. *Sex Health*. 2022;18(6):498-501. doi:10.1071/SH21089 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34883041

170. Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child*. 2022;107(11):1012-1017. doi:10.1136/archdischild-2022-324283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35902230

171. McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr*. 2021;180(9):2969-2976. doi:10.1007/s00431-021-04075-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33855617

172. Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. *J Sex Med*. 2021;18(3):632-645. doi:10.1016/j.jsxm.2020.12.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33642235

173. Nos AL, Klein DA, Adirim TA, et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. *JAMA Netw Open*. 2022;5(11):e2239758. doi:10.1001/jamanetworkopen.2022.39758 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36318207

174. O'Bryan J, Leon K, Wolf-Gould C, Scribani M, Tallman N, Gadomski A. Building a Pediatric Patient Registry to Study Health Outcomes Among Transgender and Gender Expansive Youth at a Rural Gender Clinic. *Transgend Health*. 2018;3(1):179-189. doi:10.1089/trgh.2018.0023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30581991

175. Olson KR, Durwood L, Horton R, Gallagher NM, Devor A. Gender Identity 5 Years After Social Transition. *Pediatrics*. 2022;150(2)doi:10.1542/peds.2021-056082 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35505568

176. Pullen Sansfaçon A, Temple-Newhook J, Suerich-Gulick F, et al. The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. *Int J Transgend*. 2019;20(4):371-387. doi:10.1080/15532739.2019.1652129 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999623

177. Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. *Front Psychiatry*. 2021;12:632784. doi:10.3389/fpsyt.2021.632784 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33854450

178. Turban JL, Carswell J, Keuroghlian AS. Understanding Pediatric Patients Who Discontinue Gender-Affirming Hormonal Interventions. *JAMA Pediatr*. 2018;172(10):903-904. doi:10.1001/jamapediatrics.2018.1817 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30178056

179. Vrouenraets LJJJ, de Vries MC, Hein IM, Arnoldussen M, Hannema SE, de Vries ALC. Perceptions on the function of puberty suppression of transgender adolescents who continued or discontinued treatment, their parents, and clinicians. *International journal of transgender health*. 2022;23(4):428-441. doi:10.1080/26895269.2021.1974324 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9621271/pdf/WIJT_23_1974324.pdf

180. US Food and Drug Administration. Goserelin: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

181. US Food and Drug Administration. Goserelin (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated January 24, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

182. US Food and Drug Administration. Histrelin Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

183. US Food and Drug Administration. Histrelin (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2022. Last Updated November 22, 2022. Accessed March 31, 2023. Available at http://online.lexi.com

184. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 019836 - Supprelin (Histrelin acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 4, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019836#3264

185. US Food and Drug Administration. Medroxyprogesterone Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

186. US Food and Drug Administration. Dutasteride (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 29, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

187. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 019010 - Lupron (Leuprolide acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 5, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019010#2808

188. US Food and Drug Administration. Nafarelin Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

189. US Food and Drug Administration. Nafarelin (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 9, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

190. US Food and Drug Administration. Triptorelin Pamoate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 17, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

191. US Food and Drug Administration. Triptorelin (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 22, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

192. US Food and Drug Administration. Cetrorelix (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 1, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

193. US Food and Drug Administration. Cetrorelix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

194. US Food and Drug Administration. Degarelix (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2022. Last Updated April 21, 2022. Accessed April 12, 2023. Available at http://online.lexi.com

195. US Food and Drug Administration. Degarelix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 24, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

196. US Food and Drug Administration. Elagolix (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 5, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

197. US Food and Drug Administration. Elagolix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated April 5, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

198. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 210450 - Orilissa (Elagolix Sodium). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=210450#36002

199. US Food and Drug Administration. Ganirelix (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 8, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

200. US Food and Drug Administration. Ganirelix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

201. US Food and Drug Administration. Relugolix (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 10, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

202. US Food and Drug Administration. Relugolix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated April 6, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

203. US Food and Drug Administration. Bicalutamide: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

204. US Food and Drug Administration. Bicalutamide (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 21, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

205. US Food and Drug Administration. Dutasteride: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

206. US Food and Drug Administration. Finasteride: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

207. US Food and Drug Administration. Finasteride (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 25, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

208. US Food and Drug Administration. Flutamide: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

209. US Food and Drug Administration. Flutamide (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

210. US Food and Drug Administration. Nilutamide: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

211. US Food and Drug Administration. Nilutamide (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2022. Last Updated June 13, 2022. Accessed March 31, 2023. Available at http://online.lexi.com

212. US Food and Drug Administration. Spironolactone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

213. US Food and Drug Administration. Spironolactone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 25, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

214. US Food and Drug Administration. Conjugated Estrogens: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

215. US Food and Drug Administration. Estrogens (Conjugated/Equine, Systemic) (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated January 24, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

216. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 004782 - Premarin (Estrogens, conjugated). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=004782#20144

217. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020216 - Premarin (Estrogens, conjugated). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020216#21253

218. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 010402 - Premarin (Estrogens, conjugated). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=010402#20213

219. US Food and Drug Administration. Estrogens (Esterified) (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated January 24, 2023. Accessed April 14, 2023. Available at http://online.lexi.com

220. US Food and Drug Administration. Esterified Estrogens: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 1, 2023. Accessed April 14, 2023. Available at https://www.micromedexsolutions.com

221. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084951 - Menest (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084951#28361

222. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083266 - Amnestrogen (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083266#13233

223. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084948 - Menest (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084948#28358

224. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083414 - Esterified Estrogens (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083414#13291

225. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083209 - Estratab (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083209#13205

226. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084215 - Evex (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084215#13609

227. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085076 - Femogen (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085076#14018

228. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084950 - Menest (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084950#28360

229. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083765 - Esterified Estrogens (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083765#13441

230. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085302 - Esterified Estrogens (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085302#14147

231. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083856 - Estratab (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083856#13479

232. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083376 - Evex (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083376#13278

233. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085008 - Femogen (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085008#13981

234. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084949 - Menest (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084949#28359

235. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085907 - Esterified Estrogens (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023.

Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085907#14459

236. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083857 - Estratab (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083857#13480

237. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 086715 - Estratab (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=086715#14780

238. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085007 - Femogen (Estrogens, Esterified). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085007#13980

239. US Food and Drug Administration. Estradiol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

240. US Food and Drug Administration. Estradiol (Systemic) (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

241. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084499 - Estrace (Estradiol). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 5, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084499#13705

242. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084500 - Estrace (Estradiol). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 5, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084500#13706

243. US Food and Drug Administration. Estradiol Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

244. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021367 - Femring (Estradiol acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021367#22033

245. US Food and Drug Administration. Estradiol Cypionate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

246. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085470 - Depo-Estradiol (Estradiol cypionate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085470#28314

247. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085620 - Estradiol cypionate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085620#14257

248. US Food and Drug Administration. Estradiol Valerate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

249. US Food and Drug Administration. Estradiol Valerate and Estradiol Valerate/Dienogest: FDA Uses, Non-FDA Uses, and Contraindications (Quick Answers). MicromedexSolutions.com; 2023. Last Updated April 5, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

250. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 009402 - Delestrogen (Estradiol valerate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=009402#20179

251. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083547 - Estradiol valerate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083547#13296

252. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083714 - Estradiol valerate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083714#13375

253. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083546 - Estradiol valerate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083546#13295

254. US Food and Drug Administration. Testosterone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

255. US Food and Drug Administration. Testosterone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 22, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

256. US Food and Drug Administration. Testosterone Cypionate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

257. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085635 - Depo-Testosterone (Testosterone cypionate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085635#28344

258. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084401 - Testosterone cypionate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084401#13669

259. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 086030 - Testosterone cypionate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=086030#28365

260. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 086029 - Testosterone cypionate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=086029#14507

261. US Food and Drug Administration. Testosterone Enanthate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

262. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083667 - Testosterone enanthate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083667#13376

263. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085599 - Testosterone enanthate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085599#14264

264. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085598 - Testosterone enanthate. AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085598#28343

265. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 009165 - Delatestryl (Testosterone enanthate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=009165#644

266. US Food and Drug Administration. Testosterone Undecanoate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

267. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 022219 - Aveed (Testosterone undecanoate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022219#31009

268. US Food and Drug Administration. Drospirenone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

269. US Food and Drug Administration. Drospirenone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

270. US Food and Drug Administration. Etonogestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

271. US Food and Drug Administration. Etonogestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

272. US Food and Drug Administration. Levonorgestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

273. US Food and Drug Administration. Levonorgestrel (IUD) (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date.

Lexicomp.com; 2023. Last Updated February 27, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

274. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 019897 - Norplant (Levonorgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019897#3323

275. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020088 - Norplant System in Plastic Container (Levonorgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020088#3423

276. US Food and Drug Administration. Norethindrone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

277. US Food and Drug Administration. Norethindrone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

278. US Food and Drug Administration. Norethindrone Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

279. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 012184 - Norlutate (Norethindrone acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=012184#1184

280. US Food and Drug Administration. Progesterone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

281. US Food and Drug Administration. Progesterone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

282. US Food and Drug Administration. Conjugated Estrogens/Medroxyprogesterone Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

283. US Food and Drug Administration. Estrogens (Conjugated/Equine) and Medroxyprogesterone (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions

(Contraindications). Lexicomp.com; 2023. Last Updated April 4, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

284. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020303 - Prempro (Premarin; Cycrin) (Estrogens, Conjugated; Medroxyprogesterone Acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020303#3621

285. US Food and Drug Administration. Drospirenone/Estradiol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

286. US Food and Drug Administration. Drospirenone and Estradiol (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated February 15, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

287. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021355 - Angeliq (Drospirenone; Estradiol). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021355#22081

288. US Food and Drug Administration. Estradiol and Levonorgestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated February 24, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

289. US Food and Drug Administration. Estradiol/Levonorgestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

290. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021258 - Climara Pro (Estradiol; Levonorgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021258#21962

291. US Food and Drug Administration. Estradiol/Norethindrone Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

292. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020870 - Combipatch (Estradiol; Norethindrone acetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020870#21712

293. US Food and Drug Administration. Estradiol/Norgestimate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

294. US Food and Drug Administration. Estradiol and Norgestimate (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated February 15, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

295. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021040 - Prefest (Estradiol; Norgestimate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021040#4091

296. US Food and Drug Administration. Estradiol/Progesterone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 28, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

297. US Food and Drug Administration. Estradiol and Progesterone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated February 15, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

298. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 210132 - Bijuva (Estradiol; Progesterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=210132#19751

299. US Food and Drug Administration. Elagolix, Estradiol, and Norethindrone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 5, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

300. US Food and Drug Administration. Elagolix/Estradiol/Norethindrone Acetate and Elagolix: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated April 5, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

301. US Food and Drug Administration. Relugolix, Estradiol, and Norethindrone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 2, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

302. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 022252 - Natazia (Dienogest; Estradiol Valerate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 13, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022252#22645

303. US Food and Drug Administration. Desogestrel/Ethinyl Estradiol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

304. US Food and Drug Administration. Ethinyl Estradiol and Desogestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

305. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020071 - Desogen (Desogestrel; Ethinyl estradiol). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020071#3396

306. US Food and Drug Administration. Drospirenone/Ethinyl Estradiol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

307. US Food and Drug Administration. Ethinyl Estradiol and Drospirenone (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

308. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021098 - Yasmin (Drospirenone; Ethinyl estradiol). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021098#21773

309. US Food and Drug Administration. Ethinyl Estradiol/Ethynodiol Diacetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

310. US Food and Drug Administration. Ethinyl Estradiol and Ethynodiol Diacetate (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

311. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 018168 - Demulen 1/35-21 (Ethinyl estradiol; Ethynodiol diacetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=018168#2278

312. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 018160 - Demulen 1/35-28 (Ethinyl estradiol; Ethynodiol diacetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7,

2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=018160#2272

313. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 016927 - Demulen 1/50-21 (Ethinyl estradiol; Ethynodiol diacetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=016927#1682

314. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 016936 - Demulen 1/50-28 (Ethinyl estradiol; Ethynodiol diacetate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=016936#1686

315. US Food and Drug Administration. Ethinyl Estradiol/Etonogestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

316. US Food and Drug Administration. Ethinyl Estradiol and Etonogestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

317. US Food and Drug Administration. Ethinyl Estradiol/Levonorgestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

318. US Food and Drug Administration. Ethinyl Estradiol and Levonorgestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 22, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

319. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 018668 - Nordette-21 (Ethinyl estradiol; Levonorgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=018668#2555

320. US Food and Drug Administration. Ethinyl Estradiol/Norethindrone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

321. US Food and Drug Administration. Ethinyl Estradiol and Norethindrone (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications).

Lexicomp.com; 2023. Last Updated March 31, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

322. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017716 - Ovcon-35 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017716#2040

323. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 018127 - Ovcon-35 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=018127#2246

324. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017743 - Brevicon 28-Day (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017743#2049

325. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017735 - Modicon 28 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017735#2044

326. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017488 - Modicon 21 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017488#1881

327. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017565 - Norinyl 1+35 21-Day (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017565#1959

328. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017919 - Ortho-Novum 1/35-28 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017919#2120

329. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017489 - Ortho-Novum 1/35-21 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017489#1882

330. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 018128 - Ovcon-50 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=018128#2247

331. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017566 - Brevicon 21-Day (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017566#1961

332. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017576 - Ovcon-50 (Ethinyl estradiol; Norethindrone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017576#1967

333. US Food and Drug Administration. Ethinyl Estradiol/Norelgestromin: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

334. US Food and Drug Administration. Ethinyl Estradiol and Norelgestromin (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

335. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 021180 - Ortho Evra (Ethinyl estradiol; Norelgestromin). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021180#4116

336. US Food and Drug Administration. Ethinyl Estradiol/Norgestimate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

337. US Food and Drug Administration. Ethinyl Estradiol and Norgestimate (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

338. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 019653 - Ortho Cyclen-21 (Ethinyl estradiol; Norgestimate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019653#3130

339. US Food and Drug Administration. Ethinyl Estradiol/Norgestrel: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

340. US Food and Drug Administration. Ethinyl Estradiol and Norgestrel (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

341. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017612 - Lo/Ovral (Ethinyl estradiol; Norgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017612#1991

342. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 017802 - Lo/Ovral-28 (Ethinyl estradiol; Norgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017802#2090

343. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 016672 - Ovral (Ethinyl estradiol; Norgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=016672#1564

344. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 016806 - Ovral-28 (Ethinyl estradiol; Norgestrel). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=016806#1626

345. US Food and Drug Administration. Segesterone Acetate/Ethinyl Estradiol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

346. US Food and Drug Administration. Segesterone Acetate and Ethinyl Estradiol (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

347. US Food and Drug Administration. Drospirenone/Ethinyl Estradiol/Levomefolate Calcium and Levomefolate Calcium: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 13, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

348. US Food and Drug Administration. Ethinyl Estradiol, Drospirenone, and Levomefolate (Lexi-Drugs): Uses (Labeled Indications and Off-label) and Warnings & Precautions (Contraindications). Lexicomp.com; 2023. Last Updated March 20, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

349. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 022532 - Beyaz (Drospirenone; Ethinyl estradiol; Levomefolate calcium). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 7, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022532#22752

350. US Food and Drug Administration. Anastrozole: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

351. US Food and Drug Administration. Anastrozole (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 12, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

352. US Food and Drug Administration. Exemestane (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated January 7, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

353. US Food and Drug Administration. Exemestane: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

354. US Food and Drug Administration. Letrozole: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

355. US Food and Drug Administration. Letrozole (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 4, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

356. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 020726 - Femara (Letrozole). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020726#21608

357. US Food and Drug Administration. Conjugated Estrogens/Bazedoxifene Acetate: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 1, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

358. US Food and Drug Administration. Clomiphene (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 4, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

359. US Food and Drug Administration. Clomiphene: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2022. Last Updated October 26, 2022. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

360. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 016131 - Clomid (Clomiphene Citrate). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=016131#1579

361. US Food and Drug Administration. Ospemifene (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 8, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

362. US Food and Drug Administration. Ospemifene: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

363. US Food and Drug Administration. Raloxifene (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 6, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

364. US Food and Drug Administration. Raloxifene: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

365. US Food and Drug Administration. Tamoxifen (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 8, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

366. US Food and Drug Administration. Tamoxifen: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 29, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

367. US Food and Drug Administration. Toremifene (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated February 26, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

368. US Food and Drug Administration. Toremifene: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

369. US Food and Drug Administration. Danazol: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 27, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

370. US Food and Drug Administration. Danazol (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 12, 2023. Accessed April 12, 2023. Available at http://online.lexi.com

371. US Food and Drug Administration. Methyltestosterone: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed April 12, 2023. Available at https://www.micromedexsolutions.com

372. US Food and Drug Administration. Methyltestosterone (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2022. Last Updated November 23, 2022. Accessed April 12, 2023. Available at http://online.lexi.com

373. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084967 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084967#14055

374. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083976 - Testred (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083976#13622

375. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080214 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080214#12721

376. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080767 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080767#28269

377. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 086450 - Android 10 (Methyltestosterone).

AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=086450#14796

378. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080839 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080839#13064

379. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084312 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084312#13746

380. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084244 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084244#13721

381. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080309 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080309#12760

382. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080313 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080313#12762

383. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080933 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080933#13103

384. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084331 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084331#13760

385. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 003158 - Oreton Methyl (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=003158#335

386. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 087147 - Android 25 (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=087147#28449

387. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084310 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084310#13745

388. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084241 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084241#13719

389. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085270 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085270#14226

390. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080931 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080931#13101

391. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084642 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084642#13911

392. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 087222 - Android 5 (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=087222#15082

393. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080281 - Oreton (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080281#12748

394. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for NDA 003240 - Metandren (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=003240#339

395. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 083836 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=083836#13570

396. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080256 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080256#12737

397. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 084287 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=084287#13738

398. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080308 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080308#12759

399. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080475 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080475#12891

400. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 085125 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=085125#14146

401. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080271 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080271#12743

402. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations; Product Details for ANDA 080973 - Methyltestosterone (Methyltestosterone). AccessData.FDA.gov; 2023. Last Updated April 2023. Accessed April 14, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=080973#13124

403. US Food and Drug Administration. Minoxidil: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated March 7, 2023. Accessed March 31, 2023. Available at https://www.micromedexsolutions.com

404. US Food and Drug Administration. Minoxidil (Systemic) (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated March 21, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

405. US Food and Drug Administration. Minoxidil (Topical) (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated January 13, 2023. Accessed March 31, 2023. Available at http://online.lexi.com

406. US Food and Drug Administration. Ulipristal (Lexi-Drugs): Uses (Labeled Indications and Off-label), Warnings & Precautions (Contraindications), and FDA Approval Date. Lexicomp.com; 2023. Last Updated April 4, 2023. Accessed April 13, 2023. Available at http://online.lexi.com

407. US Food and Drug Administration. Ulipristal: FDA Uses, Non-FDA Uses, and Contraindications (In-Depth Answers). MicromedexSolutions.com; 2023. Last Updated April 5, 2023. Accessed April 13, 2023. Available at https://www.micromedexsolutions.com

408. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC428525/pdf/bmj32801490.pdf

409. Swiglo BA, Murad MH, Schünemann HJ, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;93(3):666-673. doi:10.1210/jc.2007-1907 Accessed June 28, 2023. Available at https://core.ac.uk/download/18255942.pdf

410. Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). www.SBU.se. 2023. Last Updated September 1. Accessed September 7, 2023. Available at https://www.sbu.se/en/ongoing-projects/

411. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. Appendix 1. Search strategies (supplementary material). *A systematic review of hormone treatment for children with gender dysphoria and recommendations for research*. Swedish Agency for Health Technology Assessment and Assessment of Social Services; 2023:23. Accessed September 7, 2023. Available at https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-1-litteratursokning.pdf

412. Siddaway AP, Wood AM, Hedges LV. How to Do a Systematic Review: A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses. *Annu Rev Psychol*. 2019;70:747-770. doi:10.1146/annurev-psych-010418-102803 https://www.ncbi.nlm.nih.gov/pubmed/30089228

413. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi:10.1136/bmj.i4919 https://www.ncbi.nlm.nih.gov/pubmed/27733354

414. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;164(4):635-642. doi:10.1530/EJE-10-1038 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21266549

415. Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism*. 1989;38(9):869-873. doi:10.1016/0026-0495(89)90233-3 https://www.ncbi.nlm.nih.gov/pubmed/2528051

416. Auer MK, Ebert T, Pietzner M, et al. Effects of Sex Hormone Treatment on the Metabolic Syndrome in Transgender Individuals: Focus on Metabolic Cytokines. *J Clin Endocrinol Metab*. 2018;103(2):790-802. doi:10.1210/jc.2017-01559 https://www.ncbi.nlm.nih.gov/pubmed/29216353

417. Ghent University Hospital. A European Network for the Investigation of Gender Incongruence (ENIGI). NCT01072825. ClinicalTrials.gov; 2022. Last Updated December 9, 2022. Accessed September 16, 2023. Available at https://clinicaltrials.gov/study/NCT01072825

418. Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018;141(5)doi:10.1542/peds.2017-3845 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29661941

419. Bultynck C, Pas C, Defreyne J, Cosyns M, den Heijer M, T'Sjoen G. Self-perception of voice in transgender persons during cross-sex hormone therapy. *Laryngoscope*. 2017;127(12):2796-2804. doi:10.1002/lary.26716 https://www.ncbi.nlm.nih.gov/pubmed/28730692

420. Costantino A, Cerpolini S, Alvisi S, Morselli PG, Venturoli S, Meriggiola MC. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;39(4):321-335. doi:10.1080/0092623X.2012.736920 https://www.ncbi.nlm.nih.gov/pubmed/23470169

421. Defreyne J, T'Sjoen G, Bouman WP, Brewin N, Arcelus J. Prospective Evaluation of Self-Reported Aggression in Transgender Persons. *J Sex Med*. 2018;15(5):768-776. doi:10.1016/j.jsxm.2018.03.079 https://www.ncbi.nlm.nih.gov/pubmed/29699761

422. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology*. 2006;155(suppl_1)(1):S131-S137. doi:10.1530/eje.1.02231 Accessed June 1, 2023. Available at https://eje.bioscientifica.com/view/journals/eje/155/suppl_1/1550131.xml

423. Fisher AD, Castellini G, Ristori J, et al. Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data. *J Clin Endocrinol Metab*. 2016;101(11):4260-4269. doi:10.1210/jc.2016-1276 https://www.ncbi.nlm.nih.gov/pubmed/27700538

424. Fisher AD, Ristori J, Castellini G, et al. Psychological characteristics of Italian gender dysphoric adolescents: a case-control study. *J Endocrinol Invest*. 2017;40(9):953-965. doi:10.1007/s40618-017-0647-5 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28357782

425. Fuss J, Hellweg R, Van Caenegem E, et al. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). *Eur Neuropsychopharmacol*. 2015;25(1):95-99. doi:10.1016/j.euroneuro.2014.11.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25498415

426. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016;85(2):239-246. doi:10.1111/cen.13050 https://www.ncbi.nlm.nih.gov/pubmed/26932202

427. Gava G, Mancini I, Cerpolini S, Baldassarre M, Seracchioli R, Meriggiola MC. Testosterone undecanoate and testosterone enanthate injections are both effective and safe in transmen over 5 years of administration. *Clin Endocrinol (Oxf)*. 2018;89(6):878-886. doi:10.1111/cen.13821 https://www.ncbi.nlm.nih.gov/pubmed/30025172

428. Giovanardi G, Morales P, Mirabella M, et al. Transition memories: experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. *J Endocrinol Invest*. 2019;42(10):1231-1240. doi:10.1007/s40618-019-01045-2 https://www.ncbi.nlm.nih.gov/pubmed/30953318

429. Gomez-Gil E, Zubiaurre-Elorza L, Esteva I, et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;37(5):662-670. doi:10.1016/j.psyneuen.2011.08.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21937168

430. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012;9(2):531-541. doi:10.1111/j.1743-6109.2011.02564.x https://www.ncbi.nlm.nih.gov/pubmed/22145968

431. Guss CE, Williams DN, Reisner SL, Austin SB, Katz-Wise SL. Disordered Weight Management Behaviors, Nonprescription Steroid Use, and Weight Perception in Transgender Youth. *J Adolesc Health*. 2017;60(1):17-22. doi:10.1016/j.jadohealth.2016.08.027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28029539

432. Hisle-Gorman E, Schvey NA, Adirim TA, et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. *J Sex Med*. 2021;18(8):1444-1454. doi:10.1016/j.jsxm.2021.05.014 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/18/8/1444/6956103?redirectedFrom=fulltext

433. Klink DT, Caris M, van Trotsenburg M, Rotteveel J. Bone mineral density in late adolescence of transsexuals treated with GnRH-analogues in their teens. *Endocr Rev*. 2013;34(Suppl 1):3. abstract. Accessed September 15, 2023. Available at https://www.bone-abstracts.org/ba/0002/ba0002p115

434. Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis*. 1980;168(11):693-697. doi:10.1097/00005053-198011000-00009 https://www.ncbi.nlm.nih.gov/pubmed/6255090

435. Lopez CM, Solomon D, Boulware SD, Christison-Lagay ER. Trends in the use of puberty blockers among transgender children in the United States. *J Pediatr Endocrinol Metab*. 2018;31(6):665-670. doi:10.1515/jpem-2018-0048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29715194

436. Manieri C, Castellano E, Crespi C, et al. Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an Italian Public Health Center. *International Journal of Transgenderism*. 2014;15(2):53-65. doi:10.1080/15532739.2014.899174 https://doi.org/10.1080/15532739.2014.899174

437. Metzger NY, Boettger S. The effect of testosterone therapy on personality traits of trans men: a controlled prospective study in Germany and Switzerland. *Psychiatry Res*. 2019;276:31-38. doi:10.1016/j.psychres.2019.03.053 https://www.ncbi.nlm.nih.gov/pubmed/30999214

438. Motta G, Crespi C, Mineccia V, Brustio PR, Manieri C, Lanfranco F. Does Testosterone Treatment Increase Anger Expression in a Population of Transgender Men? *J Sex Med*. 2018;15(1):94-101. doi:10.1016/j.jsxm.2017.11.004 https://www.ncbi.nlm.nih.gov/pubmed/29175227

439. Mueller A, Dittrich R, Binder H, et al. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. *Eur J Endocrinol*. 2005;153(1):107-113. doi:10.1530/eje.1.01943 https://www.ncbi.nlm.nih.gov/pubmed/15994752

440. Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men. *LGBT Health*. 2014;1(3):165-167. doi:10.1089/lgbt.2014.0018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26789709

441. Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;11(12):3002-3011. doi:10.1111/jsm.12698 https://www.ncbi.nlm.nih.gov/pubmed/25250780

442. Schneider MA, Spritzer PM, Soll BMB, et al. Brain Maturation, Cognition and Voice Pattern in a Gender Dysphoria Case under Pubertal Suppression. *Front Hum Neurosci*. 2017;11:528. doi:10.3389/fnhum.2017.00528 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29184488

443. Sequeira G, Miller E, McCauley H, Eckstrand K, Rofey D. Impact of Gender Expression on Disordered Eating, Body Dissatisfaction and BMI in a Cohort of Transgender Youth. *J Adolesc Health*. 2017;60(2)(Suppl 1):S87. Accessed September 31, 2023. Available at https://www.jahonline.org/article/S1054-139X(16)30748-0/fulltext

444. Shadid S, Abosi-Appeadu K, De Maertelaere AS, et al. Effects of Gender-Affirming Hormone Therapy on Insulin Sensitivity and Incretin Responses in Transgender People. *Diabetes Care*. 2020;43(2):411-417. doi:10.2337/dc19-1061 https://www.ncbi.nlm.nih.gov/pubmed/31740479

445. Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001;40(4):472-481. doi:10.1097/00004583-200104000-00017 https://www.ncbi.nlm.nih.gov/pubmed/11314574

446. Tack LJ, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ*. 2016;7:14. doi:10.1186/s13293-016-0067-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26885361

447. Tack LJW, Craen M, Lapauw B, et al. Proandrogenic and Antiandrogenic Progestins in Transgender Youth: Differential Effects on Body Composition and Bone Metabolism. *J Clin Endocrinol Metab*. 2018;103(6):2147-2156. doi:10.1210/jc.2017-02316 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29672753

448. Tankersley AP, Grafsky EL, Dike J, Jones RT. Risk and Resilience Factors for Mental Health among Transgender and Gender Nonconforming (TGNC) Youth: A Systematic Review. *Clin Child Fam Psychol Rev*. 2021;24(2):183-206. doi:10.1007/s10567-021-00344-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33594611

449. Trotman G, Orta L, Oler L, Casey R, Damie L, Gomez-Lobo V. Metabolic Profiles in a Transgender Adolescent Population Receiving Steroid Hormone Therapy: A Pilot Study. *J Pediatr Adolesc Gynecol*. 2014;27(2):E38. Accessed September 31, 2023. Available at https://www.jpagonline.org/article/S1083-3188(14)00042-4/fulltext

450. Turan S, Aksoy Poyraz C, Usta Saglam NG, et al. Alterations in Body Uneasiness, Eating Attitudes, and Psychopathology Before and After Cross-Sex Hormonal Treatment in Patients with Female-

to-Male Gender Dysphoria. *Arch Sex Behav*. 2018;47(8):2349-2361. doi:10.1007/s10508-018-1189-4 https://www.ncbi.nlm.nih.gov/pubmed/29594702

451. Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. *Arch Sex Behav*. 2016;45(7):1697-1703. doi:10.1007/s10508-016-0764-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27251640

452. Warrier V, Greenberg DM, Weir E, et al. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. *Nat Commun*. 2020;11(1):3959. doi:10.1038/s41467-020-17794-1 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32770077

453. Wierckx K, Van Caenegem E, Elaut E, et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;8(12):3379-3388. doi:10.1111/j.1743-6109.2011.02348.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21699661

454. Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol*. 2018;178(2):163-171. doi:10.1530/EJE-17-0496 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29183889

455. Chen D, Matson M, Macapagal K, et al. Attitudes Toward Fertility and Reproductive Health Among Transgender and Gender-Nonconforming Adolescents. *J Adolesc Health*. 2018;63(1):62-68. doi:10.1016/j.jadohealth.2017.11.306 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29503031

456. Lopez CM, Solomon D, Boulware SD, Christison-Lagay E. Trends in the "Off-Label" Use of GnRH Agonists Among Pediatric Patients in the United States. *Clin Pediatr (Phila)*. 2018;57(12):1432-1435. doi:10.1177/0009922818787260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30003804

457. Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. *J Clin Endocrinol Metab*. 2022;107(9):e3937-e3943. doi:10.1210/clinem/dgac251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35452119

458. Shaffer LR, McCormack E, Sawicki GS, Keller A, Jain R. Understanding the Intersection between Gender Transition and Health Outcomes in Cystic Fibrosis. *Ann Am Thorac Soc*. 2022;19(3):504-506. doi:10.1513/AnnalsATS.202105-535RL Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34469707

459. Nahata L, Chen D, Quinn GP, et al. Reproductive Attitudes and Behaviors Among Transgender/Nonbinary Adolescents. *J Adolesc Health*. 2020;66(3):372-374. doi:10.1016/j.jadohealth.2019.09.008 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(19)30451-3/fulltext

460. James HA, Chang AY, Imhof RL, et al. A community-based study of demographics, medical and psychiatric conditions, and gender dysphoria/incongruence treatment in transgender/gender

diverse individuals. *Biol Sex Differ*. 2020;11(1):55. doi:10.1186/s13293-020-00332-5 Accessed September 15, 2023. Available at https://bsd.biomedcentral.com/counter/pdf/10.1186/s13293-020-00332-5.pdf

461. Wagner S, Panagiotakopoulos L, Nash R, et al. Progression of Gender Dysphoria in Children and Adolescents: A Longitudinal Study. *Pediatrics*. 2021;148(1)doi:10.1542/peds.2020-027722 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34099504

462. Stevens J, Gomez-Lobo V, Pine-Twaddell E. Insurance Coverage of Puberty Blocker Therapies for Transgender Youth. *Pediatrics*. 2015;136(6):1029-1031. doi:10.1542/peds.2015-2849 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26527547

463. Penney SW, Jung JH, Ballantyne AJ, Parekh DS, Klein DA, Viola SA. Affirming Hormone Treatment for a Transgender Adolescent After a Venous Thromboembolic Event. *J Pediatr Hematol Oncol*. 2022;44(5):E892-E895. doi:10.1097/MPH.0000000000002442 Accessed September 15, 2023. Available at https://www.ingentaconnect.com/content/wk/jpho/2022/00000044/00000005/art00019

464. Van Donge N, Schvey NA, Roberts TA, Klein DA. Transgender Dependent Adolescents in the U.S. Military Health Care System: Demographics, Treatments Sought, and Health Care Service Utilization. *Mil Med*. 2019;184(5-6):e447-e454. doi:10.1093/milmed/usy264 Accessed September 15, 2023. Available at https://watermark.silverchair.com/usy264.pdf

465. Parks MA, Zwayne N, Temkit M. Bleeding Patterns among Adolescents Using the Levonorgestrel Intrauterine Device: A Single Institution Review. *J Pediatr Adolesc Gynecol*. 2020;33(5):555-558. doi:10.1016/j.jpag.2020.04.006 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(20)30223-0/fulltext

466. Khazal S, Abdel-Azim H, Kapoor N, Mahadeo KM. Overcoming psychosocial and developmental barriers to blood and marrow transplantation (BMT) in an adolescent/young adult (AYA) transgender patient with chronic myelogenous leukemia. *Pediatr Hematol Oncol*. 2014;31(8):765-767. doi:10.3109/08880018.2014.909914 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24854505

467. Krishna V, Lee SL, DeUgarte DA. Optimizing pediatric histrelin implantation to improve success rates in clinic without sedation. *J Pediatr Endocrinol Metab*. 2021;34(11):1443-1448. doi:10.1515/jpem-2021-0432 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34407329

468. Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in Referrals to a Pediatric Transgender Clinic. *Pediatrics*. 2019;144(5)doi:10.1542/peds.2019-1368 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31619510

469. Adeleye AJ, Stark BA, Jalalian L, Mok-Lin E, Smith JF. Evidence of Spermatogenesis in the Presence of Hypothalamic Suppression and Low Testosterone in an Adolescent Transgender Female: A Case Report. *Transgender Health*. 2023;8(1):104-107. doi:10.1089/trgh.2021.0034 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0034

470. Ni J, Chi C, Aye T. Review of implant gonadotrophin-releasing hormone agonist use: experience in a single academic center. *Horm Res Paediatr*. 2023, 10.1159/000529733doi:10.1159/000529733 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36791687

471. Alaniz VI, Sheeder JL, Whitmore GT, et al. Menstrual Suppression in Adolescent and Young Adult Transgender Males. *J Pediatr Adolesc Gynecol*. 2023;36(2):116-121. doi:10.1016/j.jpag.2022.10.007 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2021591277&from=export

472. Sayeem M, Carter B, Phulwani P, Zempsky WT. Gender Dysphoria and Chronic Pain in Youth. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2021-050128 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34561268

473. Morrison A, Olezeski C, Cron J, Kallen AN. A Pilot Study to Assess Attitudes Toward Future Fertility and Parenthood in Transgender and Gender Expansive Adolescents. *Transgender Health*. 2020;5(2):129-137. doi:10.1089/trgh.2019.0075 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L632152015&from=export

474. Schwartz BI, Effron A, Bear B, et al. Experiences with Menses in Transgender and Gender Nonbinary Adolescents. *J Pediatr Adolesc Gynecol*. 2022;35(4):450-456. doi:10.1016/j.jpag.2022.01.015 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(22)00037-7/fulltext

475. Schwartz BI, Bear B, Short VL, Kazak AE. Outcomes of Menstrual Management Use in Transgender and Gender-Diverse Adolescents. *Obstet Gynecol*. 2023;141(4):748-755. doi:10.1097/AOG.0000000000005123 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36897186

476. Schwartz BI, Bear B, Kazak AE. Menstrual Management Choices in Transgender and Gender Diverse Adolescents. *J Adolesc Health*. 2023;72(2):207-213. doi:10.1016/j.jadohealth.2022.09.023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36443161

477. Chu L, Gold S, Harris C, et al. Incidence and Factors Associated With Acne in Transgender Adolescents on Testosterone: A Retrospective Cohort Study. *Endocr Pract*. 2023;29(5):353-355. doi:10.1016/j.eprac.2023.02.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36889581

478. Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. *J Adolesc Health*. 2017;61(1):120-123. doi:10.1016/j.jadohealth.2017.01.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28363716

479. Chen D, Bernardi LA, Pavone ME, Feinberg EC, Moravek MB. Oocyte cryopreservation among transmasculine youth: a case series. *J Assist Reprod Genet*. 2018;35(11):2057-2061. doi:10.1007/s10815-018-1292-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30136015

480. Kyweluk MA, Sajwani A, Chen D. Freezing for the future: Transgender youth respond to medical fertility preservation. *International Journal of Transgenderism*. 2018;19(4):401-416. doi:10.1080/15532739.2018.1505575 Accessed September 15, 2023. Available at https://doi.org/10.1080/15532739.2018.1505575

481. Harris RM, Kolaitis IN, Frader JE. Ethical issues involving fertility preservation for transgender youth. *J Assist Reprod Genet*. 2020;37(10):2453-2462. doi:10.1007/s10815-020-01873-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550448/pdf/10815_2020_Article_1873.pdf

482. Daniolos PT, Telingator CJ. Engendering identity. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1245-1247. doi:10.1016/j.jaac.2013.09.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24290454

483. Razzak M. Pediatrics: evaluation and management of gender identity disorder--an American tale. *Nat Rev Urol*. 2012;9(4):175. doi:10.1038/nrurol.2012.36 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22410681

484. Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3):418-425. doi:10.1542/peds.2011-0907 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22351896

485. Shumer DE, Tishelman AC. The Role of Assent in the Treatment of Transgender Adolescents. *Int J Transgend*. 2015;16(2):97-102. doi:10.1080/15532739.2015.1075929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27175107

486. Shim JY, Laufer MR, Grimstad FW. Dysmenorrhea and Endometriosis in Transgender Adolescents. *J Pediatr Adolesc Gynecol*. 2020;33(5):524-528. doi:10.1016/j.jpag.2020.06.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32535219

487. Grimstad F, Moyer Q, Williams CR, Kremen J. A Body-Neutral and Gender-Neutral Modified Ferriman-Gallwey Diagram. *J Pediatr Adolesc Gynecol*. 2022;35(3):375-378. doi:10.1016/j.jpag.2021.10.015 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34748917

488. Millington K, Hayes K, Pilcher S, et al. A serous borderline ovarian tumour in a transgender male adolescent. *Br J Cancer*. 2021;124(3):567-569. doi:10.1038/s41416-020-01129-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106582

489. Garborcauskas G, McCabe E, Boskey ER, Grimstad FW. Family Building Perspectives of Assigned Female at Birth Transgender and Gender Diverse Adolescents Seeking Testosterone Gender-Affirming Hormone Therapy. *LGBT Health*. 2022;9(7):463-470. doi:10.1089/lgbt.2022.0004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35802494

490. Garborcauskas G, Boskey ER, Guss CE, Grimstad FW. Retrospective Review of Sexual and Reproductive Health Conversations During Initial Visits of Adolescents Seeking Gender-Affirming Testosterone. *J Pediatr Adolesc Gynecol*. 2023;36(1):25-32. doi:10.1016/j.jpag.2022.09.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36162722

491. Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. *Headache*. 2023;63(4):517-522. doi:10.1111/head.14493 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36988085

492. Insogna IG, Ginsburg E, Srouji S. Fertility Preservation for Adolescent Transgender Male Patients: A Case Series. *J Adolesc Health*. 2020;66(6):750-753. doi:10.1016/j.jadohealth.2019.12.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32001141

493. Fan EM, Gordner C, Luty J. Venous Thromboembolism in a Transgender Adolescent on Testosterone Therapy: A Case Report and Literature Review. *J Pediatr Hematol Oncol*. 2020;42(5):e352-e354. doi:10.1097/MPH.0000000000001755 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32079984

494. Warwick RM, Araya AC, Shumer DE, Selkie EM. Transgender Youths' Sexual Health and Education: A Qualitative Analysis. *J Pediatr Adolesc Gynecol*. 2022;35(2):138-146. doi:10.1016/j.jpag.2021.09.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34619356

495. Parikh N, Chattha A, Gargollo P, Granberg C. Fertility Preservation: A Tale of Two Testicles. *Urology*. 2021;153:298-300. doi:10.1016/j.urology.2020.11.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33221414

496. Lin AJ, Baranski T, Chaterjee D, Chapman W, Foltz G, Kim H. Androgen-receptor-positive hepatocellular carcinoma in a transgender teenager taking exogenous testosterone. *Lancet*. 2020;396(10245):198. doi:10.1016/S0140-6736(20)31538-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32682485

497. Komorowski AS, Fisher AR, Jungheim ES, Lewis CS, Omurtag KR. Fertility preservation discussions, referral and follow-up in male-to-female and female-to-male adolescent transgender patients. *Hum Fertil (Camb)*. 2021, 10.1080/14647273.2021.2015804:1-5. doi:10.1080/14647273.2021.2015804 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34915792

498. Martin CE, Lewis C, Omurtag K. Successful oocyte cryopreservation using letrozole as an adjunct to stimulation in a transgender adolescent after GnRH agonist suppression. *Fertil Steril*. 2021;116(2):522-527. doi:10.1016/j.fertnstert.2021.02.025 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33795140

499. Salvatore L, Dancyger I, Shadianloo S, Fornari V. Caring for Transgender Youth with Eating Disorders in a Day Treatment Program. *Adolesc Psychiatry*. 2022;12(3):196-206. doi:10.2174/2210676613666221027124554 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2018683391&from=export

500. Bentsianov S, Gordon L, Goldman A, Jacobs A, Steever J. Use of Copper Intrauterine Device in Transgender Male Adolescents. *Contraception*. 2018;98(1):74-75. doi:10.1016/j.contraception.2018.02.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29490287

501. Maxwell S, Noyes N, Keefe D, Berkeley AS, Goldman KN. Pregnancy Outcomes After Fertility Preservation in Transgender Men. *Obstet Gynecol*. 2017;129(6):1031-1034. doi:10.1097/AOG.0000000000002036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28486372

502. Wolf-Gould CS, Riley MR, Carswell JM. A Trans-Feminine Youth with a BRCA1 Mutation: Case Study. *LGBT health*. 2018;5(4):270-272. doi:10.1089/lgbt.2017.0148 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626215648&from=export

503. Lee G, Ferri-Huerta R, Greenberg KB, Somers KE. Acne fulminans in a transgender boy after an increase in testosterone dosage. *JAAD Case Rep*. 2022;21:32-34. doi:10.1016/j.jdcr.2021.11.029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35141385

504. Daley T, Grossoehme D, McGuire JK, Corathers S, Conard LA, Lipstein EA. "I Couldn't See a Downside": Decision-Making About Gender-Affirming Hormone Therapy. *J Adolesc Health*. 2019;65(2):274-279. doi:10.1016/j.jadohealth.2019.02.018 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31196783

505. Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. *Int J Transgend*. 2019;20(4):413-420. doi:10.1080/15532739.2019.1631929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999626

506. Nasomyont N, Meisman AR, Ecklund K, et al. Changes in Bone Marrow Adipose Tissue in Transgender and Gender Non-Conforming Youth Undergoing Pubertal Suppression: A Pilot Study. *J Clin Densitom*. 2022;25(4):485-489. doi:10.1016/j.jocd.2022.06.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36064698

507. Akgül S, Bonny AE, Ford N, Holland-Hall C, Chelvakumar G. Experiences of Gender Minority Youth With the Intrauterine System. *J Adolesc Health*. 2019;65(1):32-38. doi:10.1016/j.jadohealth.2018.11.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691940

508. Eisenberg L. Minor Patient, Major Decisions: Caring for a Rural Child With Gender Dysphoria. *Am J Bioeth*. 2019;19(7):64-65. doi:10.1080/15265161.2019.1619346 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31237514

509. Lawlis SM, Donkin HR, Bates JR, Britto MT, Conard LAE. Health Concerns of Transgender and Gender Nonconforming Youth and Their Parents Upon Presentation to a Transgender Clinic. *J Adolesc Health*. 2017;61(5):642-648. doi:10.1016/j.jadohealth.2017.05.025 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(17)30254-9/fulltext

510. Silverstein L, Zander E, Middleman AB. Adolescent identity: The importance of the social history. *SAGE Open Med Case Rep*. 2020;8:2050313X20952980. doi:10.1177/2050313X20952980 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32922796

511. Boris JR, McClain ZBR, Bernadzikowski T. Clinical Course of Transgender Adolescents with Complicated Postural Orthostatic Tachycardia Syndrome Undergoing Hormonal Therapy in Gender Transition: A Case Series. *Transgend Health*. 2019;4(1):331-334.

doi:10.1089/trgh.2019.0041 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31754630

512. Persky RW, Gruschow SM, Sinaii N, Carlson C, Ginsberg JP, Dowshen NL. Attitudes Toward Fertility Preservation Among Transgender Youth and Their Parents. *J Adolesc Health*. 2020;67(4):583-589. doi:10.1016/j.jadohealth.2020.02.027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32359942

513. Quain KM, Kyweluk MA, Sajwani A, et al. Timing and Delivery of Fertility Preservation Information to Transgender Adolescents, Young Adults, and Their Parents. *J Adolesc Health*. 2021;68(3):619-622. doi:10.1016/j.jadohealth.2020.06.044 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32826153

514. Hobson BJ, Lett E, Hawkins LA, Swendiman RA, Nance ML, Dowshen NL. Transgender Youth Experiences with Implantable GnRH Agonists for Puberty Suppression. *Transgend Health*. 2022;7(4):364-368. doi:10.1089/trgh.2021.0006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36033209

515. Stanley K, Cooper J. Hormone Therapy and Venous Thromboembolism in a Transgender Adolescent. *J Pediatr Hematol Oncol*. 2018;40(1):e38-e40. doi:10.1097/MPH.0000000000000984 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945660

516. Donaldson AA, Hall A, Neukirch J, et al. Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series. *Int J Eat Disord*. 2018;51(5):475-479. doi:10.1002/eat.22868 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29740834

517. Abu-Ghname A, Grome L, Raj S, Axelrad ME, Chapman SG. Health Care Services Utilization by Transgender Patients in a Medicaid Managed Program. *J Health Care Poor Underserved*. 2021;32(1):435-448. doi:10.1353/hpu.2021.0033 Accessed September 15, 2023. Available at https://muse.jhu.edu/article/783119

518. Lopez X, Stewart S, Jacobson-Dickman E. Approach to Children and Adolescents with Gender Dysphoria. *Pediatr Rev*. 2016;37(3):89-96; quiz 97-88. doi:10.1542/pir.2015-0032 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26933223

519. Dilday EA, Bukulmez O, Saner K, Lopez X, Jarin J. Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy. *Transgend Health*. 2022;7(6):528-532. doi:10.1089/trgh.2021.0037 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644123

520. Mejia-Otero JD, White P, Lopez X. Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth. *Transgend Health*. 2021;6(1):31-35. doi:10.1089/trgh.2020.0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33614957

521. Day DS, Saunders JJ, Matorin A. Gender Dysphoria and Suicidal Ideation: Clinical Observations from a Psychiatric Emergency Service. *Cureus*. 2019;11(11):e6132. doi:10.7759/cureus.6132

Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6903884/pdf/cureus-0011-00000006132.pdf

522. Barthel EM, Werny DM, Hayden LL, Salehi P. Gender Affirming Hormone Replacement for the Adolescent and Young Adult Cancer Survivor with Hypogonadism. *J Adolesc Young Adult Oncol*. 2020;9(1):128-131. doi:10.1089/jayao.2019.0070 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31580768

523. Kerman HM, Pham A, Crouch JM, et al. Gender Diverse Youth on Fertility and Future Family: A Qualitative Analysis. *J Adolesc Health*. 2021;68(6):1112-1120. doi:10.1016/j.jadohealth.2021.01.002 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(21)00004-5/fulltext

524. Pham A, Kasenic A, Hayden L, et al. A Case Series on Disordered Eating Among Transgender Youth With Autism Spectrum Disorder. *J Adolesc Health*. 2021;68(6):1215-1219. doi:10.1016/j.jadohealth.2020.12.143 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33707147

525. Strang JF, Jarin J, Call D, et al. Transgender Youth Fertility Attitudes Questionnaire: Measure Development in Nonautistic and Autistic Transgender Youth and Their Parents. *J Adolesc Health*. 2018;62(2):128-135. doi:10.1016/j.jadohealth.2017.07.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29033160

526. Strang JF, Powers MD, Knauss M, et al. "They Thought It Was an Obsession": Trajectories and Perspectives of Autistic Transgender and Gender-Diverse Adolescents. *J Autism Dev Disord*. 2018;48(12):4039-4055. doi:10.1007/s10803-018-3723-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30140984

527. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010;40(8):930-936. doi:10.1007/s10803-010-0935-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20094764

528. de Vries ALC. *Gender Dysphoria in Adolescents*. PhD Thesis. Vrije Universiteit Amsterdam; 2010. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

529. de Vries ALC. Autism Spectrum Disorders in Gender Dysphoric Children and Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:51-62:chap 4. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

530. de Vries ALC. Psychiatric Comorbidity in Gender Dysphoric Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:63-76:chap 5. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

531. de Vries ALC. Puberty Suppression in Adolescents with Gender Identity Disorder: A Prospective Follow-up Study. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:77-90:chap 6. Accessed June 12, 2023. Available at

https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

532. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. doi:10.1177/1359104510378303 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21216800

533. Burke SM, van Heesewijk JO, Menks WM, et al. Postnatal Effects of Sex Hormones on Click-Evoked Otoacoustic Emissions: A Study of Adolescents with Gender Dysphoria. *Arch Sex Behav*. 2020;49(2):455-465. doi:10.1007/s10508-020-01652-8 Accessed September 15, 2023. Available at https://orbi.uliege.be/bitstream/2268/259356/1/BurkeArchSexBehav%202020.pdf

534. de Nie I, Mulder CL, Meissner A, et al. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. *Hum Reprod*. 2022;37(2):297-308. doi:10.1093/humrep/deab240 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34791270

535. Brik T, Vrouenraets L, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of Fertility Preservation Among a Cohort of Transgirls in the Netherlands. *J Adolesc Health*. 2019;64(5):589-593. doi:10.1016/j.jadohealth.2018.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691936

536. Vrouenraets LJJJ, de Vries ALC, Arnoldussen M, et al. Medical decision-making competence regarding puberty suppression: perceptions of transgender adolescents, their parents and clinicians. *Eur Child Adolesc Psychiatry*. 2022;32(11):2343-2361. doi:10.1007/s00787-022-02076-6 Accessed September 15, 2023. Available at https://link.springer.com/content/pdf/10.1007/s00787-022-02076-6.pdf

537. Riggs DW, Bartholomaeus C, Sansfacon AP. 'If they didn't support me, I most likely wouldn't be here': Transgender young people and their parents negotiating medical treatment in Australia. *International journal of transgender health*. 2020;21(1):3-15. doi:10.1080/15532739.2019.1692751 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430428/pdf/WIJT_21_1692751.pdf

538. Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust*. 2012;196(9):578-581. doi:10.5694/mja12.10222 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22621149

539. Hewitt JK, Paul C, Newman LK. Author Reply to Conway, et al. regarding “Hormone treatment of gender identity disorder in a cohort of children and adolescents”. *Med J Aust*. 2012;197(5):274. doi:10.5694/mja12.10911 Accessed June 16, 2023. Available at https://pubmed.ncbi.nlm.nih.gov/22938117/

540. Pang KC, Notini L, McDougall R, et al. Long-term Puberty Suppression for a Nonbinary Teenager. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1606 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974217

541. Pang KC, Nguyen TP, Upreti R. Case Report: Successful Use of Minoxidil to Promote Facial Hair Growth in an Adolescent Transgender Male. *Front Endocrinol (Lausanne)*. 2021;12:725269. doi:10.3389/fendo.2021.725269 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34659117

542. O'Connell MA, Nguyen TP, Ahler A, Skinner SR, Pang KC. Approach to the Patient: Pharmacological Management of Trans and Gender-Diverse Adolescents. *J Clin Endocrinol Metab*. 2022;107(1):241-257. doi:10.1210/clinem/dgab634 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34476487

543. Pullen Sansfaçon A, Temple Newhook J, Douglas L, et al. Experiences and Stressors of Parents of Trans and Gender-Diverse Youth in Clinical Care from Trans Youth CAN! *Health Soc Work*. 2022;47(2):92-101. doi:10.1093/hsw/hlac003 Accessed September 15, 2023. Available at https://academic.oup.com/hsw/article-abstract/47/2/92/6544691?redirectedFrom=fulltext

544. Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. *Transgender Health*. 2023;8(1):84-88. doi:10.1089/trgh.2021.0102 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0102

545. Clark BA, Virani A, Marshall SK, Saewyc EM. Conditions for shared decision making in the care of transgender youth in Canada. *Health Promot Int*. 2021;36(2):570-580. doi:10.1093/heapro/daaa043 Accessed September 15, 2023. Available at https://academic.oup.com/heapro/article-abstract/36/2/570/5864519?redirectedFrom=fulltext

546. Fung R, Greenaway MK, McEvenue G. Gynecomastia in a Transgender Boy: A Case Report. *AACE clinical case reports*. 2021;7(6):350-352. doi:10.1016/j.aace.2021.05.003 Accessed September 15, 2023. Available at https://www.aaceclinicalcasereports.com/article/S2376-0605(21)00065-1/pdf

547. Chiniara LN, Viner C, Palmert M, Bonifacio H. Perspectives on fertility preservation and parenthood among transgender youth and their parents. *Arch Dis Child*. 2019;104(8):739-744. doi:10.1136/archdischild-2018-316080 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30894340

548. Margolin EA, Mason RH. Female-to-male transgender patient with idiopathic intracranial hypertention. *J Neurol Sci*. 2020;415:116970. doi:10.1016/j.jns.2020.116970 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32521344

549. Nayman T, Hebert M, Ospina LH. Idiopathic intracranial hypertension in a pediatric transgender patient. *Am J Ophthalmol Case Rep*. 2021;24:101208. doi:10.1016/j.ajoc.2021.101208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34622090

550. Condat A, Bekhaled F, Mendes N, Lagrange C, Mathivon L, Cohen D. Gender dysphoria in children and adolescents: French history and clinical observations. *Neuropsychiatr Enfance Adolesc*. 2016;64(1):7-15. doi:10.1016/j.neurenf.2015.06.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L605213392&from=export

551. Martinez S, Mazoyer AV. Impacts of the sexual reassignment on the parenthood. *Ann Med Psychol (Paris)*. 2017;175(9):797-802. doi:10.1016/j.amp.2017.09.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618996605&from=export

552. Meyenburg B. [Gender dysphoria in adolescents: difficulties in treatment]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):510-522. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296511

553. Meyenburg B, Kroger A, Neugebauer R. [Gender dysphoria in children and adolescents - treatment guidelines and follow-up study]. *Z Kinder Jugendpsychiatr Psychother*. 2015;43(1):47-55. doi:10.1024/1422-4917/a000332 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25536896

554. Pierce S, Mazziotta A, Möller-Kallista B. Experiences of Children with Gender Dysphoria/Gender Incongruence and their Parents with the Health Care System in Germany. *Prax Kinderpsychol Kinderpsychiatr*. 2022;71(7):597-619. doi:10.13109/prkk.2022.71.7.597 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L639549895&from=export

555. Ristori J, Fisher AD, Castellini G, et al. Gender Dysphoria and Anorexia Nervosa Symptoms in Two Adolescents. *Arch Sex Behav*. 2019;48(5):1625-1631. doi:10.1007/s10508-019-1396-7 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s10508-019-1396-7

556. Gawlik A, Antosz A, Kasparek K, Nowak Z, Grabski B. Gender confirmation hormonal treatment use in young Polish transgender binary and non-binary persons. *Endokrynol Pol*. 2022;73(6):922-927. doi:10.5603/EP.a2022.0088 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36519648

557. Zupanič S, Kruljac I, Sostaric Zvonar M, Drobnic Radobuljac M. Case Report: Adolescent With Autism and Gender Dysphoria. *Front Psychiatry*. 2021;12:671448. doi:10.3389/fpsyt.2021.671448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34122187

558. Sanchez Lorenzo I, Mora Mesa JJ, Oviedo de Lucas O. Psychomedical care in gender identity dysphoria during adolescence. *Revista de psiquiatria y salud mental*. 2017;10(2):96-103. doi:10.1016/j.rpsm.2015.04.002 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26055932

559. Campos-Munoz L, Lopez-De Lara D, Rodriguez-Rojo ML, Conde-Taboada A, Lopez-Bran E. Transgender adolescents and acne: A cases series. *Pediatr Dermatol*. 2018;35(3):e155-e158. doi:10.1111/pde.13448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29575091

560. Fernandez Rodriguez M, Guerra Mora P, Martin Sanchez E, Grupo G. [Characteristics of Adolescents with Gender Dysphoria Referred to the Gender Identity Treatment Unit]. *Rev Esp Salud Publica*. 2017;91Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28141788

561. Fernandez M, Guerra P, Martin E, Martinez N, Alvarez-Diz JA, Grupo G. [Health care for adolescents with gender dysphoria]. *Rev Esp Salud Publica*. 2018;92Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29493565

562. Rebetez N. [I want an accepting society]. *Krankenpfl Soins Infirm*. 2014;107(11):56-57. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25438414

563. Pauli D, Günthard M, Schenker T, et al. The Zurich Specialist Clinic for Adolescent with Gender Dysphoria - Preliminary Follow-up Results. *Prax Kinderpsychol Kinderpsychiatr*. 2020;69(6):570-589. doi:10.13109/prkk.2020.69.6.570 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L633037474&from=export

564. Rogers C, Webberley M, Mateescu R, El Rakhawy Y, Daly-Gourdialsing A, Webberley H. A retrospective study of positive and negative determinants of gamete storage in transgender and gender-diverse patients. *International journal of transgender health*. 2021;22(1-2):167-178. doi:10.1080/26895269.2020.1848693 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040686/pdf/WIJT_22_1848693.pdf

565. Russell I, Pearson B, Masic U. A Longitudinal Study of Features Associated with Autism Spectrum in Clinic Referred, Gender Diverse Adolescents Accessing Puberty Suppression Treatment. *J Autism Dev Disord*. 2021;51(6):2068-2076. doi:10.1007/s10803-020-04698-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32936414

566. Churcher Clarke A, Spiliadis A. 'Taking the lid off the box': The value of extended clinical assessment for adolescents presenting with gender identity difficulties. *Clin Child Psychol Psychiatry*. 2019;24(2):338-352. doi:10.1177/1359104518825288 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L627311211&from=export

567. Gilani M, Wallach P, Kyriakou A. Levels of physical activity and barriers to sport participation in young people with gender dysphoria. *J Pediatr Endocrinol Metab*. 2021;34(6):747-753. doi:10.1515/jpem-2021-0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33818040

568. Maschião LF, Bastos FI, Wilson E, et al. Nonprescribed Sex Hormone Use Among Trans Women: The Complex Interplay of Public Policies, Social Context, and Discrimination. *Transgend Health*. 2020;5(4):205-215. doi:10.1089/trgh.2020.0012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644312

569. Akgül S, Tuzun Z, Pehlivanturk Kizilkan M, Ozon ZA. Menstrual Suppression in Gender Minority Youth. *J Clin Res Pediatr Endocrinol*. 2022;14(4):463-468. doi:10.4274/jcrpe.galenos.2021.2020.0283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34044500

570. Cesur E, Yuksel S, Basar K, Kaptan S. Clinical Follow-up of Two Adolescents Diagnosed with Gender Dysphoria. *Turk Psikiyatri Derg*. 2022;33(3):214-219. doi:10.5080/u26795 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36148573

571. Achenbach System of Empirically Based Assessment (ASEBA). The ASEBA Approach. ASEBA.org. 2022. Last Updated 2022. Accessed July 29, 2023. Available at https://aseba.org/

572. Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. *Arch Pediatr Adolesc Med*. 2012;166(12):1170-1176. doi:10.1001/archpediatrics.2012.1276 https://www.ncbi.nlm.nih.gov/pubmed/23027429

573. Beck J, Beck A, Jolly J, Steer R. *Beck Youth Inventories.* 2nd ed. Assessments P; 2005. Accessed September 28, 2023. Available at https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Personality-%26-Biopsychosocial/Beck-Youth-Inventories-%7C-Second-Edition/p/100000153.html

574. Beck A, Steer R, Brown G. *Manual for the Beck Depression Inventory-II (BDI-II).* PsychCorp; 1996. Last Updated 1996. Accessed July 29, 2023. Available at https://www.nctsn.org/measures/beck-depression-inventory-second-edition

575. Mendelson BK, Mendelson MJ, White DR. Body-esteem scale for adolescents and adults. *J Pers Assess*. 2001;76(1):90-106. doi:10.1207/S15327752JPA7601_6 https://www.ncbi.nlm.nih.gov/pubmed/11206302

576. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975;4(6):639-656. doi:10.1007/BF01544272 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/1212093

577. Eaton W, Smith C, Ybarra M, Muntaner C, Tien A. Center for Epidemiologic Studies Depression Scale: Review and Revision (CESD and CESD-R). *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment: Instruments for Adults, Vol. 3*. 3rd ed. Lawrence Erlbaum Associates Publishers; 2004:363-377.

578. Haroz EE, Ybarra ML, Eaton WW. Psychometric evaluation of a self-report scale to measure adolescent depression: the CESDR-10 in two national adolescent samples in the United States. *J Affect Disord*. 2014;158:154-160. doi:10.1016/j.jad.2014.02.009 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24655780

579. Crijnen AA, Achenbach TM, Verhulst FC. Comparisons of problems reported by parents of children in 12 cultures: total problems, externalizing, and internalizing. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1269-1277. doi:10.1097/00004583-199709000-00020 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/9291729

580. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228-1231. doi:10.1001/archpsyc.1983.01790100074010 https://www.ncbi.nlm.nih.gov/pubmed/6639293

581. Figueras Masip A, Amador-Campos JA, Gomez-Benito J, del Barrio Gandara V. Psychometric properties of the Children's Depression Inventory in community and clinical sample. *Span J Psychol*. 2010;13(2):990-999. doi:10.1017/s1138741600002638 https://www.ncbi.nlm.nih.gov/pubmed/20977046

582. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;21(4):995-998. https://www.ncbi.nlm.nih.gov/pubmed/4089116

583. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277. doi:10.1176/appi.ajp.2011.10111704 https://www.ncbi.nlm.nih.gov/pubmed/22193671

584. Neyer MA, Henry RS, Carrier ME, et al. Validity, Reliability, and Differential Item Functioning of English and French Versions of the 10-Item Connor-Davidson Resilience Scale in Systemic Sclerosis: A Scleroderma Patient-Centered Intervention Network Cohort Study. *Arthritis Care Res (Hoboken)*. 2023, 10.1002/acr.25139doi:10.1002/acr.25139 https://www.ncbi.nlm.nih.gov/pubmed/37128826

585. Bieliauskas VJ. Sexual identification in children's drawings of human figure. *J Clin Psychol*. 1960;16:42-44. doi:10.1002/1097-4679(196001)16:1<42::aid-jclp2270160117>3.0.co;2-e https://www.ncbi.nlm.nih.gov/pubmed/13800546

586. Zucker KJ, Bradley SJ, Owen-Anderson A, et al. Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *J Sex Marital Ther*. 2012;38(2):151-189. doi:10.1080/0092623X.2011.611219 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22390530

587. Habashy J, Benning SD, Renn BN, Borgogna NC, Lawrence EM, Kraus SW. Psychometric properties of the eating disorder examination questionnaire: Factor analysis and measurement invariance by race/ethnicity and gender. *Eat Behav*. 2023;48:101696. doi:10.1016/j.eatbeh.2022.101696 https://www.ncbi.nlm.nih.gov/pubmed/36516727

588. Berg KC, Peterson CB, Frazier P, Crow SJ. Psychometric evaluation of the eating disorder examination and eating disorder examination-questionnaire: a systematic review of the literature. *Int J Eat Disord*. 2012;45(3):428-438. doi:10.1002/eat.20931 https://www.ncbi.nlm.nih.gov/pubmed/21744375

589. Swenne I. Evaluation of the Compulsive Exercise Test (CET) in Adolescents with Eating Disorders: Factor Structure and Relation to Eating Disordered Psychopathology. *Eur Eat Disord Rev*. 2016;24(4):334-340. doi:10.1002/erv.2439 https://www.ncbi.nlm.nih.gov/pubmed/26892035

590. Storms M. Theories of sexual orientation. *J Pers Soc Psychol*. 1980;38(5):783-792. doi:10.1037/0022-3514.38.5.783 Accessed September 28, 2023. Available at https://psycnet.apa.org/record/1981-12707-001

591. Dahne A, Assmann B, Ettrich C, Hinz A. [Norm values for the questionnaire to assess the own body (Fragebogen zur Beurteilung des eigenen Korpers, FBeK) for adolescents]. *Prax Kinderpsychol Kinderpsychiatr*. 2004;53(7):483-496. https://www.ncbi.nlm.nih.gov/pubmed/15506261

592. Johnson LL, Bradley SJ, Birkenfeld-Adams AS, et al. A parent-report gender identity questionnaire for children. *Arch Sex Behav*. 2004;33(2):105-116. doi:10.1023/b:aseb.0000014325.68094.f3 https://www.ncbi.nlm.nih.gov/pubmed/15146143

593. Deogracias JJ, Johnson LL, Meyer-Bahlburg HF, Kessler SJ, Schober JM, Zucker KJ. The gender identity/gender dysphoria questionnaire for adolescents and adults. *J Sex Res*. 2007;44(4):370-379. doi:10.1080/00224490701586730 https://www.ncbi.nlm.nih.gov/pubmed/18321016

594. Hidalgo MA, Petras H, Chen D, Chodzen G. The Gender Minority Stress and Resilience Measure: Psychometric Validity of an Adolescent Extension. *Clin Pract Pediatr Psychol*. 2019;7(3):278-290. doi:10.1037/cpp0000297 https://www.ncbi.nlm.nih.gov/pubmed/33224698

595. Lowe B, Decker O, Muller S, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med Care*. 2008;46(3):266-274. doi:10.1097/MLR.0b013e318160d093 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/18388841

596. Fazio AF. A concurrent validational study of the NCHS General Well-Being Schedule. *Vital Health Stat 2*. 1977, (73):1-53. https://www.ncbi.nlm.nih.gov/pubmed/610049

597. Van den Bergh BR, Van Ranst N. Self-concept in children: equivalence of measurement and structure across gender and grade of Harter's Self-Perception Profile for Children. *J Pers Assess*. 1998;70(3):564-582. doi:10.1207/s15327752jpa7003_13 https://www.ncbi.nlm.nih.gov/pubmed/9760744

598. Kessler RC, Green JG, Gruber MJ, et al. Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative. *Int J Methods Psychiatr Res*. 2010;19 Suppl 1(Suppl 1):4-22. doi:10.1002/mpr.310 https://www.ncbi.nlm.nih.gov/pubmed/20527002

599. Ravens-Sieberer U, Herdman M, Devine J, et al. The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. *Qual Life Res*. 2014;23(3):791-803. doi:10.1007/s11136-013-0428-3 https://www.ncbi.nlm.nih.gov/pubmed/23686556

600. Mennin DS, Fresco DM, Heimberg RG, Schneier FR, Davies SO, Liebowitz MR. Screening for social anxiety disorder in the clinical setting: using the Liebowitz Social Anxiety Scale. *J Anxiety Disord*. 2002;16(6):661-673. doi:10.1016/s0887-6185(02)00134-2 https://www.ncbi.nlm.nih.gov/pubmed/12405524

601. Dunn EC, Johnson RM, Green JG. The Modified Depression Scale (MDS): A Brief, No-Cost Assessment Tool to Estimate the Level of Depressive Symptoms in Students and Schools. *School Ment Health*. 2012;4(1):34-45. doi:10.1007/s12310-011-9066-5 https://www.ncbi.nlm.nih.gov/pubmed/22639697

602. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the Multidimensional Scale of Perceived Social Support. *J Pers Assess*. 1990;55(3-4):610-617. doi:10.1080/00223891.1990.9674095 https://www.ncbi.nlm.nih.gov/pubmed/2280326

603. Slotkin J, Nowinski C, Hays R, et al. *NIH Toolbox Scoring and Interpretation Guide*. (NIH) NIoH; 2012: 58 pages. Last Updated September 18, 2012. Accessed July 29, 2023. Available at https://www.epicrehab.com/epic/documents/crc/crc-201307-nih-toolbox-scoring-and-interpretation-manual%209-27-12.pdf

604. Campbell-Sills L, Norman SB, Craske MG, et al. Validation of a brief measure of anxiety-related severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). *J Affect Disord*. 2009;112(1-3):92-101. doi:10.1016/j.jad.2008.03.014 https://www.ncbi.nlm.nih.gov/pubmed/18486238

605. Richardson LP, McCauley E, Grossman DC, et al. Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. *Pediatrics*. 2010;126(6):1117-1123. doi:10.1542/peds.2010-0852 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21041282

606. Irwin DE, Stucky B, Langer MM, et al. An item response analysis of the pediatric PROMIS anxiety and depressive symptoms scales. *Qual Life Res*. 2010;19(4):595-607. doi:10.1007/s11136-010-9619-3 https://www.ncbi.nlm.nih.gov/pubmed/20213516

607. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321-326. Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/8290681

608. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583. doi:10.1016/s0006-3223(02)01866-8 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/12946886

609. Veale JF. Factorial Validity and Invariance Assessment of a Short Version of the Recalled Childhood Gender Identity/Role Questionnaire. *Arch Sex Behav*. 2016;45(3):537-550. doi:10.1007/s10508-015-0684-0 https://www.ncbi.nlm.nih.gov/pubmed/26864871

610. Reynolds C, Richmond B. *Revised Children's Manifest Anxiety Scale, Second Edition (RCMAS-2)*. Western Psychological Services (WPS); 2008. Last Updated 2008. Accessed July 29, 2023. Available at https://www.wpspublish.com/rcmas-2-revised-childrens-manifest-anxiety-scale-second-edition

611. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess*. 1985;49(1):71-75. doi:10.1207/s15327752jpa4901_13 https://www.ncbi.nlm.nih.gov/pubmed/16367493

612. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230-1236. doi:10.1097/00004583-199910000-00011 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/10517055

613. Aitken M, VanderLaan DP, Wasserman L, Stojanovski S, Zucker KJ. Self-Harm and Suicidality in Children Referred for Gender Dysphoria. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):513-520. doi:10.1016/j.jaac.2016.04.001 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27238070

614. Van Meter AR, Algorta GP, Youngstrom EA, et al. Assessing for suicidal behavior in youth using the Achenbach System of Empirically Based Assessment. *Eur Child Adolesc Psychiatry*. 2018;27(2):159-169. doi:10.1007/s00787-017-1030-y Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28748484

615. Deutz MH, Geeraerts SB, van Baar AL, Dekovic M, Prinzie P. The Dysregulation Profile in middle childhood and adolescence across reporters: factor structure, measurement invariance, and links with self-harm and suicidal ideation. *Eur Child Adolesc Psychiatry*. 2016;25(4):431-442.

doi:10.1007/s00787-015-0745-x Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26226917

616. Langevin R. *Sexual Strands: Understanding and Treating Sexual Anomalies in Men*. Routledge; 1983:556.

617. Azevedo FB, Wang YP, Goulart AC, Lotufo PA, Bensenor IM. Application of the Spielberger's State-Trait Anger Expression Inventory in clinical patients. *Arq Neuropsiquiatr*. 2010;68(2):231-234. doi:10.1590/s0004-282x2010000200015 https://www.ncbi.nlm.nih.gov/pubmed/20464291

618. Carey MP, Faulstich ME, Carey TC. Assessment of anxiety in adolescents: concurrent and factorial validities of the Trait Anxiety scale of Spielberger's State-Trait Anxiety Inventory for Children. *Psychol Rep*. 1994;75(1 Pt 1):331-338. https://www.ncbi.nlm.nih.gov/pubmed/7984747

619. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. *Assessment*. 2001;8(4):443-454. doi:10.1177/107319110100800409 https://www.ncbi.nlm.nih.gov/pubmed/11785588

620. Kozee HB, Tylka TL, Bauerband LA. Measuring Transgender Individuals' Comfort With Gender Identity and Appearance. *Psychol Women Q*. 2012;36(2):179-196. doi:10.1177/0361684312442161 Accessed July 29, 2023. Available at https://psycnet.apa.org/record/2012-14737-007

621. Canivez GL, Watkins MW, Dombrowski SC. Structural validity of the Wechsler Intelligence Scale for Children-Fifth Edition: Confirmatory factor analyses with the 16 primary and secondary subtests. *Psychol Assess*. 2017;29(4):458-472. doi:10.1037/pas0000358 https://www.ncbi.nlm.nih.gov/pubmed/27442624

622. Skevington SM, Lotfy M, O'Connell KA, Group W. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res*. 2004;13(2):299-310. doi:10.1023/B:QURE.0000018486.91360.00 https://www.ncbi.nlm.nih.gov/pubmed/15085902

623. Verhulst FC, Achenbach TM, van der Ende J, et al. Comparisons of problems reported by youths from seven countries. *Am J Psychiatry*. 2003;160(8):1479-1485. doi:10.1176/appi.ajp.160.8.1479 Accessed July 29, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/12900311

624. van de Grift TC, Pigot GLS, Boudhan S, et al. A Longitudinal Study of Motivations Before and Psychosexual Outcomes After Genital Gender-Confirming Surgery in Transmen. *J Sex Med*. 2017;14(12):1621-1628. doi:10.1016/j.jsxm.2017.10.064 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29128275

APPENDIX I.A: PHARMACOLOGIC AGENTS BY DRUG CLASS

Return to TOC

Table I.A.1. Indications for gonadotropin-releasing hormone analogs used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Goserelin acetate[180,181] December 29, 1989	None	• Breast cancer • Endometriosis • Hypoplasia of the endometrium • Prostate cancer	Precocious puberty • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–MTF transgender individuals; adjunct • Effective • Recommended, in most cases (B)	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use					
	• Hypersensitivity to the active ingredient, any excipient, GnRH, or GnRH analog analogs • Treating endometriosis or endometrial thinning during pregnancy					
Histrelin acetate[e,182,183] December 24, 1991[184]	• Central precocious puberty	• Prostate cancer	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient, any excipient, GnRH, or GnRH analog analogs • Pregnancy					
Leuprolide[185,186] April 9, 1985[187]	• Central precocious puberty[f]	• Anemia related to uterine leiomyomata (fibroids) • Endometriosis • Prostate cancer	None	Gender dysphoria–MTF transgender individuals; adjunct • Evidence favors efficacy • Recommended, in some cases (B)	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use					
	• Hypersensitivity to the active ingredient, any excipient, GnRH, or GnRH analog analogs • Pregnancy • Undiagnosed abnormal uterine bleeding					
Nafarelin acetate [188,189]	• Central precocious puberty	• Endometriosis	None		None	
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book).*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Vantas, a brand name product of histrelin, was indicated for the palliative treatment of advanced prostate cancer, but this product has been discontinued in the US for more than 1 year. However, Supprelin LA continues to be on the market for the treatment of central precocious puberty in children aged 2 years and older.*

[f] *Treatment of central precocious puberty is indicated only for certain formulations of leuprolide: Lupron Depot-Ped and Fensolvi*

[g] *Of the available products for triptorelin, only Triptodur is approved for the treatment of central precocious puberty*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; RCTs, randomized controlled trials

Return to TOC

Table I.A.1. Indications for gonadotropin-releasing hormone analogs used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
February 13, 1990	• Breastfeeding or pregnancy • Hypersensitivity to the active ingredient, any excipient, GnRH, or GnRH analog analogs • Undiagnosed abnormal vaginal bleeding					
Triptorelin pamoate [190,191] June 15, 2000	• Central precocious puberty[g]	• Prostate cancer	Drug treatment to suppress puberty in gender dysphoria • Effective • Recommended, in most cases (B) Growth hormone deficiency • Evidence is inconclusive • Not Recommended (B) Short stature disorder, idiopathic • Evidence is inconclusive • Not Recommended (B)	None	None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient, any excipient, GnRH, or GnRH analog analogs • Pregnancy					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book).*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Vantas, a brand name product of histrelin, was indicated for the palliative treatment of advanced prostate cancer, but this product has been discontinued in the US for more than 1 year. However, Supprelin LA continues to be on the market for the treatment of central precocious puberty in children aged 2 years and older.*

[f] *Treatment of central precocious puberty is indicated only for certain formulations of leuprolide: Lupron Depot-Ped and Fensolvi*

[g] *Of the available products for triptorelin, only Triptodur is approved for the treatment of central precocious puberty*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; RCTs, randomized controlled trials

Return to TOC

Table I.A.2. Indications for gonadotropin-releasing hormone antanalogs used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Cetrorelix acetate[192,193] August 11, 2000	None	• Ovulation induction, controlled ovarian stimulation; adjunct	None		None	
	Contraindications for use					
	• Breastfeeding or pregnancy • Hypersensitivity to the active ingredient, any excipient, extrinsic peptide hormones, mannitol, GnRH, or any other GnRH analogs • Severe renal impairment					
Degarelix acetate[194,195] December 24, 2008	None	• Prostate cancer	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient					
Elagolix sodium[196,197] July 23, 2018[198]	None	• Endometriosis related pain	None		None	
	Contraindications for use					
	• Concomitant use with strong OATP 1B1 inhibitors • Hypersensitivity to the active ingredient or any excipient • Osteoporosis • Pregnancy • Severe hepatic impairment					
Ganirelix acetate[199,200] July 29, 1999	None	• Female infertility, adjunct to controlled ovarian hyperstimulation	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient, any excipient, GnRH, or any other GnRH analogs • Pregnancy					
Relugolix[201,202] December 18, 2020	None	• Prostate cancer	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; OATP, organic anion transporting polypeptide; RCTs, randomized controlled trials

Return to TOC

Table I.A.3. Indications for antiandrogens used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Bicalutamide[203,204] October 4, 1995	None	• Prostate cancer	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Use in women, including during pregnancy					
Dutasteride[186,205] November 20, 2001	None	• Benign prostatic hyperplasia	None		None	
	Contraindications for use					
	• Clinically significant hypersensitivity (eg, serious skin reactions, angioedema) to the active ingredient, any excipient, or other 5-alpha-reductase inhibitors • Pregnancy					
Finasteride[206,207] June 19, 1992	None	• Benign prostatic hyperplasia • Male pattern alopecia	None	Gender dysphoria–MTF transgender individuals; adjunct • Ineffective • Not Recommended (B)	None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Pregnancy					
Flutamide[208,209] January 27, 1989	None	• Prostate cancer	Congenital adrenal hyperplasia • Evidence is inconclusive • Not Recommended (B)	None	None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Severe hepatic impairment					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; RCTs, randomized controlled trials.

Return to TOC

Table I.A.3. Indications for antiandrogens used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Nilutamide[210,211] September 19, 1996	None	• Prostate cancer	None	Drug-induced feminization–transgender individuals • Evidence is inconclusive • Recommended, in some cases (B)	None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Severe hepatic impairment • Severe respiratory insufficiency					
Spironolactone[212,213] January 21, 1960	None	• Ascites due to cirrhosis • Edema – Nephrotic syndrome • Heart failure with reduced ejection fraction • Hypertension • Primary hyperaldosteronism	Hyperaldosteronism • Effective • Recommended, in most cases (B) Bronchopulmonary dysplasia of newborn • Evidence is inconclusive • Recommended, in some cases (B)	Gender dysphoria–MTF transgender individuals; adjunct • Evidence is inconclusive • Recommended, in some cases (B)	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use					
	• Addison disease • Concomitant eplerenone use • Hyperkalemia					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; RCTs, randomized controlled trials.

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Conjugated estrogens[214,215] Approved prior to January 1, 1982[216-218]	None	• Abnormal uterine bleeding • Breast cancer • Female hypogonadism syndrome • Menopause-related dyspareunia • Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Postmenopausal osteoporosis; prophylaxis • Prostate cancer • Secondary amenorrhea, hypoestrogenism	Hemorrhagic cystitis • Evidence favors efficacy • Recommended, in some cases (B) Postoperative hemorrhage • Evidence favors efficacy • Recommended, in some cases (B) Turner syndrome • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–MTF transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Angioedema or anaphylactic reaction to the active ingredient or any excipient • Breast cancer (known, suspected, or history of); except in appropriately selected patients being treated for metastatic disease • Estrogen-dependent neoplasia • Hepatic disease or impairment • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Esterified estrogens[219,220] Approved prior to January 1, 1982[221-238]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Metastatic breast cancer • Prostate cancer • Secondary amenorrhea, hypoestrogenism	None		None	
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of); except in appropriately selected patients being treated for metastatic disease • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Estradiol[239,240] Approved prior to January 1, 1982[241,242]	None	• Breast cancer • Menopause-related dyspareunia • Menopause-related vasomotor symptoms • Menopause-related vulvar, urethral, and vaginal atrophy • Postmenopausal osteoporosis, prophylaxis • Prostate cancer • Secondary amenorrhea, hypoestrogenism	Gender dysphoria–MTF transgender individuals • Evidence favors efficacy Recommended, in most cases (B)	Gender dysphoria–MTF transgender individuals • Evidence favors efficacy Recommended, in some cases (B)	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use • Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Breast cancer (known, suspected, or history of); except in appropriately selected patients being treated for metastatic disease • Estrogen-dependent neoplasia • Hepatic disease or impairment • Known angioedema, anaphylactic reaction, or hypersensitivity to the active ingredient or any excipient • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					
Estradiol acetate[243] March 20, 2003[244]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy	None		None	

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Known angioedema, anaphylactic reaction, or hypersensitivity to the active ingredient or any excipient • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					
Estradiol cypionate[245] Approved prior to January 1, 1982[246,247]	None	• Female hypogonadism syndrome • Menopause-related vasomotor symptoms	None	Gender dysphoria–MTF transgender individuals • No efficacy or recommendation is reported	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Estradiol valerate[248,249] Approved prior to January 1, 1982[250-253]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Prostate cancer • Secondary amenorrhea, hypoestrogenism	None	Gender dysphoria–MTF transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	None	Gender dysphoria–MTF transgender individuals LOE: G
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity to the active ingredient • Pregnancy • Undiagnosed abnormal genital bleeding					
Testosterone[254,255] December 24, 1953	None	• Hypogonadism, male	Gender dysphoria–FTM transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–FTM transgender individuals • Effective • Recommended, in most cases (B)	None	Gender dysphoria–FTM transgender individuals LOE: G
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Breast cancer (males) • Breastfeeding • Hypersensitivity to the active ingredient or any excipient • Pregnancy, or those who may become pregnant • Prostate cancer (known or suspected)					
Testosterone cypionate[256] Approved prior to January 1, 1982[257-260]	• Primary hypogonadism, male		Gender dysphoria–FTM transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–FTM transgender individuals • Effective • Recommended, in most cases (B)	None	Gender dysphoria–FTM transgender individuals LOE: G
	Contraindications for use					
	• Breast cancer (males) • Hypersensitivity to the active ingredient or any excipient • Pregnancy, or those who may become pregnant • Prostate cancer (known or suspected) • Serious cardiac, renal, or hepatic disease					
Testosterone enanthate[e,261] Approved prior to January 1, 1982[262-265]	• Delayed puberty, male • Hypogonadism, male	• Hypogonadism, male • Metastatic breast cancer, female	Gender dysphoria–FTM transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–FTM transgender individuals • Effective • Recommended, in most cases (B)	None	Gender dysphoria–FTM transgender individuals LOE: G
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.4. Indications for single-ingredient sex hormone agents used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Breast cancer (males) • Hypersensitivity to the active ingredient or any excipient • Hypogonadal conditions that are not attributed to genetic or structural etiologies (eg, age-related hypogonadism) • Pregnancy, or those who may become pregnant • Prostate cancer (known or suspected)					
Testosterone undecanoate[266] March 5, 2014[267]	None	• Hypogonadism, male	Gender dysphoria–FTM transgender individuals • Evidence favors efficacy • Recommended, in some cases (B)	Gender dysphoria–FTM transgender individuals • Effective • Recommended, in most cases (B)	None	Gender dysphoria–FTM transgender individuals LOE: G
	Contraindications for use					
	• Breast cancer (males) • Breastfeeding • Hypersensitivity to the active ingredient or any excipient • Hypogonadal conditions that are not attributed to genetic or structural etiologies (eg, age-related hypogonadism) • Pregnancy, or those who may become pregnant • Prostate cancer (known or suspected)					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Only the intramuscular injection of testosterone enanthate is FDA-approved in adolescent males to treat delayed puberty and hypogonadism*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MTF, male-to-female; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.5. Indications for single-ingredient progestin agents used for gender dysphoria

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Drospirenone[268,269] May 23, 2019	• Contraception (post-menarche)		None		None	
	Contraindications for use					
	• Active or prior history of cervical cancer or progestin-sensitive cancers • Adrenal insufficiency • Benign or malignant hepatic tumors • Renal or hepatic impairment • Undiagnosed abnormal uterine bleeding					
Etonogestrel[270,271] July 17, 2006	None	• Contraception	None		None	
	Contraindications for use					
	• Active hepatic disease • Active or prior history of progestin-sensitive cancer • Active or prior history of thrombosis or thromboembolic disorders • Benign or malignant hepatic tumors • Breast cancer (known, suspected, or history of) • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal genital bleeding					
Levonorgestrel[272,273] December 10, 1990[274,275]	• Contraception (post-menarche) • Postcoital contraception (post-menarche)	• Contraception • Menorrhagia • Postcoital contraception	None		None	Menstrual suppression–FTM transgender individuals[e] (IUD) LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who do not desire or are not ready to start masculinizing hormones*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; FTM, female-to-male; IUD, intrauterine device; AIDS, acquired immune deficiency syndrome; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; MTF, male-to-female; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.5. Indications for single-ingredient progestin agents used for gender dysphoria

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of breast cancer (known or suspected), or hormone-sensitive cancer (known or suspected), including progestin • Active or prior history of PID, or active endometritis, except in cases where there has been a subsequent pregnancy within the uterus • Active thrombophlebitis or thromboembolic disorders • Benign or malignant hepatic tumors, or acute hepatic disease • Conditions that increase infection vulnerability (eg, AIDS, leukemia) • Genital or uterine bleeding of unknown cause • Hypersensitivity to the active ingredient or any excipient • Infected abortion in the past 3 months			• Known or suspected pregnancy • Post-partum endometritis • Unremoved IUD • Unresolved abnormal Pap smear • Untreated vaginitis or cervicitis, including bacterial vaginosis or other lower genital tract infections • Use of intrauterine system as emergency contraception • Uterine anomaly (acquired or congenital), including fibroids, that disrupts the uterine cavity making proper intrauterine placement incompatible • Uterine or cervical neoplasia (known or suspected)		
Medroxyprogesterone (acetate)[185] June 18, 1959	• Contraception • Endometriosis (SC suspension only)	• Abnormal uterine bleeding • Contraception • Endometrial cancer • Endometriosis • Estrogen therapy-associated endometrial hyperplasia, prophylaxis • Renal cell carcinoma • Secondary amenorrhea, diagnostic aid	Alveolar hypoventilation • Evidence favors efficacy • Recommended, in some cases (B) Central precocious puberty • Evidence is inconclusive • Recommended, in some cases (B)	None	None	Menstrual suppression–FTM transgender individuals LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who do not desire or are not ready to start masculinizing hormones*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; FTM, female-to-male; IUD, intrauterine device; AIDS, acquired immune deficiency syndrome; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; MTF, male-to-female; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.5. Indications for single-ingredient progestin agents used for gender dysphoria

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Active or prior history of thromboembolic conditions, cerebral vascular disease, or thrombophlebitis • Breast cancer (known, suspected, or history of) • Estrogen- or progesterone-dependent neoplasia (known or suspected) • Hepatic disease or impairment • Known angioedema, anaphylactic reaction, or hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal vaginal or genital bleeding					
Norethindrone[276,277] January 2, 1973	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Acute hepatic disease • Benign or malignant hepatic tumors • Breast cancer (known, suspected, or history of) • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who do not desire or are not ready to start masculinizing hormones*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; FTM, female-to-male; IUD, intrauterine device; AIDS, acquired immune deficiency syndrome; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; MTF, male-to-female; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.5. Indications for single-ingredient progestin agents used for gender dysphoria

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Norethindrone acetate[278] Approved prior to January 1, 1982[279]	None	• Abnormal uterine bleeding • Endometriosis • Estrogen therapy-associated endometrial hyperplasia, prophylaxis • Secondary amenorrhea, diagnostic aid	None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Hepatic disease or impairment • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Undiagnosed abnormal vaginal bleeding • Use as a diagnostic pregnancy test					
Progesterone[280,281] May 11, 1978	None	• Abnormal uterine bleeding • Assisted reproductive technology • Estrogen therapy-associated endometrial hyperplasia, prophylaxis • Secondary amenorrhea, diagnostic aid	None		None	
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who do not desire or are not ready to start masculinizing hormones*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; FTM, female-to-male; IUD, intrauterine device; AIDS, acquired immune deficiency syndrome; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; MTF, male-to-female; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.5. Indications for single-ingredient progestin agents used for gender dysphoria

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) or thromboembolic disorders (eg, DVT, PE) • Active or prior history of cerebral apoplexy • Breast cancer (known, suspected, or history of) • Ectopic pregnancy or missed abortion • Genital cancer (known or suspected)			• Hepatic disease or impairment • Hypersensitivity to the active ingredient or any excipient • Pregnancy • Thrombophlebitis (known or history of) • Undiagnosed abnormal genital or vaginal bleeding		

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who do not desire or are not ready to start masculinizing hormones*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; FTM, female-to-male; IUD, intrauterine device; AIDS, acquired immune deficiency syndrome; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; MTF, male-to-female; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Conjugated/equine estrogens and medroxyprogesterone acetate[282,283] December 30, 1994[284]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Postmenopausal osteoporosis; prophylaxis	None		None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Angioedema or anaphylactic reaction to the active ingredients or any excipient • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					
Estradiol and drospirenone[285,286] September 28, 2005[287]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy	None		None	
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Adrenal insufficiency • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment			• Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Renal impairment • Undiagnosed abnormal genital bleeding		
Estradiol and levonorgestrel[288,289] November 21, 2003[290]	None	• Menopause-related vasomotor symptoms • Postmenopausal osteoporosis, prophylaxis	None		None	
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Estradiol and norethindrone acetate[291] August 7, 1998[292]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Postmenopausal osteoporosis, prophylaxis • Secondary amenorrhea, hypoestrogenism	None		None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					
Estradiol and norgestimate[293,294] October 22, 1999[295]	None	• Menopause-related vasomotor symptoms • Menopause-related vulvar and vaginal atrophy • Postmenopausal osteoporosis, prophylaxis	None		None	

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	Contraindications for use					
	• Active or prior history of DVT or PE • Active or recent history of arterial thromboembolic disease (eg, MI, stroke) • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity to the active ingredients or any excipient • Pregnancy • Undiagnosed abnormal genital bleeding					
Estradiol and progesterone[296,297] October 28, 2018[298]	None	• Menopause-related vasomotor symptoms	None		None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Breast cancer (known, suspected, or history of) • Estrogen-dependent neoplasia • Hepatic disease or impairment • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal genital bleeding					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Estradiol, elagolix, and norethindrone[299,300] May 29, 2020	None	• Menorrhagia associated with uterine leiomyoma (premenopausal women)	None		None	
	Contraindications for use					
	• Active or prior history of DVT or PE • Breast cancer (active, or history of) or other hormonally-sensitive malignancies, and those with increased risk for hormonally-sensitive malignancies • Concomitant use with OATP 1B1 inhibitors • Headaches with focal neurological symptoms, or migraine headaches with aura if > 35 years of age • Hepatic disease or impairment • High risk of thrombotic or thromboembolic conditions (venous or arterial) • Hypercoagulopathies (acquired or inherited)			• Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Osteoporosis • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Uncontrolled hypertension • Undiagnosed abnormal uterine bleeding • Vascular disease (eg, coronary artery disease)		
Estradiol, relugolix, and norethindrone[301] May 26, 2021	None	• Endometriosis related pain • Menorrhagia associated with uterine leiomyoma (premenopausal women)	None		None	
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of DVT or PE • Breast cancer (active, or history of) or other hormonally-sensitive malignancies, and those with increased risk for hormonally-sensitive malignancies • Headaches with focal neurological symptoms, or migraine headaches with aura if > 35 years of age • Hepatic disease or impairment • High risk of thrombotic or thromboembolic conditions (venous or arterial) • Hypercoagulopathies (acquired or inherited) • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient			• Osteoporosis • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Uncontrolled hypertension • Undiagnosed abnormal uterine bleeding • Vascular disease (eg, coronary artery disease)		
Estradiol valerate and dienogest [249] May 6, 2010[302]	• Abnormal uterine bleeding, without organic pathology (post-menarche) • Contraception (post-menarche)		Likely None[e]		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Active or prior history of breast cancer, or other progestin- or estrogen-sensitive cancer • Active or prior history of DVT or PE • Benign or malignant hepatic tumors, or hepatic disease • Cerebrovascular or coronary artery disease • Diabetes mellitus with vascular disease • Headaches with focal neurological symptoms or migraine headaches without or with aura if > 35 years of age			• High risk of thrombotic conditions (venous or arterial) • Hypercoagulopathies (acquired or inherited) • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Uncontrolled hypertension • Undiagnosed abnormal uterine bleeding		
Ethinyl estradiol and desogestrel[303,304]	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
December 10, 1992[305]	• Benign or malignant hepatic tumors, or hepatic disease • Breast cancer (known, suspected, or history of) • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with vascular disease • Endometrial cancer, or other estrogen-dependent neoplasia (known or suspected) • Headaches with focal neurological symptoms • Hepatocellular disease with abnormal liver function • Hypercoagulopathies (acquired or inherited)			• Hypersensitivity to the active ingredient or any excipient • Hypertension (systolic: ≥ 160 mm Hg; diastolic: ≥ 100 mm Hg), uncontrolled or severe • Jaundice with previous oral hormonal contraceptive pill use or cholestatic jaundice of pregnancy • Major surgery with prolonged immobilization • Pregnancy • Prior history of DVT or other thromboembolic conditions • Smoking and > 35 years of age • Thrombophlebitis, thromboembolic disorders, or known thrombophilic disorders • Undiagnosed abnormal genital bleeding • Valvular cardiac disease with thrombogenic complications		
Ethinyl estradiol and drospirenone[306,307] May 11, 2001[308]	• Acne vulgaris, moderate to severe (≥ 14 years of age) • Contraception (post-menarche) • Premenstrual dysphoric disorder (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Active or prior history of breast cancer, or other progestin- or estrogen-sensitive cancer • Active or prior history of DVT or PE • Adrenal insufficiency • Benign or malignant hepatic tumors • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Headaches with focal neurological symptoms or migraine headaches without or with aura if > 35 years of age			• Diabetes mellitus with vascular disease • Hepatic or renal impairment • Hypercoagulopathies (acquired or inherited) • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Uncontrolled hypertension • Undiagnosed abnormal uterine bleeding		
Ethinyl estradiol and ethynodiol diacetate[309,310] Approved prior to January 1, 1982[311-314]	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Benign or malignant hepatic tumors or hepatic disease • Breast cancer (known, suspected, or history of) • Carcinoma of the female reproductive organs (known or suspected), or estrogen-dependent neoplasia (current, suspected, or history of) • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir			• Cerebrovascular or coronary artery disease, or MI • Jaundice with previous oral hormonal contraceptive pill use or cholestatic jaundice of pregnancy • Pregnancy • Prior history of DVT or other thromboembolic conditions • Thrombophlebitis or thromboembolic disorders • Undiagnosed abnormal genital bleeding		
Ethinyl estradiol and etonogestrel[315,316]	• Contraception (post-menarche)		None		None	
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
October 3, 2001	• Active or prior history of DVT or PE • Benign or malignant hepatic tumors, or hepatic disease • Breast cancer (known, suspected, or history of), or other estrogen- or progestin-sensitive neoplasia • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with vascular disease • Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches if > 35 years of age			• High risk of thrombotic conditions (venous or arterial) • Hypercoagulopathies (acquired or inherited) • Hypersensitivity to the active ingredient or any excipient • Hypertension, uncontrolled • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Undiagnosed abnormal uterine bleeding		
Ethinyl estradiol and levonorgestrel[317,318]	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
May 10, 1982[319]	• Benign or malignant hepatic tumors, or hepatic disease (eg, acute viral hepatitis or severe decompensated cirrhosis) • BMI ≥ 30 kg/m² (patch only) • Breast cancer (known, suspected, or history of) • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Current or prior history of DVT or other thromboembolic conditions (eg, PE) • Diabetes mellitus with hypertension, vascular disease, or other end-organ injury; > 35 years of age; or a disease duration of > 20 years • Endometrial cancer, or other estrogen- or progestin-sensitive neoplasia (known or suspected) • Hypercoagulopathies (acquired or inherited)			• Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches with or without aura if > 35 years of age • Hypersensitivity to the active ingredient or any excipient • Hypertension, uncontrolled • Jaundice with previous oral hormonal contraceptive pill use or cholestatic jaundice of pregnancy • Major surgery with prolonged immobilization • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Thrombophlebitis, thromboembolic disorders, or thrombophilias (acquired or hereditary) • Undiagnosed abnormal genital or uterine bleeding • Valvular cardiac disease with thrombogenic complications		
Ethinyl estradiol and norethindrone[320,321] Approved prior to January 1, 1982[322-332]	• Acne vulgaris, moderate to severe (≥ 15 years of age) • Contraception (post-menarche)	• Acne vulgaris, moderate to severe • Contraception • Menopause-related vasomotor symptoms • Postmenopausal osteoporosis, prophylaxis	None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
	• Benign or malignant hepatic tumors, or hepatic disease • Breast cancer (known, suspected, or history of) • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with vascular disease • Endometrial cancer, or other estrogen- or progestin-sensitive neoplasia (known or suspected) • Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches if > 35 years of age • Hepatocellular disease with abnormal liver function • Hypercoagulopathies (acquired or inherited)			• Hypersensitivity to the active ingredient or any excipient • Hypertension (systolic: ≥ 160 mm Hg; diastolic: ≥ 100 mm Hg), uncontrolled or severe • Jaundice with previous oral hormonal contraceptive pill use or cholestatic jaundice of pregnancy • Major surgery with prolonged immobilization • Pregnancy • Prior history of DVT or other thromboembolic conditions • Smoking and > 35 years of age • Thrombophlebitis, thromboembolic disorders, or known thrombophilic disorders • Undiagnosed abnormal genital bleeding • Valvular cardiac disease with thrombogenic complications		
Ethinyl estradiol and norelgestromin[333,334] November 20, 2001[335]	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Active or prior history of DVT or PE • Benign or malignant hepatic tumors, or hepatic disease • BMI ≥ 30 kg/m² • Breast cancer, or other estrogen- or progestin-sensitive neoplasia (known or history of) • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with vascular disease			• Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches with or without aura if > 35 years of age • Hypercoagulopathies (acquired or inherited) • Hypertension, uncontrolled • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Undiagnosed abnormal uterine bleeding		

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Ethinyl estradiol and norgestimate[336,337] December 29, 1989[338]	• Acne vulgaris, moderate to severe (≥ 15 years of age) • Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Active or prior history of DVT or PE • Benign or malignant hepatic tumors, or hepatic disease • Breast cancer (known, suspected, or history of), or other estrogen- or progestin-sensitive neoplasia • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches if > 35 years of age			• Diabetes mellitus with vascular disease • High risk of thrombotic conditions (venous or arterial) • Hypercoagulopathies (acquired or inherited) • Hypertension, uncontrolled • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Undiagnosed abnormal uterine bleeding		
Ethinyl estradiol and norgestrel[339,340]	• Contraception (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Approved prior to January 1, 1982[341-344]	• Benign or malignant hepatic tumors, or hepatic disease • Breast cancer (known, suspected, or history of) • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with vascular disease • Endometrial cancer, or other estrogen-dependent neoplasia (known or suspected) • Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches with or without aura if > 35 years of age • Hypersensitivity to the active ingredient or any excipient			• Hypertension, uncontrolled • Jaundice with previous oral hormonal contraceptive pill use or cholestatic jaundice of pregnancy • Major surgery with prolonged immobilization • Pregnancy • Prior history of DVT or other thromboembolic conditions • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Thrombophlebitis, thromboembolic disorders, or thrombophilias (acquired or hereditary) • Undiagnosed abnormal genital or uterine bleeding • Valvular cardiac disease with thrombogenic complications		
Ethinyl estradiol and segesterone acetate[345,346] August 10, 2018	• Contraception (post-menarche)		None		None	
	Contraindications for use					
	• Active or prior history of DVT or PE • Benign or malignant hepatic tumors, or hepatic disease (eg, acute viral hepatitis or severe decompensated cirrhosis) • Breast cancer (current or history of), or other estrogen- or progestin-sensitive neoplasia • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Diabetes mellitus with hypertension, vascular disease, or other end-organ injury; > 35 years of age; or a disease duration of > 20 years • High risk of thrombotic conditions (venous or arterial)			• Headaches with focal neurological symptoms, migraine headaches with aura, or migraine headaches with or without aura if > 35 years of age • Hypercoagulopathies (acquired or inherited) • Hypersensitivity to the active ingredient or any excipient • Hypertension, uncontrolled or with vascular disease • Pregnancy • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Undiagnosed abnormal uterine bleeding		

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.6. Indications for combination sex-hormone/progestin products used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Ethinyl estradiol, drospirenone, and levomefolate[347,348] September 24, 2010[349]	• Acne vulgaris (≥ 14 years of age) • Contraception (post-menarche) • Folate supplementation (post-menarche) • Premenstrual dysphoric disorder (post-menarche)		None		None	Menstrual suppression–FTM transgender individuals[f] LOE: C
	Contraindications for use					
	• Active or prior history of DVT or PE • Adrenal insufficiency • Benign or malignant hepatic tumors or hepatic disease • Breast cancer (current or history of), or other estrogen- or progestin-sensitive neoplasia • Cerebrovascular or coronary artery disease • Concomitant use of hepatitis C regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir • Headaches with focal neurological symptoms or migraine headaches with or without aura if > 35 years of age			• Diabetes mellitus with vascular disease • Hypercoagulopathies (acquired or inherited) • Hypertension, uncontrolled • Pregnancy • Renal impairment • Smoking and > 35 years of age • Thrombogenic rhythm or thrombogenic valvular cardiac diseases • Undiagnosed abnormal uterine bleeding		

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Off-label uses for the combination product of estradiol and dienogest were based on the 'Quick Answers' view in the database; note that some off-label uses are only displayed in the 'In-Depth Answers' view, which was unable to be displayed appropriately for this combination product.*

[f] *According to Lexicomp, this agent may be used based on clinical experience to suppress menstruation in FTM transgender adults who experience continual menstrual bleeding while taking testosterone or progestogen treatment (and who are not against receiving estrogen if applicable)*

Table abbreviations: FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; OATP, organic anion transporting polypeptide; FTM, female-to-male; RCTs, randomized controlled trials

Return to TOC

Table I.A.7. Indications for aromatase inhibitors used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Anastrozole[350,351] December 27, 1995	None	• Advanced breast cancer, following disease progression on tamoxifen (postmenopausal women) • Early hormone receptor-positive breast cancer, adjuvant (postmenopausal women) • Hormone receptor-positive or -unknown, metastatic or locally advanced breast cancer (postmenopausal women), first-line	Pubertal gynecomastia • Evidence is inconclusive • Not Recommended (B)	None	None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient					
Exemestane[352,353] October 21, 1999	None	• Advanced breast cancer, following disease progression on tamoxifen (postmenopausal women) • Estrogen receptor-positive breast cancer, adjuvant (following 2 to 3 years of tamoxifen; postmenopausal women)	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book).*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports.*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: FDA, Food-and Drug Administration; LOE, level of evidence; SOE, strength of evidence; TGNB, transgender, nonbinary, or gender diverse; RCTs, randomized controlled trials

Return to TOC

Table I.A.7. Indications for aromatase inhibitors used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Letrozole[354,355] July 25, 1997[356]	None	• Advanced breast cancer, following disease progression on antiestrogen therapy (postmenopausal women) • Breast cancer, extended adjuvant (following 5 years of tamoxifen; postmenopausal women) • Early hormone receptor-positive breast cancer, adjuvant (postmenopausal women) • Hormone receptor-positive or -unknown, metastatic or locally advanced breast cancer (postmenopausal women), first-line	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Pregnancy					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book).*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports.*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: FDA, Food-and Drug Administration; LOE, level of evidence; SOE, strength of evidence; TGNB, transgender, nonbinary, or gender diverse; RCTs, randomized controlled trials

Return to TOC

Table I.A.8. Indications for selective estrogen receptor modulators (SERMs) used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Bazedoxifene acetate and conjugated/equine estrogens[357] October 3, 2013	None	• Menopause-related vasomotor symptoms • Postmenopausal osteoporosis, prophylaxis	None		None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Breast cancer (known, suspected, or history of) • Breastfeeding • Estrogen-dependent neoplasia		• Hepatic disease or impairment • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredients or any excipient • Pregnancy • Protein S, protein C, or antithrombin deficiency, or other thrombophilic condition • Undiagnosed abnormal uterine bleeding			
Clomiphene citrate[358,359] Approved prior to January 1, 1982[360]	None	• Female infertility, ovulatory dysfunction	None		None	
	Contraindications for use					
	• Abnormal uterine bleeding of unknown cause • Hepatic disease or history of hepatic impairment • Hypersensitivity to the active ingredient or any excipient • Organic intracranial lesion (eg, pituitary tumor) • Ovarian cysts, or enlargement of ovarian cysts not due to polycystic ovarian syndrome • Pregnancy • Uncontrolled adrenal or thyroid dysfunction					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE):Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: SERM, selective estrogen receptor modulator; FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.8. Indications for selective estrogen receptor modulators (SERMs) used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Ospemifene[361,362] February 26, 2013	None	• Dyspareunia due to menopause-related vulvar and vaginal atrophy • Vaginal dryness due to menopause-related vulvar and vaginal atrophy	None		None	
	Contraindications for use					
	• Active or prior history of arterial thromboembolic disease (eg, MI, stroke) • Active or prior history of DVT or PE • Estrogen-dependent neoplasia • Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredient or any excipient • Pregnancy, or those who may become pregnant • Undiagnosed abnormal genital bleeding					
Raloxifene hydrochloride[363,364] December 9, 1997	None	• Postmenopausal osteoporosis, treatment and prophylaxis • Risk reduction for invasive breast cancer (postmenopausal women at high-risk or with osteoporosis)	None		None	
	Contraindications for use					
	• Active or prior history of venous thromboembolic conditions (eg, DVT, PE, retinal vein thrombosis) • Pregnancy					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE):Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: SERM, selective estrogen receptor modulator; FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.8. Indications for selective estrogen receptor modulators (SERMs) used for gender dysphoria [a]

Active ingredient Original FDA-approval date[b]	**FDA-approved uses**		**Micromedex-indexed off-label uses** (Efficacy; Recommendation [SOE][c])		**Lexicomp-indexed off-label uses** (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Tamoxifen citrate[365,366] December 30, 1977	None	• Breast cancer, adjunct • Breast cancer, ductal carcinoma in situ • Breast cancer, prophylaxis in those at high-risk • Metastatic breast cancer	Gynecomastia • Evidence favors efficacy • Recommended, in some cases (B) Polyostotic fibrous dysplasia of bone • Evidence favors efficacy • Recommended, in some cases (B) Retinoblastoma • Evidence favors efficacy • Recommended, in some cases (C) Retroperitoneal fibrosis • Evidence favors efficacy • Recommended, in some cases (C)	None	None	
	Contraindications for use					
	• Hypersensitivity (eg, angioedema, anaphylactic reaction) to the active ingredient or any excipient • The following contraindications only apply when used for breast cancer risk reduction in high-risk patients, or in those treated for ductal carcinoma in situ of the breast: ○ Concomitant warfarin use ○ History of DVT or PE					
Toremifene citrate[367,368] May 29, 1997	None	• Metastatic breast cancer (postmenopausal women)	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Hypokalemia • Hypomagnesemia • QT prolongation (acquired or congenital)					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE):Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

Table abbreviations: SERM, selective estrogen receptor modulator; FDA, Food and Drug Administration; SOE, strength of evidence; LOE, level of evidence; TGNB, transgender, nonbinary, or gender diverse; MI, myocardial infarction; DVT, deep vein thrombophlebitis; PE, pulmonary embolism; RCTs, randomized controlled trials

Return to TOC

Table I.A.9. Indications for miscellaneous other agents used for gender dysphoria [a]

Active ingredient (Drug class) Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Danazol[369,370] (Androgen) June 21, 1976	None	• Endometriosis • Fibrocystic breast changes • Hereditary angioedema, prophylaxis	Thrombocytopenic purpura, idiopathic or immune • Evidence is inconclusive • Not Recommended (B)	None	None	
	Contraindications for use					
	• Active or prior history of thrombosis or thromboembolic disease • Androgen-dependent neoplasia • Breastfeeding or pregnancy • Hypersensitivity to the active ingredient or any excipient • Porphyria • Significantly impaired cardiac, renal, or hepatic function • Undiagnosed abnormal genital bleeding					
Methyltestosterone[e,371,372] (Androgen) Approved prior to January 1, 1982[373-402]	• Delay in puberty and/or sexual development (males) • Hypogonadotropic or primary hypogonadism	• Delay in puberty and/or sexual development (males) • Hypogonadotropic or primary hypogonadism • Metastatic breast cancer (natal females who are 1 to 5 years postmenopausal)	None		None	
	Contraindications for use					
	• Breast cancer (males) • Pregnancy • Prostate cancer (known or suspected)					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports;*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Although methyltestosterone is FDA-approved to treat metastatic breast cancer, delayed puberty, and hypogonadism (primary or hypogonadotropic), Lexicomp notes that other agents are often used to treat these conditions due to concerns of hepatic toxicity with chronic use.*

Table abbreviations: FDA, Food and Drug Administration; LOE, level of evidence; SOE, strength of evidence; TGNB, transgender, nonbinary, or gender diverse; SPRM, selective progestin receptor modulator; OTC, over-the-counter; RCTs, randomized controlled trials

Return to TOC

Table I.A.9. Indications for miscellaneous other agents used for gender dysphoria [a]

Active ingredient (Drug class) Original FDA-approval date[b]	FDA-approved uses		Micromedex-indexed off-label uses (Efficacy; Recommendation [SOE][c])		Lexicomp-indexed off-label uses (LOE)[d]	
	Any pediatric indications	**Any adult indications**	**Any pediatric uses**	**Adult TGNB uses**	**Any pediatric uses**	**Adult TGNB uses**
Minoxidil[403-405] (Vasodilator) October 18, 1979	• Hypertension	• Hypertension • Male-pattern alopecia, including in natal females	None		None	
	Contraindications for use					
	• Hypersensitivity to the active ingredient or any excipient • Per OTC labeling for the topical formulation: ○ Apply other medications to the scalp ○ Hair loss does not correspond to product labeling ○ Hair loss is sudden and/or patchy, related to childbirth, or unknown etiology ○ Labeled products for males should not be used on natal females ○ No family history of hair loss ○ Patients < 18 years of age ○ Scalp is irritated, inflamed, red, infected, or painful • Pheochromocytoma					
Ulipristal acetate[406,407] (SPRM) August 13, 2010	• Postcoital contraception (post-menarche)		None		None	
	Contraindications for use					
	• Pregnancy					

[a] *Information is reported based on Lexicomp and Micromedex. Because the indications and contraindications vary based on the formulation of the product, please refer to the drug-specific product labeling (ie, package inserts) for complete details.*

[b] *US FDA approval date for each agent was obtained from either Lexicomp or the Approved Drug Products with Therapeutic Equivalence Evaluations (often referred to as the Orange Book). Notably, the Orange Book does not provide an approval date for agents approved before January 1, 1982.*

[c] *Micromedex categories for the strength of evidence (SOE): Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies; Category C: based on expert consensus or opinion, case series or case reports;*

[d] *Lexicomp level of evidence (LOE) definitions: A: based on consistent evidence from well-conducted RCTs, or substantial evidence (other than RCTs) supporting the off-label use. Estimate of effect is unlikely to change with additional evidence.; B: based on RCTs with significant limitations (eg, methodological weaknesses, inconsistent results), or very strong evidence of another design. Estimate of effect may change with additional evidence.; C: based on observational studies, unsystematic clinical experience, or possibly faulty RCTs. Estimate of effect is uncertain.; G: use has been substantiated through its incorporation into either an evidence- or consensus-based clinical practice guideline.*

[e] *Although methyltestosterone is FDA-approved to treat metastatic breast cancer, delayed puberty, and hypogonadism (primary or hypogonadotropic), Lexicomp notes that other agents are often used to treat these conditions due to concerns of hepatic toxicity with chronic use.*

Table abbreviations: FDA, Food and Drug Administration; LOE, level of evidence; SOE, strength of evidence; TGNB, transgender, nonbinary, or gender diverse; SPRM, selective progestin receptor modulator; OTC, over-the-counter; RCTs, randomized controlled trials

Return to TOC

APPENDIX I.B: SEARCH STRATEGIES OF BIBLIOGRAPHIC DATABASES

Bibliographic database searches were conducted in phases over a period of months and are summarized in **Table I.B**.1.

Initial searches (ie, "first- corpus" searches) included structured vocabulary only (ie, medical subject headings [MeSH] in Medline and Emtree in Embase) and were initially conducted between March 9 and 23, 2023. We first ran these initial searches with filters for guidelines and systematic reviews, followed by searches for experimental, observational, descriptive, and qualitative studies.

While screening the citations that were retrieved in these initial searches, we discovered that we had excluded some additional agents that are used in patients with gender dysphoria. After adding search terms for those agents, all the structured vocabulary searches were rerun on April 11, 2023. Details of the searches with structured vocabulary only are in **Table I.B**.2 through **Table I.B**.6 (searches of Ovid Medline) and **Table I.B**.7 through **Table I.B**.11 (searches of Embase).

Comprehensive searches (ie, "second- corpus" searches, or those that included a combination of structured vocabulary and free text keywords) were run after the screening was complete for the MeSH- and Emtree-only searches, between May 15 and June 5, 2023. The combination of structured vocabulary and free-text terms is a best practice for comprehensive searches. Free text terms increase the sensitivity of searches and also increase the likelihood of identifying relevant citations that are incorrectly or incompletely indexed. These also included searches for additional guidelines and SRs, as well as additional experimental, observational, descriptive, and qualitative studies. Details of these searches are summarized in **Table I.B**.12 through **Table I.B**.17 (Ovid Medline) and **Table I.B**.18 through **Table I.B**.22 (Embase).

Table I.B.1. Summary of searches uploaded to Covidence, March 9, 2023 through June 5, 2023

Search Date	Database	Search File Name (*.ris)	Study Type	Search Term Type	Rerun/ Redo?	# References	# Duplicates	# Merged	# Added to Screening
3/9/2023	MEDLINE	Ovid 41 Guidelines Mesh-Only 3.9.23.ris	Guideline	MeSH only		41	0	0	41
3/9/2023	MEDLINE	Ovid 12 SRs Mesh-Only 3.9.23.ris	Systematic Review	MeSH only		12	3	0	9
3/20/2023	MEDLINE	Ovid 3 RCTs Mesh-Only 3.20.23.ris	RCT	MeSH only		3	0	0	3
3/21/2023	Embase	Embase 31 SRs Emtree Search 3.21.23.ris	Systematic Review	Emtree only		31	4	0	27
3/22/2023	MEDLINE	Gender Dysphoria_Ovid-Medline MESH-only search_results with RCT-CCT filter_3.22.23.ris	RCT-CCT	MeSH only		25	5	0	20
3/22/2023	MEDLINE	Gender Dysphoria_Ovid-Medline MESH-only search_observational filter_ 3.22.23.ris	Observational	MeSH only		190	29	0	161
3/23/2023	Embase	Embase 110 Guidelines Emtree-only 3.23.23.ris	Guideline	Emtree only		110	33	0	77
3/23/2023	MEDLINE	MeshOnly_Qualitative_GenderDysphoria.ris	Qualitative	MeSH only		72	42	0	30
3/31/2023	Embase	Embase 55 Experimental Studies Emtree-only Search 3.31.23.ris	Experimental	Emtree only		55	27	0	28
4/7/2023	Embase	Embase 448 Observational_Descriptive Emtree-only Search 4.7.23.ris	Observational/ Descriptive	Emtree only		448	181	0	267
4/7/2023	Embase	Embase 158 Qualitative Emtree-only Search 4.7.23.ris	Qualitative	Emtree only		158	131	0	27
4/11/2023	MEDLINE	Ovid 13 SRs Reran Mesh-Only Search 4.11.23.ris	Systematic Review	MeSH only	Yes	13	12	0	1

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.1. Summary of searches uploaded to Covidence, March 9, 2023 through June 5, 2023

Search Date	Database	Search File Name (*.ris)	Study Type	Search Term Type	Rerun/ Redo?	# References	# Duplicates	# Merged	# Added to Screening
4/11/2023	MEDLINE	Ovid 41 Guidelines Reran Mesh-Only Search 4.11.23.ris	Guideline	MeSH only	Yes	41	41	0	0
4/11/2023	MEDLINE	Ovid 3 RCTs Reran Mesh-Only Search 4.11.23.ris	RCT	MeSH only	Yes	3	3	0	0
4/11/2023	MEDLINE	Ovid 25 RCT-CCT Reran Mesh-Only Search 4.11.23.ris	RCT-CCT	MeSH only	Yes	25	25	0	0
4/11/2023	MEDLINE	Ovid 197 Observational Re-ran Mesh-Only Search 4.11.23.ris	Observational	MeSH only	Yes	197	197	0	0
4/11/2023	MEDLINE	Ovid 72 Qualitative Re-ran Mesh-Only Search 4.11.23.ris	Qualitative	MeSH only	Yes	72	72	0	0
4/11/2023	Embase	Embase 158 Qualitative Re-ran Emtree-Only Search 4.11.23.ris	Qualitative	Emtree only	Yes	158	158	0	0
4/11/2023	Embase	Embase 449 Observational Re-ran Emtree-Only Search 4.11.23.ris	Observational	Emtree only	Yes	449	448	0	1
4/11/2023	Embase	Embase 56 Experimental Re-ran Emtree-Only Search 4.11.23.ris	Experimental	Emtree only	Yes	56	56	0	0
4/11/2023	Embase	Embase 110 Guidelines Re-ran Emtree-Only Search 4.11.23.ris	Guideline	Emtree only	Yes	110	110	0	0
4/11/2023	Embase	Embase 31 SRs Re-ran Emtree-Only Search 4.11.23.ris	Systematic Review	Emtree only	Yes	31	31	0	0
5/15/2023	Embase	Embase 67 SRs free text + controlled vocabulary_5.15.23.ris	Systematic Review	free text + controlled vocabulary		67	30	0	37
5/15/2023	Embase	Embase 192 Guidelines free text + controlled vocabulary_5.15.23.ris	Guideline	free text + controlled vocabulary		192	128	0	64

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.1. Summary of searches uploaded to Covidence, March 9, 2023 through June 5, 2023

Search Date	Database	Search File Name (*.ris)	Study Type	Search Term Type	Rerun/ Redo?	# References	# Duplicates	# Merged	# Added to Screening
5/15/2023	MEDLINE	Ovid 54 SRs free text + controlled vocabulary_5.15.23.ris	Systematic Review	free text + controlled vocabulary		54	37	0	17
5/15/2023	MEDLINE	Ovid 112 Guidelines free text + controlled vocabulary_5.15.23.ris	Guideline	free text + controlled vocabulary		112	93	0	19
5/22/2023	Embase	Embase 93 Experimental studies free text + controlled vocabulary_5.22.23.ris	Experimental	free text + controlled vocabulary		93	67	0	26
5/22/2023	Embase	Embase 400 Observational_Descriptive (batch 1) studies free text + controlled vocabulary_5.22.23.ris	Observational/ Descriptive	free text + controlled vocabulary	Batch 1	400	297	0	103
5/22/2023	Embase	Embase 324 Observational_Descriptive (batch 2) studies free text + controlled vocabulary_5.22.23.ris	Observational/ Descriptive	free text + controlled vocabulary	Batch 2	324	233	0	91
5/22/2023	MEDLINE	Ovid Medline 14 RCTs free text + controlled vocabulary_5.22.23.ris	RCT	free text + controlled vocabulary		14	13	0	1
5/22/2023	MEDLINE	Ovid Medline 61 RCT-CCT free text + controlled vocabulary_5.22.23.ris	RCT-CCT	free text + controlled vocabulary		61	54	0	7
5/22/2023	MEDLINE	Ovid Medline 499 Observational_ Descriptive studies free text + controlled vocabulary_5.22.23.ris	Observational/ Descriptive	free text + controlled vocabulary		499	429	0	70
6/5/2023	Embase	Embase 380 Qualitative studies free text + controlled vocabulary_6.05.23.ris	Qualitative	free text + controlled vocabulary		380	300	0	80
6/5/2023	MEDLINE	Ovid 297 Qualitative studies free text + controlled vocabulary_6.05.23.ris	Qualitative	free text + controlled vocabulary		297	268	0	29

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

MeSH-only Searches of Ovid Medline Conducted between March 9 and April 11, 2023

Table I.B.2. MeSH-only search of Ovid Medline for guidelines and systematic reviews, initially March 9, 2023; rerun April 11, 2023

Search step	Query	Results
For the systematic review filter, we combined our traditional DRRC SR filter with a University of Texas SR filter to broaden our results.[37] The search also uses the CADTH broad guideline filter for Medline/Embase/PsycInfo.[33]		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	28,992
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,139,986
#3	1 and 2	9,126
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	347,472
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,833
#6	4 or 5	365,884
#7	3 and 6	549
#8	7 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	546
#9	limit 8 to yr = "2010 -Current"	370
#10	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or ("research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. or meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic-review?).jw. or systematic review.tw. or meta-analysis.pt.	706,329
#11	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or Clinical Decision Rules/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf. or (standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or	736,217

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.2. MeSH-only search of Ovid Medline for guidelines and systematic reviews, initially March 9, 2023; rerun April 11, 2023

Search step	Query	Results
	CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq = 2 or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf. or recommendat*.ti,kf. or guideline recommendation*.ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf. or (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf. or (guideline* or standards or consensus* or recommendat*).au.	
#12	9 and 10	12
#13	9 and 11	41
We re-ran all searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug class per Lexicomp. Deduplication was performed in Covidence.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,210
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,147,994
#3	1 and 2	9,170
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	348,064
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,939
#6	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,359
#7	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,557
#8	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,571
#9	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#10	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,153
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	398,775
#12	3 and 11	558
#13	12 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	555
#14	limit 13 to yr = "2010 -Current"	378
#15	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or ("research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or embase or medline or psyclit or (psycinfo not "psycinfo	714,668

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.2. MeSH-only search of Ovid Medline for guidelines and systematic reviews, initially March 9, 2023; rerun April 11, 2023

Search step	Query	Results
	database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. or meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic-review?).jw. or systematic review.tw. or meta-analysis.pt.	
#16	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or Clinical Decision Rules/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf. or (standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq = 2 or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf. or recommendat*.ti,kf. or guideline recommendation*.ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf. or (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf. or (guideline* or standards or consensus* or recommendat*).au.	740,221
#17	14 and 15	13
#18	14 and 16	41

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.3. MeSH-only search of Ovid Medline for randomized controlled trials, initially March 20, 2023; rerun April 11, 2023

Search step	Query	Results
For randomized controlled trials.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,069
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,142,313
#3	1 and 2	9,141
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	347,631
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,854
#6	4 or 5	366,060
#7	3 and 6	549
#8	7 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	546
#9	limit 8 to yr = "2010 -Current"	370
#10	(randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1,555,480
#11	9 and 10	3
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,210
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,147,994
#3	1 and 2	9,170
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	348,064
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,939
#6	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,359
#7	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,557
#8	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,571
#9	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.3. MeSH-only search of Ovid Medline for randomized controlled trials, initially March 20, 2023; rerun April 11, 2023

Search step	Query	Results
#10	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,153
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	398,775
#12	3 and 11	558
#13	12 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	555
#14	limit 13 to yr = "2010 -Current"	378
#15	(randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1,560,821
#16	14 and 15	3

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.4. MeSH-only search of Ovid Medline for randomized controlled trials and other experimental studies (eg, controlled clinical trials), initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
For a more sensitive search for experimental studies, we used the CADTH RCT/CCT filter for Medline/Embase/ PsycInfo.[33]		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,103
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,144,053
#3	1 and 2	9,149
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	347,736
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,880
#6	4 or 5	366,181
#7	3 and 6	549
#8	7 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	546
#9	limit 8 to yr = "2010 -Current"	370
#10	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	684,464
#11	Randomized Controlled Trial/	589,274
#12	exp Randomized Controlled Trials as Topic/	164,947
#13	"Randomized Controlled Trial (topic)"/	0
#14	Controlled Clinical Trial/	95,223
#15	exp Controlled Clinical Trials as Topic/	170,651
#16	"Controlled Clinical Trial (topic)"/	0
#17	Randomization/	106,911
#18	Random Allocation/	106,911
#19	Double-Blind Method/	174,672
#20	Double Blind Procedure/	0
#21	Double-Blind Studies/	174,672
#22	Single-Blind Method/	32,582
#23	Single Blind Procedure/	0
#24	Single-Blind Studies/	32,582
#25	Placebos/	35,926
#26	Placebo/	0

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.4. MeSH-only search of Ovid Medline for randomized controlled trials and other experimental studies (eg, controlled clinical trials), initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
#27	Control Groups/	1,925
#28	Control Group/	1,925
#29	(random* or sham or placebo*).ti,ab,hw,kf.	1,785,429
#30	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	265,145
#31	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	1,550
#32	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	1,203,930
#33	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	53,609
#34	allocated.ti,ab,hw.	82,266
#35	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	43,828
#36	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	11,756
#37	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	580
#38	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	7,511
#39	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.	11,801
#40	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.	34,820
#41	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	2,560,367
#42	9 and 41	25
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,210
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,147,994
#3	1 and 2	9,170
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	348,064
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,939
#6	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,359
#7	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,557
#8	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,571

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.4. MeSH-only search of Ovid Medline for randomized controlled trials and other experimental studies (eg, controlled clinical trials), initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
#9	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#10	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,153
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	398,775
#12	3 and 11	558
#13	12 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	555
#14	limit 13 to yr = "2010 -Current"	378
#15	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. or Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ or Randomization/ or Randomization/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or Control Groups/ or Control Group/ or (random* or sham or placebo*).ti,ab,hw,kf. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or (control* adj3 (study or studies or trial* or group*)).ti,ab,kf. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.	2,568,334
#16	14 and 15	25

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.5. MeSH-only search of Ovid Medline for observational and descriptive studies, initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
For observational and descriptive studies, we used the CADTH observational studies filter for Medline/Embase/PsycInfo.[34]		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,103
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,144,053
#3	1 and 2	9,149
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	347,736
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,880
#6	4 or 5	366,181
#7	3 and 6	549
#8	7 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	546
#9	limit 8 to yr = "2010 -Current"	370
#10	epidemiologic methods.sh.	31,613
#11	epidemiologic studies.sh.	9,285
#12	observational study/	139,665
#13	observational studies as topic/	8,597
#14	clinical studies as topic/	784
#15	controlled before-after studies/	718
#16	cross-sectional studies/	460,566
#17	historically controlled study/	225
#18	interrupted time series analysis/	1,793
#19	exp seroepidemiologic studies/	27,779
#20	national longitudinal study of adolescent health/	103
#21	cohort studies/	326,279
#22	cohort analysis/	326,279
#23	longitudinal studies/	163,864
#24	longitudinal study/	163,864
#25	prospective studies/	654,181
#26	prospective study/	654,181
#27	follow-up studies/	690,498

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.5. MeSH-only search of Ovid Medline for observational and descriptive studies, initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
#28	follow up/	0
#29	followup studies/	0
#30	retrospective studies/	1,103,777
#31	retrospective study/	1,103,777
#32	case-control studies/	326,734
#33	exp case control study/	1,401,173
#34	cross-sectional study/	460,566
#35	observational study/	139,665
#36	quasi experimental methods/	0
#37	quasi experimental study/	1,060
#38	single-case studies as topic/	98
#39	(observational study or validation studies or clinical study).pt.	145,080
#40	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	213,523
#41	cohort*.ti,ab,kf.	834,281
#42	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	523,640
#43	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	166,904
#44	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	339,131
#45	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	662,831
#46	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	156,914
#47	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	636
#48	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	228,792
#49	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	106,255
#50	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	4,842
#51	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	422,893
#52	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3,184
#53	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	19,759
#54	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	1,677
#55	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.	48,580

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.5. MeSH-only search of Ovid Medline for observational and descriptive studies, initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
#56	case series.ti,ab,kf.	101,005
#57	case reports.pt.	2,325,255
#58	case report/	0
#59	case study/	2,325,255
#60	(case adj3 (report or reports or study or studies or histories)).ti,ab,kf.	963,322
#61	organizational case studies.sh.	12,633
#62	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61	6,713,161
#63	9 and 62	190
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,210
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,147,994
#3	1 and 2	9,170
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	348,064
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,939
#6	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,359
#7	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,557
#8	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,571
#9	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#10	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,153
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	398,775
#12	3 and 11	558
#13	12 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	555
#14	limit 13 to yr = "2010 -Current"	378

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.5. MeSH-only search of Ovid Medline for observational and descriptive studies, initially March 22, 2023; rerun April 11, 2023

Search step	Query	Results
#15	(epidemiologic methods or epidemiologic studies).sh. or observational study/ or observational studies as topic/ or clinical studies as topic/ or controlled before-after studies/ or cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or exp seroepidemiologic studies/ or national longitudinal study of adolescent health/ or cohort studies/ or cohort analysis/ or longitudinal studies/ or longitudinal study/ or prospective studies/ or prospective study/ or follow-up studies/ or follow up/ or followup studies/ or retrospective studies/ or retrospective study/ or case-control studies/ or exp case control study/ or cross-sectional study/ or observational study/ or quasi experimental methods/ or quasi experimental study/ or single-case studies as topic/ or (observational study or validation studies or clinical study).pt. or (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or cohort*.ti,ab,kf. or (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf. or (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf. or ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf. or (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf. or ((natural adj experiment) or (natural adj experiments)).ti,ab,kf. or (quasi adj (experiment or experiments or experimental)).ti,ab,kf. or ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf. or case series.ti,ab,kf. or case reports.pt. or case report/ or case study/ or (case adj3 (report or reports or study or studies or histories)).ti,ab,kf. or organizational case studies.sh.	6,733,172
#16	14 and 15	197

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.6. MeSH-only search of Ovid Medline for qualitative studies, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
To find qualitative studies, we used the pragmatically-validated filters from CADTH.[35,36]		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,072
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,143,449
#3	1 and 2	9,144
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/ or Sex Reassignment Procedures/	366,143
#5	3 and 4	550
#6	limit 5 to yr = "2010 -Current"	373
#7	6 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	371
#8	exp Empirical Research/ or Interviews as Topic/ or Personal Narratives as Topic/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/	177,777
#9	(Interview or Personal Narrative).pt.	36,749
#10	interview*.ti,ab,kf.	444,084
#11	qualitative.ti,ab,kf,jw.	317,319
#12	(theme* or thematic).ti,ab,kf.	161,783
#13	ethnological research.ti,ab,kf.	8
#14	ethnograph*.ti,ab,kf.	13,677
#15	ethnomedicine.ti,ab,kf.	961
#16	ethnonursing.ti,ab,kf.	127
#17	phenomenol*.ti,ab,kf.	33,195
#18	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.	14,941
#19	life stor*.ti,ab,kf.	1,539
#20	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.	21,585
#21	(data adj1 saturat$).ti,ab,kf.	1,989
#22	participant observ*.ti,ab,kf.	5,419
#23	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern*).ti,ab,kf.	4,212
#24	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.	5,571
#25	(humanistic or existential or experiential or paradigm*).ti,ab,kf.	190,077
#26	(field adj (study or studies or research or work)).ti,ab,kf.	21,124

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.6. MeSH-only search of Ovid Medline for qualitative studies, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
#27	(human science or social science).ti,ab,kf.	6,702
#28	biographical method.ti,ab,kf.	22
#29	theoretical sampl*.ti,ab,kf.	901
#30	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.	81,883
#31	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.	173,375
#32	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.	17,855
#33	((lived or life) adj experience*).ti,ab,kf.	18,266
#34	cluster sampl*.ti,ab,kf.	9,331
#35	observational method*.ti,ab,kf.	967
#36	content analysis.ti,ab,kf.	41,472
#37	(constant adj (comparative or comparison)).ti,ab,kf.	5,903
#38	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.	3,163
#39	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.	4,723
#40	(van adj manen*).ti,ab,kf.	530
#41	(van adj kaam*).ti,ab,kf.	44
#42	(corbin* adj2 strauss*).ti,ab,kf.	433
#43	or/8-42	1,147,921
#44	"Surveys and Questionnaires"/	556,176
#45	Health Care Surveys/	33,997
#46	self report/	42,485
#47	questionnaire*.ti,ab,kf.	652,803
#48	survey*.ti,ab,kf.	823,578
#49	or/44-48	1,521,538
#50	43 or 49	2,420,873
#51	50 and 7	72
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,210
#2	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,147,994
#3	1 and 2	9,170

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.6. MeSH-only search of Ovid Medline for qualitative studies, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
#4	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/	348,064
#5	exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	27,939
#6	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,359
#7	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,557
#8	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,571
#9	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#10	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,153
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	398,775
#12	3 and 11	558
#13	12 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	555
#14	limit 13 to yr = "2010 -Current"	378
#15	exp Empirical Research/ or Interviews as Topic/ or Personal Narratives as Topic/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/ or (Interview or Personal Narrative).pt. or interview*.ti,ab,kf. or qualitative.ti,ab,kf,jw. or (theme* or thematic).ti,ab,kf. or ethnological research.ti,ab,kf. or ethnograph*.ti,ab,kf. or ethnomedicine.ti,ab,kf. or ethnonursing.ti,ab,kf. or phenomenol*.ti,ab,kf. or (grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf. or life stor*.ti,ab,kf. or (emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf. or (data adj1 saturat$).ti,ab,kf. or participant observ*.ti,ab,kf. or (social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern*).ti,ab,kf. or (action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf. or (humanistic or existential or experiential or paradigm*).ti,ab,kf. or (field adj (study or studies or research or work)).ti,ab,kf. or (human science or social science).ti,ab,kf. or biographical method.ti,ab,kf. or theoretical sampl*.ti,ab,kf. or ((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf. or (open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf. or (life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf. or ((lived or life) adj experience*).ti,ab,kf. or cluster sampl*.ti,ab,kf. or observational method*.ti,ab,kf. or content analysis.ti,ab,kf. or (constant adj (comparative or comparison)).ti,ab,kf. or ((discourse* or discurs*) adj3 analys?s).ti,ab,kf. or (heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf. or (van adj manen*).ti,ab,kf. or (van adj kaam*).ti,ab,kf. or (corbin* adj2 strauss*).ti,ab,kf.	1,153,851

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.6. MeSH-only search of Ovid Medline for qualitative studies, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
#16	"Surveys and Questionnaires"/ or Health Care Surveys/ or self report/ or questionnaire*.ti,ab,kf. or survey*.ti,ab,kf.	1,528,319
#17	15 or 16	2,432,307
#18	14 and 17	72

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Emtree-only Searches of Embase Conducted between March 21 and April 11, 2023

Table I.B.7. Emtree-only searches of Embase for systematic reviews, initially March 21, 2023; rerun April 11, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,724,785
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,111,455
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,712,617
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,337,688
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp	922,017
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	35,827
#7	#4 AND #5 AND #6	1,475
#8	#7 NOT (#1 OR #2 OR #3)	996
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	757
#10	'systematic review':jt,ab,kw OR 'meta-analy*':jt,ab,kw OR metaanalys*:jt,ab,kw OR (((systematic* OR comprehensive*) NEAR/3 (review* OR overview* OR literature OR bibliographic)):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR ((methodologic* NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab,kw) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab,kw) OR ((integrative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((pool* NEAR/3 analy*):ti,ab,kw) OR 'data synthes*':ti,ab,kw OR 'data extraction*':ti,ab,kw OR 'data abstraction*':ti,ab,kw OR handsearch*:ti,ab,kw OR 'hand search*':ti,ab,kw OR 'mantel	858,830

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.7. Emtree-only searches of Embase for systematic reviews, initially March 21, 2023; rerun April 11, 2023

Search step	Query	Results
	haenszel':ti,ab,kw OR peto:ti,ab,kw OR 'der simonian':ti,ab,kw OR dersimonian:ti,ab,kw OR 'fixed effect*':ti,ab,kw OR 'latin square*':ti,ab,kw OR 'met analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR 'technology assessment*':ti,ab,kw OR hta:ti,ab,kw OR htas:ti,ab,kw OR 'technology overview*':ti,ab,kw OR 'technology appraisal*':ti,ab,kw OR 'meta regression*':ti,ab,kw OR metaregression*:ti,ab,kw OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR psyclit:ab OR (psycinfo:ab NOT 'psycinfo database':ab) OR scopus:ab OR 'sociological abstracts':ab OR 'web of science':ab OR cochrane:it OR ((health NEXT/2 'technology assessment'):it) OR 'evidence report':it OR ((comparative NEXT/3 (efficacy OR effectiveness)):ti,ab,kw) OR 'outcomes research':ti,ab,kw OR 'relative effectiveness':ti,ab,kw OR (((indirect OR 'indirect treatment' OR 'mixed treatment' OR bayesian) NEXT/3 comparison*):ti,ab,kw) OR ((multi* NEXT/3 treatment NEXT/2 comparison*):ti,ab,kw) OR 'umbrella review*':ti,ab,kw OR ((multiparamet* NEXT/3 synthesis):ti,ab,kw) OR (('multi paramet*' NEXT/3 synthesis):ti,ab,kw)	
#11	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review (topic)'/exp OR 'meta analysis (topic)'/exp OR 'biomedical technology assessment'/exp	593,824
#12	#10 OR #11	988,917
#13	#9 AND #12	31
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	'conference abstract'/it OR 'conference review'/it	4,744,219
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,941
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,726
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,724
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp OR 'gonadorelin	989,250

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.7. Emtree-only searches of Embase for systematic reviews, initially March 21, 2023; rerun April 11, 2023

Search step	Query	Results
	antagonist'/exp OR 'elagolix'/exp OR 'degarelix'/exp OR 'ganirelix'/exp OR 'elagolix plus estradiol plus norethisterone acetate'/exp OR 'aromatase inhibitor'/exp OR 'selective estrogen receptor modulator'/exp OR 'antiestrogen'/exp OR 'progesterone receptor modulator'/de OR 'ulipristal'/exp OR 'hormonal contraceptive agent'/exp	
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,130
#7	#4 AND #5 AND #6	1,503
#8	#7 NOT (#1 OR #2 OR #3)	1,002
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	763
#10	'systematic review':jt,ab,kw OR 'meta-analy*':jt,ab,kw OR metaanalys*:jt,ab,kw OR (((systematic* OR comprehensive*) NEAR/3 (review* OR overview* OR literature OR bibliographic)):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR ((methodologic* NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab,kw) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab,kw) OR ((integrative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((pool* NEAR/3 analy*):ti,ab,kw) OR 'data synthes*':ti,ab,kw OR 'data extraction*':ti,ab,kw OR 'data abstraction*':ti,ab,kw OR handsearch*:ti,ab,kw OR 'hand search*':ti,ab,kw OR 'mantel haenszel':ti,ab,kw OR peto:ti,ab,kw OR 'der simonian':ti,ab,kw OR dersimonian:ti,ab,kw OR 'fixed effect*':ti,ab,kw OR 'latin square*':ti,ab,kw OR 'met analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR 'technology assessment*':ti,ab,kw OR hta:ti,ab,kw OR htas:ti,ab,kw OR 'technology overview*':ti,ab,kw OR 'technology appraisal*':ti,ab,kw OR 'meta regression*':ti,ab,kw OR metaregression*:ti,ab,kw OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR psyclit:ab OR (psycinfo:ab NOT 'psycinfo database':ab) OR scopus:ab OR 'sociological abstracts':ab OR 'web of science':ab OR cochrane:it OR ((health NEXT/2 'technology assessment'):it) OR 'evidence report':it OR ((comparative NEXT/3 (efficacy OR effectiveness)):ti,ab,kw) OR 'outcomes research':ti,ab,kw OR 'relative effectiveness':ti,ab,kw OR (((indirect OR 'indirect treatment' OR 'mixed treatment' OR bayesian) NEXT/3 comparison*):ti,ab,kw) OR ((multi* NEXT/3 treatment NEXT/2 comparison*):ti,ab,kw) OR 'umbrella review*':ti,ab,kw OR ((multiparamet* NEXT/3 synthesis):ti,ab,kw) OR (('multi paramet*' NEXT/3 synthesis):ti,ab,kw)	864,611
#11	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review (topic)'/exp OR 'meta analysis (topic)'/exp OR 'biomedical technology assessment'/exp	597,972
#12	#10 OR #11	995,437
#13	#9 AND #12	31

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.8. Emtree-only searches of Embase for guidelines, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,727,606
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,112,070
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,714,271
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,339,393
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp	922,697
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	35,864
#7	#4 AND #5 AND #6	1,482
#8	#7 NOT (#1 OR #2 OR #3)	996
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	757
#10	'clinical protocol'/exp OR 'consensus'/exp OR 'consensus development'/exp OR 'clinical pathway'/exp OR 'guideline'/exp OR 'practice guideline'/exp OR 'clinical decision rule'/exp OR 'position statement*':ti,ab,kw OR 'policy statement*':ti,ab,kw OR 'practice parameter*':ti,ab,kw OR 'best practice*':ti,ab,kw OR 'standards':ti,kw OR 'guideline':ti,kw OR 'guidelines':ti,kw OR ((('practice' OR 'treatment*' OR 'clinical') NEXT/1 'guideline*'):ab) OR 'cpg':ti OR 'cpgs':ti OR 'consensus*':ti,kw OR ((('critical' OR 'clinical' OR 'practice') NEXT/2 ('path' OR 'paths' OR 'pathway' OR 'pathways' OR 'protocol*')):ti,ab,kw) OR 'recommendat*':ti,kw OR 'guideline recommendation*':ab OR (('care' NEAR/2 ('standard' OR 'path' OR 'paths' OR 'pathway' OR 'pathways' OR 'map' OR 'maps' OR 'plan' OR 'plans')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('screening' OR 'examination' OR 'test' OR 'tested' OR 'testing' OR 'assessment*' OR 'diagnosis' OR 'diagnoses' OR 'diagnosed' OR 'diagnosing')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('pharmacotherap*' OR 'chemotherap*'	1,156,211

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.8. Emtree-only searches of Embase for guidelines, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
	OR 'chemotreatment*' OR 'therap*' OR 'treatment*' OR 'intervention*')):ti,ab,kw) OR 'guideline*':au OR 'standards':au OR 'consensus*':au OR 'recommendat*':au	
#11	#9 AND #10	110
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	'conference abstract'/it OR 'conference review'/it	4,744,219
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,941
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,726
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,724
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp OR 'gonadorelin antagonist'/exp OR 'elagolix'/exp OR 'degarelix'/exp OR 'ganirelix'/exp OR 'elagolix plus estradiol plus norethisterone acetate'/exp OR 'aromatase inhibitor'/exp OR 'selective estrogen receptor modulator'/exp OR 'antiestrogen'/exp OR 'progesterone receptor modulator'/de OR 'ulipristal'/exp OR 'hormonal contraceptive agent'/exp	989,250
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,130
#7	#4 AND #5 AND #6	1,503
#8	#7 NOT (#1 OR #2 OR #3)	1,002
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	763
#10	'clinical protocol'/exp OR 'consensus'/exp OR 'consensus development'/exp OR 'clinical pathway'/exp OR 'guideline'/exp OR 'practice guideline'/exp OR 'clinical decision rule'/exp OR 'position statement*':ti,ab,kw OR 'policy statement*':ti,ab,kw OR 'practice	1,160,702

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.8. Emtree-only searches of Embase for guidelines, initially March 23, 2023; rerun April 11, 2023

Search step	Query	Results
	parameter*':ti,ab,kw OR 'best practice*':ti,ab,kw OR 'standards':ti,kw OR 'guideline':ti,kw OR 'guidelines':ti,kw OR ((('practice' OR 'treatment*' OR 'clinical') NEXT/1 'guideline*'):ab) OR 'cpg':ti OR 'cpgs':ti OR 'consensus*':ti,kw OR ((('critical' OR 'clinical' OR 'practice') NEXT/2 ('path' OR 'paths' OR 'pathway' OR 'pathways' OR 'protocol*')):ti,ab,kw) OR 'recommendat*':ti,kw OR 'guideline recommendation*':ab OR (('care' NEAR/2 ('standard' OR 'path' OR 'paths' OR 'pathway' OR 'pathways' OR 'map' OR 'maps' OR 'plan' OR 'plans')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('screening' OR 'examination' OR 'test' OR 'tested' OR 'testing' OR 'assessment*' OR 'diagnosis' OR 'diagnoses' OR 'diagnosed' OR 'diagnosing')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('pharmacotherap*' OR 'chemotherap*' OR 'chemotreatment*' OR 'therap*' OR 'treatment*' OR 'intervention*')):ti,ab,kw) OR 'guideline*':au OR 'standards':au OR 'consensus*':au OR 'recommendat*':au	
#11	#9 AND #10	110

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.9. Emtree-only searches of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), initially March 31, 2023; rerun April 11, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,736,809
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,114,206
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,719,652
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,344,127
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp	924,277
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,036
#7	#4 AND #5 AND #6	1,497
#8	#7 NOT (#1 OR #2 OR #3)	998
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	759
#10	'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'noninferiority trial'/exp OR 'randomization'/de OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'random*':ti,ab,de,kw OR 'sham':ti,ab,de,kw OR 'placebo*':ti,ab,de,kw OR ((('singl*' OR 'doubl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR ((('tripl*' OR 'trebl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR (('control*' NEAR/3 ('study' OR 'studies' OR 'trial*' OR 'group*')):ti,ab,kw) OR 'nonrandom*':ti,ab,de,kw OR 'non-random*':ti,ab,de,kw OR 'quasi-random*':ti,ab,de,kw OR 'quasirandom*':ti,ab,de,kw OR 'allocated':ti,ab,de OR (('open-label' NEAR/5 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('equivalence' OR 'superiority' OR 'non-inferiority' OR 'noninferiority') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR 'pragmatic study':ti,ab,de,kw OR 'pragmatic studies':ti,ab,de,kw OR ((('pragmatic' OR 'practical') NEAR/3 trial*):ti,ab,de,kw) OR ((('quasiexperimental' OR	4,431,083

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.9. Emtree-only searches of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), initially March 31, 2023; rerun April 11, 2023

Search step	Query	Results
	'quasi-experimental') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('phase' NEAR/3 ('iii' OR '3')):ti,de,kw) AND ('study':ti,de,kw OR 'studies':ti,de,kw OR 'trial*':ti,de,kw))	
#11	#9 AND #10	55
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	'conference abstract'/it OR 'conference review'/it	4,744,219
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,941
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,726
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,724
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp OR 'gonadorelin antagonist'/exp OR 'elagolix'/exp OR 'degarelix'/exp OR 'ganirelix'/exp OR 'elagolix plus estradiol plus norethisterone acetate'/exp OR 'aromatase inhibitor'/exp OR 'selective estrogen receptor modulator'/exp OR 'antiestrogen'/exp OR 'progesterone receptor modulator'/de OR 'ulipristal'/exp OR 'hormonal contraceptive agent'/exp	989,250
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,130
#7	#4 AND #5 AND #6	1,503
#8	#7 NOT (#1 OR #2 OR #3)	1,002
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	763
#10	'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'clinical trial'/exp	4,437,758

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.9. Emtree-only searches of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), initially March 31, 2023; rerun April 11, 2023

Search step	Query	Results
	OR 'clinical trial (topic)'/exp OR 'noninferiority trial'/exp OR 'randomization'/de OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'random*':ti,ab,de,kw OR 'sham':ti,ab,de,kw OR 'placebo*':ti,ab,de,kw OR ((('singl*' OR 'doubl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR ((('tripl*' OR 'trebl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR (('control*' NEAR/3 ('study' OR 'studies' OR 'trial*' OR 'group*')):ti,ab,kw) OR 'nonrandom*':ti,ab,de,kw OR 'non-random*':ti,ab,de,kw OR 'quasi-random*':ti,ab,de,kw OR 'quasirandom*':ti,ab,de,kw OR 'allocated':ti,ab,de OR (('open-label' NEAR/5 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('equivalence' OR 'superiority' OR 'non-inferiority' OR 'noninferiority') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR 'pragmatic study':ti,ab,de,kw OR 'pragmatic studies':ti,ab,de,kw OR ((('pragmatic' OR 'practical') NEAR/3 trial*):ti,ab,de,kw) OR ((('quasiexperimental' OR 'quasi-experimental') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('phase' NEAR/3 ('iii' OR '3')):ti,de,kw) AND ('study':ti,de,kw OR 'studies':ti,de,kw OR 'trial*':ti,de,kw))	
#11	#9 AND #10	56

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.10. Emtree-only searches of Embase for observational and descriptive studies, initially April 7, 2023; rerun April 11, 2023

Step search	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,742,383
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,800
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,377
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,298
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp	925,060
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,122
#7	#4 AND #5 AND #6	1,500
#8	#7 NOT (#1 OR #2 OR #3)	1,001
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	762
#10	'epidemiology'/de OR 'observational study'/de OR 'clinical study'/exp OR 'cross-sectional study'/exp OR 'seroepidemiology'/exp OR 'national longitudinal study of adolescent health'/de OR 'cohort analysis'/de OR 'longitudinal study'/de OR 'prospective study'/de OR 'follow up'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'quasi experimental study'/de OR 'single-case study'/de OR 'validation study'/de OR 'pilot study'/de OR 'controlled study'/de OR 'pretest posttest control group design'/de OR 'comparative study'/de OR 'comparative effectiveness'/de OR (('observational' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'cohort*':ti,ab,kw OR (('prospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('follow up' OR 'followup') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('longitudinal' OR 'longterm' OR 'long-term') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data')):ti,ab,kw) OR (('retrospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data' OR 'review')):ti,ab,kw) OR (('case' NEXT/1	19,514,851

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.10. Emtree-only searches of Embase for observational and descriptive studies, initially April 7, 2023; rerun April 11, 2023

Step search	Query	Results
	'control'):ti,ab,kw) OR (('case' NEXT/1 'comparison'):ti,ab,kw) OR (('case' NEXT/1 'controlled'):ti,ab,kw) OR (('case-referent' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('population' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('descriptive' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('multidimensional' OR 'multi-dimensional') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('cross-sectional' NEAR/7 ('study' OR 'studies' OR 'design' OR 'research' OR 'analysis' OR 'analyses' OR 'survey' OR 'findings')):ti,ab,kw) OR (('natural' NEXT/1 'experiment'):ti,ab,kw) OR (('natural' NEXT/1 'experiments'):ti,ab,kw) OR (('quasi' NEXT/1 ('experiment' OR 'experiments' OR 'experimental')):ti,ab,kw) OR ((('non experiment' OR 'nonexperiment' OR 'non experimental' OR 'nonexperimental') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('prevalence' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'case series':ti,ab,kw OR 'case report'/de OR 'case study'/exp OR (('case' NEAR/3 ('report' OR 'reports' OR 'study' OR 'studies' OR 'histories')):ti,ab,kw) OR 'health services research'/de	
#11	#9 AND #10	448
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	'conference abstract'/it OR 'conference review'/it	4,744,219
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,941
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,726
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,724
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp OR 'gonadorelin antagonist'/exp OR 'elagolix'/exp OR 'degarelix'/exp OR 'ganirelix'/exp OR	989,250

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.10. Emtree-only searches of Embase for observational and descriptive studies, initially April 7, 2023; rerun April 11, 2023

Step search	Query	Results
	'elagolix plus estradiol plus norethisterone acetate'/exp OR 'aromatase inhibitor'/exp OR 'selective estrogen receptor modulator'/exp OR 'antiestrogen'/exp OR 'progesterone receptor modulator'/de OR 'ulipristal'/exp OR 'hormonal contraceptive agent'/exp	
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,130
#7	#4 AND #5 AND #6	1,503
#8	#7 NOT (#1 OR #2 OR #3)	1,002
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	763
#10	'epidemiology'/de OR 'observational study'/de OR 'clinical study'/exp OR 'cross-sectional study'/exp OR 'seroepidemiology'/exp OR 'national longitudinal study of adolescent health'/de OR 'cohort analysis'/de OR 'longitudinal study'/de OR 'prospective study'/de OR 'follow up'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'quasi experimental study'/de OR 'single-case study'/de OR 'validation study'/de OR 'pilot study'/de OR 'controlled study'/de OR 'pretest posttest control group design'/de OR 'comparative study'/de OR 'comparative effectiveness'/de OR (('observational' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'cohort*':ti,ab,kw OR (('prospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('follow up' OR 'followup') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('longitudinal' OR 'longterm' OR 'long-term') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data')):ti,ab,kw) OR (('retrospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data' OR 'review')):ti,ab,kw) OR (('case' NEXT/1 'control'):ti,ab,kw) OR (('case' NEXT/1 'comparison'):ti,ab,kw) OR (('case' NEXT/1 'controlled'):ti,ab,kw) OR (('case-referent' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('population' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('descriptive' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('multidimensional' OR 'multi-dimensional') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('cross-sectional' NEAR/7 ('study' OR 'studies' OR 'design' OR 'research' OR 'analysis' OR 'analyses' OR 'survey' OR 'findings')):ti,ab,kw) OR (('natural' NEXT/1 'experiment'):ti,ab,kw) OR (('natural' NEXT/1 'experiments'):ti,ab,kw) OR (('quasi' NEXT/1 ('experiment' OR 'experiments' OR 'experimental')):ti,ab,kw) OR ((('non experiment' OR 'nonexperiment' OR 'non experimental' OR 'nonexperimental') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('prevalence' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'case series':ti,ab,kw OR 'case report'/de OR 'case study'/exp OR (('case' NEAR/3 ('report' OR 'reports' OR 'study' OR 'studies' OR 'histories')):ti,ab,kw) OR 'health services research'/de	19,517,871
#11	#9 AND #10	449

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.11. Emtree-only searches of Embase for qualitative studies, initially April 7, 2023; rerun April 11, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,742,383
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,800
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,377
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,298
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp	925,060
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,122
#7	#4 AND #5 AND #6	1,500
#8	#7 NOT (#1 OR #2 OR #3)	1,001
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	762
#10	'empirical research'/exp OR 'interview'/exp OR 'literature'/exp OR 'focus group'/exp OR 'information processing'/exp OR 'verbal communication'/exp OR 'nursing methodology research'/de OR 'narrative medicine'/de OR 'interview*':ti,ab,kw OR 'qualitative':ti,ab,kw,jt OR 'theme*':ti,ab,kw OR 'thematic':ti,ab,kw OR 'ethnological research':ti,ab,kw OR 'ethnograph*':ti,ab,kw OR 'ethnomedicine':ti,ab,kw OR 'ethnonursing':ti,ab,kw OR 'phenomenol*':ti,ab,kw OR (('grounded' NEXT/1 ('theor*' OR 'study' OR 'studies' OR 'research' OR 'analys?s')):ti,ab,kw) OR 'life stor*':ti,ab,kw OR 'emic':ti,ab,kw OR 'etic':ti,ab,kw OR 'hermeneutic*':ti,ab,kw OR 'heuristic*':ti,ab,kw OR 'semiotic*':ti,ab,kw OR (('data' NEAR/1 'saturat*'):ti,ab,kw) OR 'participant observ*':ti,ab,kw OR 'social construct*':ti,ab,kw OR 'postmodern*':ti,ab,kw OR 'post-structural*':ti,ab,kw OR 'poststructural*':ti,ab,kw OR 'post-modern*':ti,ab,kw OR 'action research':ti,ab,kw OR 'cooperative inquir*':ti,ab,kw OR 'co-operative inquir*':ti,ab,kw OR 'humanistic':ti,ab,kw OR 'existential':ti,ab,kw OR 'experiential':ti,ab,kw OR 'paradigm*':ti,ab,kw OR (('field' NEXT/1 ('study' OR 'studies' OR 'research' OR 'work')):ti,ab,kw) OR 'human	4,231,970

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.11. Emtree-only searches of Embase for qualitative studies, initially April 7, 2023; rerun April 11, 2023

Search step	Query	Results
	science':ti,ab,kw OR 'social science':ti,ab,kw OR 'biographical method':ti,ab,kw OR 'theoretical sampl*':ti,ab,kw OR (('purpos*' NEAR/4 'sampl*'):ti,ab,kw) OR (('focus' NEXT/1 'group*'):ti,ab,kw) OR 'open-ended':ti,ab,kw OR 'narrative*':ti,ab,kw OR 'textual':ti,ab,kw OR 'texts':ti,ab,kw OR 'semi-structured':ti,ab,kw OR 'life-world*':ti,ab,kw OR 'conversation analys?s':ti,ab,kw OR 'personal experience*':ti,ab,kw OR 'theoretical saturation':ti,ab,kw OR ((('lived' OR 'life') NEXT/1 'experience*'):ti,ab,kw) OR 'cluster sampl*':ti,ab,kw OR 'observational method*':ti,ab,kw OR 'content analysis':ti,ab,kw OR (('constant' NEXT/1 ('comparative' OR 'comparison')):ti,ab,kw) OR ((('discourse*' OR 'discurs*') NEAR/3 'analys?s'):ti,ab,kw) OR 'heidegger*':ti,ab,kw OR 'colaizzi*':ti,ab,kw OR 'spiegelberg*':ti,ab,kw OR 'merleau*':ti,ab,kw OR 'husserl*':ti,ab,kw OR 'foucault*':ti,ab,kw OR 'ricoeur':ti,ab,kw OR 'glaser*':ti,ab,kw OR (('van' NEXT/1 'manen*'):ti,ab,kw) OR (('van' NEXT/1 'kaam*'):ti,ab,kw) OR (('corbin*' NEAR/2 'strauss*'):ti,ab,kw)	
#11	'questionnaire'/exp OR 'health care survey'/de OR 'self report'/de OR 'questionnaire*':ti,ab,kw OR 'survey*':ti,ab,kw	2,055,085
#12	#10 OR #11	5,744,629
#13	#9 AND #12	158
We re-ran the searches to include additional agents for menstrual suppression that were missing from our initial literature searches. We used information from Grimstad et al (2021)[81] to inform which agents should be included, and we added other agents in the same drug classes (per Lexicomp).[28] Deduplication was performed in Covidence.		
#1	'conference abstract'/it OR 'conference review'/it	4,744,219
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,116,941
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,726,726
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR 'pediatric'/exp OR 'child'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	4,348,724
#5	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'gender dysphoria'/exp/dd_dt OR 'puberty suppression'/exp OR 'gonadorelin antagonist'/exp OR 'elagolix'/exp OR 'degarelix'/exp OR 'ganirelix'/exp OR 'elagolix plus	989,250

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.11. Emtree-only searches of Embase for qualitative studies, initially April 7, 2023; rerun April 11, 2023

Search step	Query	Results
	estradiol plus norethisterone acetate'/exp OR 'aromatase inhibitor'/exp OR 'selective estrogen receptor modulator'/exp OR 'antiestrogen'/exp OR 'progesterone receptor modulator'/de OR 'ulipristal'/exp OR 'hormonal contraceptive agent'/exp	
#6	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,130
#7	#4 AND #5 AND #6	1,503
#8	#7 NOT (#1 OR #2 OR #3)	1,002
#9	#7 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	763
#10	'empirical research'/exp OR 'interview'/exp OR 'literature'/exp OR 'focus group'/exp OR 'information processing'/exp OR 'verbal communication'/exp OR 'nursing methodology research'/de OR 'narrative medicine'/de OR 'interview*':ti,ab,kw OR 'qualitative':ti,ab,kw,jt OR 'theme*':ti,ab,kw OR 'thematic':ti,ab,kw OR 'ethnological research':ti,ab,kw OR 'ethnograph*':ti,ab,kw OR 'ethnomedicine':ti,ab,kw OR 'ethnonursing':ti,ab,kw OR 'phenomenol*':ti,ab,kw OR (('grounded' NEXT/1 ('theor*' OR 'study' OR 'studies' OR 'research' OR 'analys?s')):ti,ab,kw) OR 'life stor*':ti,ab,kw OR 'emic':ti,ab,kw OR 'etic':ti,ab,kw OR 'hermeneutic*':ti,ab,kw OR 'heuristic*':ti,ab,kw OR 'semiotic*':ti,ab,kw OR (('data' NEAR/1 'saturat*'):ti,ab,kw) OR 'participant observ*':ti,ab,kw OR 'social construct*':ti,ab,kw OR 'postmodern*':ti,ab,kw OR 'post-structural*':ti,ab,kw OR 'poststructural*':ti,ab,kw OR 'post-modern*':ti,ab,kw OR 'action research':ti,ab,kw OR 'cooperative inquir*':ti,ab,kw OR 'co-operative inquir*':ti,ab,kw OR 'humanistic':ti,ab,kw OR 'existential':ti,ab,kw OR 'experiential':ti,ab,kw OR 'paradigm*':ti,ab,kw OR (('field' NEXT/1 ('study' OR 'studies' OR 'research' OR 'work')):ti,ab,kw) OR 'human science':ti,ab,kw OR 'social science':ti,ab,kw OR 'biographical method':ti,ab,kw OR 'theoretical sampl*':ti,ab,kw OR (('purpos*' NEAR/4 'sampl*'):ti,ab,kw) OR (('focus' NEXT/1 'group*'):ti,ab,kw) OR 'open-ended':ti,ab,kw OR 'narrative*':ti,ab,kw OR 'textual':ti,ab,kw OR 'texts':ti,ab,kw OR 'semi-structured':ti,ab,kw OR 'life-world*':ti,ab,kw OR 'conversation analys?s':ti,ab,kw OR 'personal experience*':ti,ab,kw OR 'theoretical saturation':ti,ab,kw OR ((('lived' OR 'life') NEXT/1 'experience*'):ti,ab,kw) OR 'cluster sampl*':ti,ab,kw OR 'observational method*':ti,ab,kw OR 'content analysis':ti,ab,kw OR (('constant' NEXT/1 ('comparative' OR 'comparison')):ti,ab,kw) OR ((('discourse*' OR 'discurs*') NEAR/3 'analys?s'):ti,ab,kw) OR 'heidegger*':ti,ab,kw OR 'colaizzi*':ti,ab,kw OR 'spiegelberg*':ti,ab,kw OR 'merleau*':ti,ab,kw OR 'husserl*':ti,ab,kw OR 'foucault*':ti,ab,kw OR 'ricoeur':ti,ab,kw OR 'glaser*':ti,ab,kw OR (('van' NEXT/1 'manen*'):ti,ab,kw) OR (('van' NEXT/1 'kaam*'):ti,ab,kw) OR (('corbin*' NEAR/2 'strauss*'):ti,ab,kw)	4,232,886
#11	'questionnaire'/exp OR 'health care survey'/de OR 'self report'/de OR 'questionnaire*':ti,ab,kw OR 'survey*':ti,ab,kw	2,055,402
#12	#10 OR #11	5,745,753

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.11. Emtree-only searches of Embase for qualitative studies, initially April 7, 2023; rerun April 11, 2023

Search step	Query	Results
#13	#9 AND #12	158

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Free Text and Controlled Vocabulary Searches of Ovid Medline Conducted between May 15 and June 5, 2023

Table I.B.12. Free text and controlled vocabulary search of Ovid Medline for systematic reviews, May 15, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,154,915
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,138,237
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	295,441
#4	1 or 2 or 3	4,019,870
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,058
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	983
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,589
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,600
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,197
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,168
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	455
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,514
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,895
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or	447,368

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.12. Free text and controlled vocabulary search of Ovid Medline for systematic reviews, May 15, 2023

Search step	Query	Results
	medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,109
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,678
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,606
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,545
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,784
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	676,692
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,387
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,789
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	2,964
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	887
#27	23 or 24 or 25 or 26	37,984
#28	4 and 22 and 27	1,686
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,667
#30	limit 29 to yr = "2010 -Current"	1,133
#31	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or ("research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. or meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview	721,963

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.12. Free text and controlled vocabulary search of Ovid Medline for systematic reviews, May 15, 2023

Search step	Query	Results
	adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic-review?).jw. or systematic review.tw. or meta-analysis.pt.	
#32	30 and 31	54

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.13. Free text and controlled vocabulary search of Ovid Medline for guidelines, May 15, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,154,915
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,138,237
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	295,441
#4	1 or 2 or 3	4,019,870
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,058
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	983
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,589
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,600
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,197
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,168
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	455
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,514
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,895
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	447,368

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.13. Free text and controlled vocabulary search of Ovid Medline for guidelines, May 15, 2023

Search step	Query	Results
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,109
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,678
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,606
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,545
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,784
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	676,692
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,387
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,789
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	2,964
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	887
#27	23 or 24 or 25 or 26	37,984
#28	4 and 22 and 27	1,686
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,667
#30	limit 29 to yr = "2010 -Current"	1,133
#31	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or Clinical Decision Rules/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf. or (standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq = 2 or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf. or recommendat*.ti,kf. or guideline recommendation*.ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf. or (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf. or (guideline* or standards or consensus* or recommendat*).au.	743,713
#32	30 and 31	112

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.14. Free text and controlled vocabulary search of Ovid Medline for randomized controlled trials, May 22, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,156,084
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,140,449
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	295,801
#4	1 or 2 or 3	4,022,329
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,170
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	981
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,603
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,611
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,202
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,198
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	455
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,533
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,898
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or	447,681

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.14. Free text and controlled vocabulary search of Ovid Medline for randomized controlled trials, May 22, 2023

Search step	Query	Results
	norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,188
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,705
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,634
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,576
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,792
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	677,117
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,396
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,839
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	2,980
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	887
#27	23 or 24 or 25 or 26	38,036
#28	4 and 22 and 27	1,688
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,669
#30	limit 29 to yr = "2010 -Current"	1,135
#31	(randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1,568,977
#32	30 and 31	14

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.15. Free text and controlled vocabulary search of Ovid Medline for randomized controlled trials, May 22, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,156,084
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,140,449
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	295,801
#4	1 or 2 or 3	4,022,329
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,170
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	981
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,603
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,611
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,202
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,198
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	455
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,533
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,898
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or	447,681

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.15. Free text and controlled vocabulary search of Ovid Medline for randomized controlled trials, May 22, 2023

Search step	Query	Results
	norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,188
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,705
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,634
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,576
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,792
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	677,117
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,396
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,839
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	2,980
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	887
#27	23 or 24 or 25 or 26	38,036
#28	4 and 22 and 27	1,688
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,669
#30	limit 29 to yr = "2010 -Current"	1,135
#31	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. or Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ or Randomization/ or Randomization/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or Control Groups/ or Control Group/ or (random* or sham or placebo*).ti,ab,hw,kf. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or (control* adj3 (study or studies or trial* or group*)).ti,ab,kf. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or	2,583,567

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.15. Free text and controlled vocabulary search of Ovid Medline for randomized controlled trials, May 22, 2023

Search step	Query	Results
	pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.	
#32	30 and 31	61

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.16. Free text and controlled vocabulary search of Ovid Medline for observational and descriptive studies, May 22, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,156,084
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,140,449
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	295,801
#4	1 or 2 or 3	4,022,329
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,170
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	981
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,603
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,611
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,202
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,198
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	455
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,533
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,898
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or	447,681

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.16. Free text and controlled vocabulary search of Ovid Medline for observational and descriptive studies, May 22, 2023

Search step	Query	Results
	norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,188
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,705
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,634
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,576
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,792
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	677,117
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,396
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,839
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	2,980
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	887
#27	23 or 24 or 25 or 26	38,036
#28	4 and 22 and 27	1,688
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,669
#30	limit 29 to yr = "2010 -Current"	1,135
#31	(epidemiologic methods or epidemiologic studies).sh. or observational study/ or observational studies as topic/ or clinical studies as topic/ or controlled before-after studies/ or cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or exp seroepidemiologic studies/ or national longitudinal study of adolescent health/ or cohort studies/ or cohort analysis/ or longitudinal studies/ or longitudinal study/ or prospective studies/ or prospective study/ or follow-up studies/ or follow up/ or followup studies/ or retrospective studies/ or retrospective study/ or case-control studies/ or exp case control study/ or cross-sectional study/ or observational study/ or quasi experimental methods/ or quasi experimental study/ or single-case studies as topic/ or (observational study or validation studies or clinical study).pt. or (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or cohort*.ti,ab,kf. or (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((longitudinal or longterm or (long adj term)) adj7 (study or studies	6,771,779

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.16. Free text and controlled vocabulary search of Ovid Medline for observational and descriptive studies, May 22, 2023

Search step	Query	Results
	or design or analysis or analyses or data)).ti,ab,kf. or (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf. or ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf. or (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf. or ((natural adj experiment) or (natural adj experiments)).ti,ab,kf. or (quasi adj (experiment or experiments or experimental)).ti,ab,kf. or ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf. or case series.ti,ab,kf. or case reports.pt. or case report/ or case study/ or (case adj3 (report or reports or study or studies or histories)).ti,ab,kf. or organizational case studies.sh.	
#32	30 and 31	499

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.17. Free text and controlled vocabulary search of Ovid Medline for qualitative studies, June 5, 2023

Search step	Query	Results
#1	Pediatrics/ or Child/ or Minors/ or Adolescent/ or Puberty/	3,158,365
#2	(adolescen* or boy* or girl* or child or children or juvenile or minors or paediatr* or pediatr* or pre-pubertal or prepubertal or pre-pubesc* or prepubesc* or pubesc* or pubertal or puberty or teen* or youth* or school-aged).ti,ab,kw,kf.	2,144,528
#3	(adolescen* or child* or paediatr* or pediatr*).jn.	296,222
#4	1 or 2 or 3	4,026,855
#5	exp Gonadotropin-releasing hormone/ or exp Gonadal Steroid Hormones/ or exp Hormone Replacement Therapy/ or exp Androgens/ or exp Estrogens/ or exp Progesterone/ or Sex Reassignment Procedures/ or exp Androgen antagonists/ or Bicalutamide/ or Finasteride/ or Dutasteride/ or exp Cyproterone/ or Spironolactone/	367,444
#6	Gender dysphoria/dt or Gender dysphoria/th or Transsexualism/dt or Transsexualism/th	982
#7	Elagolix/ or Cetrorelix/ or Degarelix/ or Ganirelix/ or Relugolix/ or Danazol/	2,360
#8	Selective Estrogen Receptor Modulators/ or exp Tamoxifen/ or exp Clomiphene/ or Ospemifene/ or Bazedoxifene/	29,611
#9	Aromatase Inhibitors/ or Letrozole/ or Anastrozole/ or Exemestane/	8,618
#10	Selective progesterone receptor modulator EC313/ or Ulipristal/ or Ulipristal acetate/	0
#11	Contraceptive Agents, Hormonal/ or Progestins/ or Etonogestrel/ or exp Norethindrone/ or Drospirenone/ or Desogestrel/ or Ethynodiol diacetate/ or Norelgestromin/ or exp Norgestrel/ or Norgestimate/ or Segesterone acetate/	22,211
#12	(gn-rh* or gnrh* or gonadotropin-releasing hormone* or 5-alpha reductase inhibitor* or 5alpha reductase inhibitor* or goserelin or histrelin or leuprolide or leuprorelin or nafarelin or triptorelin or elagolix or cetrorelix or degarelix or ganirelix or relugolix).ti,ab,kw,kf.	35,258
#13	(puberty adj3 (inhibit* or block* or suppress*)).ti,ab,kw,kf.	456
#14	(antiandrogen* or anti-androgen* or bicalutamide or finasteride or dutasteride or spironolactone or flutamide or nilutamide).ti,ab,kw,kf.	21,562
#15	(androgen adj3 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.	5,907
#16	(sex hormon* or sex steroid hormon* or gonadal steroid* or androgen* or androst* or estrogen* or oestrogen* or estradiol* or oestradiol* or dehydroepiandrosterone or prasterone or dhea or dihydrotestosterone or dht or dihydroprogesterone or dihydroepitestosterone or epiandrosterone or epitestosterone or epiestriol or equilenin or equilin or estrane* or estrenolone or estrone or etiocholanolone or folliculin or gestagen* or hermaphrodiol or hydroxyestrone* or hydroxypregnenolone* or hydroxysteroid* or hydroxytestosterone* or isotestosterone or ketosteroid* or medroxyprogesterone or mestranol or methyltestosterone or danazol or nandrolone or nortestosterone or oxosteroid* or pregnenolone* or progestational hormon* or progest* or quinestrol or stanolone or testosterone or dydrogesterone or levonorgestrel or dienogest or	448,236

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.17. Free text and controlled vocabulary search of Ovid Medline for qualitative studies, June 5, 2023

Search step	Query	Results
	norethindrone or norgestimate or drospirenone or desogestrel or etonogestrel or norelgestromin or norgestrel or segesterone or ethynodiol).ti,ab,kw,kf.	
#17	(hormon* adj3 (replacement or suppress* or therap* or treat* or cross-sex or gender-affirming)).ti,ab,kw,kf.	80,291
#18	(gender-affirming pharmaceutical* or contraceptive*).ti,ab,kw,kf.	65,776
#19	(aromatase inhibitor* or anastrozole or exemestane or letrozole).ti,ab,kw,kf.	11,646
#20	(selective estrogen receptor modulator* or serm or antiestrogen* or anti-estrogen* or bazedoxifene or clomiphene or clomifene or ospemifene or raloxifene or tamoxifen or toremifene).ti,ab,kw,kf.	40,601
#21	(progestin receptor modulator* or ulipristal or minoxidil).ti,ab,kw,kf.	2,796
#22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	677,878
#23	Gender Dysphoria/ or Transgender Persons/ or Gender Identity/ or Transsexualism/	29,449
#24	(gender dysphor* or 'gender minorit* or gender divers* or gender identity or gender incongruenc* or gender transition* or trans-female* or transfemale* or trans-feminine or transfeminine or trans-gender* or transgender* or trans-sexual* or transsex* or trans-male* or transmale* or trans-masculine or transmasculine or transboy* or transgirl*).ti,ab,kw,kf.	18,951
#25	(gender adj1 (affirm* or confirm* or reassign*)).ti,ab,kw,kf.	3,007
#26	((sex or medical) adj1 (reassign* or transition*)).ti,ab,kw,kf.	888
#27	23 or 24 or 25 or 26	38,167
#28	4 and 22 and 27	1,694
#29	28 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.)	1,674
#30	limit 29 to yr = "2010 -Current"	1,140
#31	exp Empirical Research/ or Interviews as Topic/ or Personal Narratives as Topic/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/ or (Interview or Personal Narrative).pt. or interview*.ti,ab,kf. or qualitative.ti,ab,kf,jw. or (theme* or thematic).ti,ab,kf. or ethnological research.ti,ab,kf. or ethnograph*.ti,ab,kf. or ethnomedicine.ti,ab,kf. or ethnonursing.ti,ab,kf. or phenomenol*.ti,ab,kf. or (grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf. or life stor*.ti,ab,kf. or (emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf. or (data adj1 saturat$).ti,ab,kf. or participant observ*.ti,ab,kf. or (social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern*).ti,ab,kf. or (action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf. or (humanistic or existential or experiential or paradigm*).ti,ab,kf. or (field adj (study or studies or research or work)).ti,ab,kf. or (human science or social science).ti,ab,kf. or biographical method.ti,ab,kf. or theoretical sampl*.ti,ab,kf. or ((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf. or (open-ended or narrative* or textual or texts or semi-	1,166,909

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.17. Free text and controlled vocabulary search of Ovid Medline for qualitative studies, June 5, 2023

Search step	Query	Results
	structured).ti,ab,kf. or (life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf. or ((lived or life) adj experience*).ti,ab,kf. or cluster sampl*.ti,ab,kf. or observational method*.ti,ab,kf. or content analysis.ti,ab,kf. or (constant adj (comparative or comparison)).ti,ab,kf. or ((discourse* or discurs*) adj3 analys?s).ti,ab,kf. or (heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf. or (van adj manen*).ti,ab,kf. or (van adj kaam*).ti,ab,kf. or (corbin* adj2 strauss*).ti,ab,kf.	
#32	"Surveys and Questionnaires"/ or Health Care Surveys/ or self report/ or questionnaire*.ti,ab,kf. or survey*.ti,ab,kf.	1,543,405
#33	31 or 32	2,457,803
#34	30 and 33	297

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Free Text and Controlled Vocabulary Searches of Embase Conducted between May 15 and June 5, 2023

Table I.B.18. Free text and controlled vocabulary search of Embase for systematic reviews, May 15, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,782,437
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,126,975
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,753,850
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'juvenile'/de OR 'child'/de OR 'pediatrics'/exp OR 'pediatric'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	3,426,389
#5	'adolescen*':ti,ab,kw OR 'boy*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'juvenile':ti,ab,kw OR 'minors':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'pre-pubertal':ti,ab,kw OR 'prepubertal':ti,ab,kw OR 'pre-pubesc*':ti,ab,kw OR 'prepubesc*':ti,ab,kw OR 'pubesc*':ti,ab,kw OR 'pubertal':ti,ab,kw OR 'puberty':ti,ab,kw OR 'teen*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'school-aged':ti,ab,kw OR 'adolescen*':jt OR 'child*':jt OR 'paediatr*':jt OR 'pediatr*':jt	3,268,795
#6	#4 OR #5	4,677,465
#7	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'puberty suppression'/exp OR 'gender dysphoria'/exp/dm_dt OR 'gender dysphoria'/exp/dm_th	929,685
#8	'gn-rh*':ti,ab,kw OR 'gnrh*':ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR '5-alpha reductase inhibitor*':ti,ab,kw OR '5alpha reductase inhibitor*':ti,ab,kw OR 'goserelin':ti,ab,kw OR 'histrelin':ti,ab,kw OR 'leuprolide':ti,ab,kw OR 'leuprorelin':ti,ab,kw OR 'nafarelin':ti,ab,kw OR 'triptorelin':ti,ab,kw OR 'elagolix':ti,ab,kw OR 'cetrorelix':ti,ab,kw OR 'degarelix':ti,ab,kw OR 'ganirelix':ti,ab,kw OR 'relugolix':ti,ab,kw	46,093
#9	('puberty' NEAR/3 ('inhibit*' OR 'block*' OR 'suppress*')):ti,ab,kw	636
#10	'antiandrogen*':ti,ab,kw OR 'anti-androgen*':ti,ab,kw OR 'bicalutamide':ti,ab,kw OR 'finasteride':ti,ab,kw OR 'dutasteride':ti,ab,kw OR 'spironolactone':ti,ab,kw OR 'flutamide':ti,ab,kw OR 'nilutamide':ti,ab,kw	31,484

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.18. Free text and controlled vocabulary search of Embase for systematic reviews, May 15, 2023

Search step	Query	Results
#11	('androgen' NEAR/3 ('antagonist*' OR 'inhibit*' OR 'block*')):ti,ab,kw	8,639
#12	'sex hormon*':ti,ab,kw OR 'sex steroid hormon*':ti,ab,kw OR 'gonadal steroid*':ti,ab,kw OR 'androgen*':ti,ab,kw OR 'androst*':ti,ab,kw OR 'estrogen*':ti,ab,kw OR 'oestrogen*':ti,ab,kw OR 'estradiol*':ti,ab,kw OR 'oestradiol*':ti,ab,kw OR 'dehydroepiandrosterone':ti,ab,kw OR 'prasterone':ti,ab,kw OR 'dhea':ti,ab,kw OR 'dihydrotestosterone':ti,ab,kw OR 'dht':ti,ab,kw OR 'dihydroprogesterone':ti,ab,kw OR 'dihydroepitestosterone':ti,ab,kw OR 'epiandrosterone':ti,ab,kw OR 'epitestosterone':ti,ab,kw OR 'epiestriol':ti,ab,kw OR 'equilenin':ti,ab,kw OR 'equilin':ti,ab,kw OR 'estrane*':ti,ab,kw OR 'estrenolone':ti,ab,kw OR 'estrone':ti,ab,kw OR 'etiocholanolone':ti,ab,kw OR 'folliculin':ti,ab,kw OR 'gestagen*':ti,ab,kw OR 'hermaphrodiol':ti,ab,kw OR 'hydroxyestrone*':ti,ab,kw OR 'hydroxypregnenolone*':ti,ab,kw OR 'hydroxysteroid*':ti,ab,kw OR 'hydroxytestosterone*':ti,ab,kw OR 'isotestosterone':ti,ab,kw OR 'ketosteroid*':ti,ab,kw OR 'medroxyprogesterone':ti,ab,kw OR 'mestranol':ti,ab,kw OR 'methyltestosterone':ti,ab,kw OR 'danazol':ti,ab,kw OR 'nandrolone':ti,ab,kw OR 'nortestosterone':ti,ab,kw OR 'oxosteroid*':ti,ab,kw OR 'pregnenolone*':ti,ab,kw OR 'progestational hormon*':ti,ab,kw OR 'progest*':ti,ab,kw OR 'quinestrol':ti,ab,kw OR 'stanolone':ti,ab,kw OR 'testosterone':ti,ab,kw OR 'dydrogesterone':ti,ab,kw OR 'levonorgestrel':ti,ab,kw OR 'dienogest':ti,ab,kw OR 'norethindrone':ti,ab,kw OR 'norgestimate':ti,ab,kw OR 'drospirenone':ti,ab,kw OR 'desogestrel':ti,ab,kw OR 'etonogestrel':ti,ab,kw OR 'norelgestromin':ti,ab,kw OR 'norgestrel':ti,ab,kw OR 'segesterone':ti,ab,kw OR 'ethynodiol':ti,ab,kw	569,723
#13	('hormon*' NEAR/3 ('replacement' OR 'suppress*' OR 'therap*' OR 'treat*' OR 'cross-sex' OR 'gender-affirming')):ti,ab,kw	113,288
#14	'gender-affirming pharmaceutical*':ti,ab,kw OR 'contraceptive*':ti,ab,kw	73,316
#15	'aromatase inhibitor*':ti,ab,kw OR 'anastrozole':ti,ab,kw OR 'exemestane':ti,ab,kw OR 'letrozole':ti,ab,kw	20,333
#16	'selective estrogen receptor modulator*':ti,ab,kw OR 'serm':ti,ab,kw OR 'antiestrogen*':ti,ab,kw OR 'anti-estrogen*':ti,ab,kw OR 'bazedoxifene':ti,ab,kw OR 'clomiphene':ti,ab,kw OR 'clomifene':ti,ab,kw OR 'ospemifene':ti,ab,kw OR 'raloxifene':ti,ab,kw OR 'tamoxifen':ti,ab,kw OR 'toremifene':ti,ab,kw	59,823
#17	'progestin receptor modulator*':ti,ab,kw OR 'ulipristal':ti,ab,kw OR 'minoxidil':ti,ab,kw	4,111
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,185,819
#19	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,608
#20	'gender dysphor*':ti,ab,kw OR 'gender minorit*':ti,ab,kw OR 'gender divers*':ti,ab,kw OR 'gender identity':ti,ab,kw OR 'gender incongruenc*':ti,ab,kw OR 'gender transition*':ti,ab,kw OR 'trans-female*':ti,ab,kw OR 'transfemale*':ti,ab,kw OR 'trans-	24,167

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.18. Free text and controlled vocabulary search of Embase for systematic reviews, May 15, 2023

Search step	Query	Results
	feminine':ti,ab,kw OR 'transfeminine':ti,ab,kw OR 'trans-gender*':ti,ab,kw OR 'transgender*':ti,ab,kw OR 'trans-sexual*':ti,ab,kw OR 'transsex*':ti,ab,kw OR 'trans-male*':ti,ab,kw OR 'transmale*':ti,ab,kw OR 'trans-masculine':ti,ab,kw OR 'transmasculine':ti,ab,kw OR 'transboy*':ti,ab,kw OR 'transgirl*':ti,ab,kw	
#21	('gender' NEAR/1 ('affirm*' OR 'confirm*' OR 'reassign*')):ti,ab,kw	4,058
#22	(('sex' OR 'medical') NEXT/1 ('reassign*' OR 'transition*')):ti,ab,kw	1,248
#23	#19 OR #20 OR #21 OR #22	42,539
#24	#6 AND #18 AND #23	2,585
#25	#24 NOT (#1 OR #2 OR #3)	1,865
#26	#24 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	1,372
#27	'systematic review':jt,ab,kw OR 'meta-analy*':jt,ab,kw OR metaanalys*:jt,ab,kw OR (((systematic* OR comprehensive*) NEAR/3 (review* OR overview* OR literature OR bibliographic)):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR ((methodologic* NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab,kw) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab,kw) OR ((integrative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((pool* NEAR/3 analy*):ti,ab,kw) OR 'data synthes*':ti,ab,kw OR 'data extraction*':ti,ab,kw OR 'data abstraction*':ti,ab,kw OR handsearch*:ti,ab,kw OR 'hand search*':ti,ab,kw OR 'mantel haenszel':ti,ab,kw OR peto:ti,ab,kw OR 'der simonian':ti,ab,kw OR dersimonian:ti,ab,kw OR 'fixed effect*':ti,ab,kw OR 'latin square*':ti,ab,kw OR 'met analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR 'technology assessment*':ti,ab,kw OR hta:ti,ab,kw OR htas:ti,ab,kw OR 'technology overview*':ti,ab,kw OR 'technology appraisal*':ti,ab,kw OR 'meta regression*':ti,ab,kw OR metaregression*:ti,ab,kw OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR psyclit:ab OR (psycinfo:ab NOT 'psycinfo database':ab) OR scopus:ab OR 'sociological abstracts':ab OR 'web of science':ab OR cochrane:it OR ((health NEXT/2 'technology assessment'):it) OR 'evidence report':it OR ((comparative NEXT/3 (efficacy OR effectiveness)):ti,ab,kw) OR 'outcomes research':ti,ab,kw OR 'relative effectiveness':ti,ab,kw OR (((indirect OR 'indirect treatment' OR 'mixed treatment' OR bayesian) NEXT/3 comparison*):ti,ab,kw) OR ((multi* NEXT/3 treatment NEXT/2 comparison*):ti,ab,kw) OR 'umbrella review*':ti,ab,kw OR ((multiparamet* NEXT/3 synthesis):ti,ab,kw) OR (('multi paramet*' NEXT/3 synthesis):ti,ab,kw)	874,065
#28	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review (topic)'/exp OR 'meta analysis (topic)'/exp OR 'biomedical technology assessment'/exp	605,165
#29	#27 OR #28	1,006,136
#30	#26 AND #29	67

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.19. Free text and controlled vocabulary search of Embase for guidelines, May 15, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,782,437
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,126,975
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,753,850
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'juvenile'/de OR 'child'/de OR 'pediatrics'/exp OR 'pediatric'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	3,426,389
#5	'adolescen*':ti,ab,kw OR 'boy*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'juvenile':ti,ab,kw OR 'minors':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'pre-pubertal':ti,ab,kw OR 'prepubertal':ti,ab,kw OR 'pre-pubesc*':ti,ab,kw OR 'prepubesc*':ti,ab,kw OR 'pubesc*':ti,ab,kw OR 'pubertal':ti,ab,kw OR 'puberty':ti,ab,kw OR 'teen*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'school-aged':ti,ab,kw OR 'adolescen*':jt OR 'child*':jt OR 'paediatr*':jt OR 'pediatr*':jt	3,268,795
#6	#4 OR #5	4,677,465
#7	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'puberty suppression'/exp OR 'gender dysphoria'/exp/dm_dt OR 'gender dysphoria'/exp/dm_th	929,685
#8	'gn-rh*':ti,ab,kw OR 'gnrh*':ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR '5-alpha reductase inhibitor*':ti,ab,kw OR '5alpha reductase inhibitor*':ti,ab,kw OR 'goserelin':ti,ab,kw OR 'histrelin':ti,ab,kw OR 'leuprolide':ti,ab,kw OR 'leuprorelin':ti,ab,kw OR 'nafarelin':ti,ab,kw OR 'triptorelin':ti,ab,kw OR 'elagolix':ti,ab,kw OR 'cetrorelix':ti,ab,kw OR 'degarelix':ti,ab,kw OR 'ganirelix':ti,ab,kw OR 'relugolix':ti,ab,kw	46,093
#9	('puberty' NEAR/3 ('inhibit*' OR 'block*' OR 'suppress*')):ti,ab,kw	636
#10	'antiandrogen*':ti,ab,kw OR 'anti-androgen*':ti,ab,kw OR 'bicalutamide':ti,ab,kw OR 'finasteride':ti,ab,kw OR 'dutasteride':ti,ab,kw OR 'spironolactone':ti,ab,kw OR 'flutamide':ti,ab,kw OR 'nilutamide':ti,ab,kw	31,484
#11	('androgen' NEAR/3 ('antagonist*' OR 'inhibit*' OR 'block*')):ti,ab,kw	8,639
#12	'sex hormon*':ti,ab,kw OR 'sex steroid hormon*':ti,ab,kw OR 'gonadal steroid*':ti,ab,kw OR 'androgen*':ti,ab,kw OR 'androst*':ti,ab,kw OR 'estrogen*':ti,ab,kw OR 'oestrogen*':ti,ab,kw OR 'estradiol*':ti,ab,kw OR 'oestradiol*':ti,ab,kw OR	569,723

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.19. Free text and controlled vocabulary search of Embase for guidelines, May 15, 2023

Search step	Query	Results
	'dehydroepiandrosterone':ti,ab,kw OR 'prasterone':ti,ab,kw OR 'dhea':ti,ab,kw OR 'dihydrotestosterone':ti,ab,kw OR 'dht':ti,ab,kw OR 'dihydroprogesterone':ti,ab,kw OR 'dihydroepitestosterone':ti,ab,kw OR 'epiandrosterone':ti,ab,kw OR 'epitestosterone':ti,ab,kw OR 'epiestriol':ti,ab,kw OR 'equilenin':ti,ab,kw OR 'equilin':ti,ab,kw OR 'estrane*':ti,ab,kw OR 'estrenolone':ti,ab,kw OR 'estrone':ti,ab,kw OR 'etiocholanolone':ti,ab,kw OR 'folliculin':ti,ab,kw OR 'gestagen*':ti,ab,kw OR 'hermaphrodiol':ti,ab,kw OR 'hydroxyestrone*':ti,ab,kw OR 'hydroxypregnenolone*':ti,ab,kw OR 'hydroxysteroid*':ti,ab,kw OR 'hydroxytestosterone*':ti,ab,kw OR 'isotestosterone':ti,ab,kw OR 'ketosteroid*':ti,ab,kw OR 'medroxyprogesterone':ti,ab,kw OR 'mestranol':ti,ab,kw OR 'methyltestosterone':ti,ab,kw OR 'danazol':ti,ab,kw OR 'nandrolone':ti,ab,kw OR 'nortestosterone':ti,ab,kw OR 'oxosteroid*':ti,ab,kw OR 'pregnenolone*':ti,ab,kw OR 'progestational hormon*':ti,ab,kw OR 'progest*':ti,ab,kw OR 'quinestrol':ti,ab,kw OR 'stanolone':ti,ab,kw OR 'testosterone':ti,ab,kw OR 'dydrogesterone':ti,ab,kw OR 'levonorgestrel':ti,ab,kw OR 'dienogest':ti,ab,kw OR 'norethindrone':ti,ab,kw OR 'norgestimate':ti,ab,kw OR 'drospirenone':ti,ab,kw OR 'desogestrel':ti,ab,kw OR 'etonogestrel':ti,ab,kw OR 'norelgestromin':ti,ab,kw OR 'norgestrel':ti,ab,kw OR 'segesterone':ti,ab,kw OR 'ethynodiol':ti,ab,kw	
#13	('hormon*' NEAR/3 ('replacement' OR 'suppress*' OR 'therap*' OR 'treat*' OR 'cross-sex' OR 'gender-affirming')):ti,ab,kw	113,288
#14	'gender-affirming pharmaceutical*':ti,ab,kw OR 'contraceptive*':ti,ab,kw	73,316
#15	'aromatase inhibitor*':ti,ab,kw OR 'anastrozole':ti,ab,kw OR 'exemestane':ti,ab,kw OR 'letrozole':ti,ab,kw	20,333
#16	'selective estrogen receptor modulator*':ti,ab,kw OR 'serm':ti,ab,kw OR 'antiestrogen*':ti,ab,kw OR 'anti-estrogen*':ti,ab,kw OR 'bazedoxifene':ti,ab,kw OR 'clomiphene':ti,ab,kw OR 'clomifene':ti,ab,kw OR 'ospemifene':ti,ab,kw OR 'raloxifene':ti,ab,kw OR 'tamoxifen':ti,ab,kw OR 'toremifene':ti,ab,kw	59,823
#17	'progestin receptor modulator*':ti,ab,kw OR 'ulipristal':ti,ab,kw OR 'minoxidil':ti,ab,kw	4,111
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,185,819
#19	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,608
#20	'gender dysphor*':ti,ab,kw OR 'gender minorit*':ti,ab,kw OR 'gender divers*':ti,ab,kw OR 'gender identity':ti,ab,kw OR 'gender incongruenc*':ti,ab,kw OR 'gender transition*':ti,ab,kw OR 'trans-female*':ti,ab,kw OR 'transfemale*':ti,ab,kw OR 'trans-feminine':ti,ab,kw OR 'transfeminine':ti,ab,kw OR 'trans-gender*':ti,ab,kw OR 'transgender*':ti,ab,kw OR 'trans-sexual*':ti,ab,kw OR 'transsex*':ti,ab,kw OR 'trans-male*':ti,ab,kw OR 'transmale*':ti,ab,kw OR 'trans-masculine':ti,ab,kw OR 'transmasculine':ti,ab,kw OR 'transboy*':ti,ab,kw OR 'transgirl*':ti,ab,kw	24,167
#21	('gender' NEAR/1 ('affirm*' OR 'confirm*' OR 'reassign*')):ti,ab,kw	4,058

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.19. Free text and controlled vocabulary search of Embase for guidelines, May 15, 2023

Search step	Query	Results
#22	(('sex' OR 'medical') NEXT/1 ('reassign*' OR 'transition*')):ti,ab,kw	1,248
#23	#19 OR #20 OR #21 OR #22	42,539
#24	#6 AND #18 AND #23	2,585
#25	#24 NOT (#1 OR #2 OR #3)	1,865
#26	#24 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	1,372
#27	'clinical protocol'/exp OR 'consensus'/exp OR 'consensus development'/exp OR 'clinical pathway'/exp OR 'guideline'/exp OR 'practice guideline'/exp OR 'clinical decision rule'/exp OR 'position statement*':ti,ab,kw OR 'policy statement*':ti,ab,kw OR 'practice parameter*':ti,ab,kw OR 'best practice*':ti,ab,kw OR 'standards':ti,kw OR 'guideline':ti,kw OR 'guidelines':ti,kw OR ((('practice' OR 'treatment*' OR 'clinical') NEXT/1 'guideline*'):ab) OR 'cpg':ti OR 'cpgs':ti OR 'consensus*':ti,kw OR ((('critical' OR 'clinical' OR 'practice') NEXT/2 ('path' OR 'paths' OR 'pathway' OR 'pathways' OR 'protocol*')):ti,ab,kw) OR 'recommendat*':ti,kw OR 'guideline recommendation*':ab OR (('care' NEAR/2 ('standard' OR 'path' OR 'paths' OR 'pathway' OR 'pathways' OR 'map' OR 'maps' OR 'plan' OR 'plans')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('screening' OR 'examination' OR 'test' OR 'tested' OR 'testing' OR 'assessment*' OR 'diagnosis' OR 'diagnoses' OR 'diagnosed' OR 'diagnosing')):ti,ab,kw) OR (('algorithm*' NEAR/2 ('pharmacotherap*' OR 'chemotherap*' OR 'chemotreatment*' OR 'therap*' OR 'treatment*' OR 'intervention*')):ti,ab,kw) OR 'guideline*':au OR 'standards':au OR 'consensus*':au OR 'recommendat*':au	1,170,181
#28	#26 AND #27	192

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.20. Free text and controlled vocabulary search of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), May 22, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,794,639
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,128,633
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,758,077
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'juvenile'/de OR 'child'/de OR 'pediatrics'/exp OR 'pediatric'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	3,429,175
#5	'adolescen*':ti,ab,kw OR 'boy*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'juvenile':ti,ab,kw OR 'minors':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'pre-pubertal':ti,ab,kw OR 'prepubertal':ti,ab,kw OR 'pre-pubesc*':ti,ab,kw OR 'prepubesc*':ti,ab,kw OR 'pubesc*':ti,ab,kw OR 'pubertal':ti,ab,kw OR 'puberty':ti,ab,kw OR 'teen*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'school-aged':ti,ab,kw OR 'adolescen*':jt OR 'child*':jt OR 'paediatr*':jt OR 'pediatr*':jt	3,271,977
#6	#4 OR #5	4,681,266
#7	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'puberty suppression'/exp OR 'gender dysphoria'/exp/dm_dt OR 'gender dysphoria'/exp/dm_th	930,567
#8	'gn-rh*':ti,ab,kw OR 'gnrh*':ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR '5-alpha reductase inhibitor*':ti,ab,kw OR '5alpha reductase inhibitor*':ti,ab,kw OR 'goserelin':ti,ab,kw OR 'histrelin':ti,ab,kw OR 'leuprolide':ti,ab,kw OR 'leuprorelin':ti,ab,kw OR 'nafarelin':ti,ab,kw OR 'triptorelin':ti,ab,kw OR 'elagolix':ti,ab,kw OR 'cetrorelix':ti,ab,kw OR 'degarelix':ti,ab,kw OR 'ganirelix':ti,ab,kw OR 'relugolix':ti,ab,kw	46,126
#9	('puberty' NEAR/3 ('inhibit*' OR 'block*' OR 'suppress*')):ti,ab,kw	640
#10	'antiandrogen*':ti,ab,kw OR 'anti-androgen*':ti,ab,kw OR 'bicalutamide':ti,ab,kw OR 'finasteride':ti,ab,kw OR 'dutasteride':ti,ab,kw OR 'spironolactone':ti,ab,kw OR 'flutamide':ti,ab,kw OR 'nilutamide':ti,ab,kw	31,534
#11	('androgen' NEAR/3 ('antagonist*' OR 'inhibit*' OR 'block*')):ti,ab,kw	8,658
#12	'sex hormon*':ti,ab,kw OR 'sex steroid hormon*':ti,ab,kw OR 'gonadal steroid*':ti,ab,kw OR 'androgen*':ti,ab,kw OR 'androst*':ti,ab,kw OR 'estrogen*':ti,ab,kw OR	570,233

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.20. Free text and controlled vocabulary search of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), May 22, 2023

Search step	Query	Results
	'oestrogen*':ti,ab,kw OR 'estradiol*':ti,ab,kw OR 'oestradiol*':ti,ab,kw OR 'dehydroepiandrosterone':ti,ab,kw OR 'prasterone':ti,ab,kw OR 'dhea':ti,ab,kw OR 'dihydrotestosterone':ti,ab,kw OR 'dht':ti,ab,kw OR 'dihydroprogesterone':ti,ab,kw OR 'dihydroepitestosterone':ti,ab,kw OR 'epiandrosterone':ti,ab,kw OR 'epitestosterone':ti,ab,kw OR 'epiestriol':ti,ab,kw OR 'equilenin':ti,ab,kw OR 'equilin':ti,ab,kw OR 'estrane*':ti,ab,kw OR 'estrenolone':ti,ab,kw OR 'estrone':ti,ab,kw OR 'etiocholanolone':ti,ab,kw OR 'folliculin':ti,ab,kw OR 'gestagen*':ti,ab,kw OR 'hermaphrodiol':ti,ab,kw OR 'hydroxyestrone*':ti,ab,kw OR 'hydroxypregnenolone*':ti,ab,kw OR 'hydroxysteroid*':ti,ab,kw OR 'hydroxytestosterone*':ti,ab,kw OR 'isotestosterone':ti,ab,kw OR 'ketosteroid*':ti,ab,kw OR 'medroxyprogesterone':ti,ab,kw OR 'mestranol':ti,ab,kw OR 'methyltestosterone':ti,ab,kw OR 'danazol':ti,ab,kw OR 'nandrolone':ti,ab,kw OR 'nortestosterone':ti,ab,kw OR 'oxosteroid*':ti,ab,kw OR 'pregnenolone*':ti,ab,kw OR 'progestational hormon*':ti,ab,kw OR 'progest*':ti,ab,kw OR 'quinestrol':ti,ab,kw OR 'stanolone':ti,ab,kw OR 'testosterone':ti,ab,kw OR 'dydrogesterone':ti,ab,kw OR 'levonorgestrel':ti,ab,kw OR 'dienogest':ti,ab,kw OR 'norethindrone':ti,ab,kw OR 'norgestimate':ti,ab,kw OR 'drospirenone':ti,ab,kw OR 'desogestrel':ti,ab,kw OR 'etonogestrel':ti,ab,kw OR 'norelgestromin':ti,ab,kw OR 'norgestrel':ti,ab,kw OR 'segesterone':ti,ab,kw OR 'ethynodiol':ti,ab,kw	
#13	('hormon*' NEAR/3 ('replacement' OR 'suppress*' OR 'therap*' OR 'treat*' OR 'cross-sex' OR 'gender-affirming')):ti,ab,kw	113,417
#14	'gender-affirming pharmaceutical*':ti,ab,kw OR 'contraceptive*':ti,ab,kw	73,365
#15	'aromatase inhibitor*':ti,ab,kw OR 'anastrozole':ti,ab,kw OR 'exemestane':ti,ab,kw OR 'letrozole':ti,ab,kw	20,361
#16	'selective estrogen receptor modulator*':ti,ab,kw OR 'serm':ti,ab,kw OR 'antiestrogen*':ti,ab,kw OR 'anti-estrogen*':ti,ab,kw OR 'bazedoxifene':ti,ab,kw OR 'clomiphene':ti,ab,kw OR 'clomifene':ti,ab,kw OR 'ospemifene':ti,ab,kw OR 'raloxifene':ti,ab,kw OR 'tamoxifen':ti,ab,kw OR 'toremifene':ti,ab,kw	59,866
#17	'progestin receptor modulator*':ti,ab,kw OR 'ulipristal':ti,ab,kw OR 'minoxidil':ti,ab,kw	4,123
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,186,884
#19	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,718
#20	'gender dysphor*':ti,ab,kw OR 'gender minorit*':ti,ab,kw OR 'gender divers*':ti,ab,kw OR 'gender identity':ti,ab,kw OR 'gender incongruenc*':ti,ab,kw OR 'gender transition*':ti,ab,kw OR 'trans-female*':ti,ab,kw OR 'transfemale*':ti,ab,kw OR 'trans-feminine':ti,ab,kw OR 'transfeminine':ti,ab,kw OR 'trans-gender*':ti,ab,kw OR 'transgender*':ti,ab,kw OR 'trans-sexual*':ti,ab,kw OR 'transsex*':ti,ab,kw OR 'trans-	24,274

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.20. Free text and controlled vocabulary search of Embase for experimental studies (eg, randomized controlled trials, controlled clinical trials), May 22, 2023

Search step	Query	Results
	male*':ti,ab,kw OR 'transmale*':ti,ab,kw OR 'trans-masculine':ti,ab,kw OR 'transmasculine':ti,ab,kw OR 'transboy*':ti,ab,kw OR 'transgirl*':ti,ab,kw	
#21	('gender' NEAR/1 ('affirm*' OR 'confirm*' OR 'reassign*')):ti,ab,kw	4,100
#22	(('sex' OR 'medical') NEXT/1 ('reassign*' OR 'transition*')):ti,ab,kw	1,249
#23	#19 OR #20 OR #21 OR #22	42,685
#24	#6 AND #18 AND #23	2,594
#25	#24 NOT (#1 OR #2 OR #3)	1,868
#26	#24 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	1,375
#27	'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'noninferiority trial'/exp OR 'randomization'/de OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'random*':ti,ab,de,kw OR 'sham':ti,ab,de,kw OR 'placebo*':ti,ab,de,kw OR ((('singl*' OR 'doubl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR ((('tripl*' OR 'trebl*') NEXT/1 ('blind*' OR 'dumm*' OR 'mask*')):ti,ab,de,kw) OR (('control*' NEAR/3 ('study' OR 'studies' OR 'trial*' OR 'group*')):ti,ab,kw) OR 'nonrandom*':ti,ab,de,kw OR 'non-random*':ti,ab,de,kw OR 'quasi-random*':ti,ab,de,kw OR 'quasirandom*':ti,ab,de,kw OR 'allocated':ti,ab,de OR (('open-label' NEAR/5 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('equivalence' OR 'superiority' OR 'non-inferiority' OR 'noninferiority') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR 'pragmatic study':ti,ab,de,kw OR 'pragmatic studies':ti,ab,de,kw OR ((('pragmatic' OR 'practical') NEAR/3 trial*):ti,ab,de,kw) OR ((('quasiexperimental' OR 'quasi-experimental') NEAR/3 ('study' OR 'studies' OR 'trial*')):ti,ab,de,kw) OR ((('phase' NEAR/3 ('iii' OR '3')):ti,de,kw) AND ('study':ti,de,kw OR 'studies':ti,de,kw OR 'trial*':ti,de,kw))	4,470,992
#28	#26 AND #27	93

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.21. Free text and controlled vocabulary search of Embase for observational and descriptive studies, May 22, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,794,639
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,128,633
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,758,077
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'juvenile'/de OR 'child'/de OR 'pediatrics'/exp OR 'pediatric'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	3,429,175
#5	'adolescen*':ti,ab,kw OR 'boy*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'juvenile':ti,ab,kw OR 'minors':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'pre-pubertal':ti,ab,kw OR 'prepubertal':ti,ab,kw OR 'pre-pubesc*':ti,ab,kw OR 'prepubesc*':ti,ab,kw OR 'pubesc*':ti,ab,kw OR 'pubertal':ti,ab,kw OR 'puberty':ti,ab,kw OR 'teen*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'school-aged':ti,ab,kw OR 'adolescen*':jt OR 'child*':jt OR 'paediatr*':jt OR 'pediatr*':jt	3,271,977
#6	#4 OR #5	4,681,266
#7	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'puberty suppression'/exp OR 'gender dysphoria'/exp/dm_dt OR 'gender dysphoria'/exp/dm_th	930,567
#8	'gn-rh*':ti,ab,kw OR 'gnrh*':ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR '5-alpha reductase inhibitor*':ti,ab,kw OR '5alpha reductase inhibitor*':ti,ab,kw OR 'goserelin':ti,ab,kw OR 'histrelin':ti,ab,kw OR 'leuprolide':ti,ab,kw OR 'leuprorelin':ti,ab,kw OR 'nafarelin':ti,ab,kw OR 'triptorelin':ti,ab,kw OR 'elagolix':ti,ab,kw OR 'cetrorelix':ti,ab,kw OR 'degarelix':ti,ab,kw OR 'ganirelix':ti,ab,kw OR 'relugolix':ti,ab,kw	46,126
#9	('puberty' NEAR/3 ('inhibit*' OR 'block*' OR 'suppress*')):ti,ab,kw	640
#10	'antiandrogen*':ti,ab,kw OR 'anti-androgen*':ti,ab,kw OR 'bicalutamide':ti,ab,kw OR 'finasteride':ti,ab,kw OR 'dutasteride':ti,ab,kw OR 'spironolactone':ti,ab,kw OR 'flutamide':ti,ab,kw OR 'nilutamide':ti,ab,kw	31,534
#11	('androgen' NEAR/3 ('antagonist*' OR 'inhibit*' OR 'block*')):ti,ab,kw	8,658
#12	'sex hormon*':ti,ab,kw OR 'sex steroid hormon*':ti,ab,kw OR 'gonadal steroid*':ti,ab,kw OR 'androgen*':ti,ab,kw OR 'androst*':ti,ab,kw OR 'estrogen*':ti,ab,kw OR	570,233

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.21. Free text and controlled vocabulary search of Embase for observational and descriptive studies, May 22, 2023

Search step	Query	Results
	'oestrogen*':ti,ab,kw OR 'estradiol*':ti,ab,kw OR 'oestradiol*':ti,ab,kw OR 'dehydroepiandrosterone':ti,ab,kw OR 'prasterone':ti,ab,kw OR 'dhea':ti,ab,kw OR 'dihydrotestosterone':ti,ab,kw OR 'dht':ti,ab,kw OR 'dihydroprogesterone':ti,ab,kw OR 'dihydroepitestosterone':ti,ab,kw OR 'epiandrosterone':ti,ab,kw OR 'epitestosterone':ti,ab,kw OR 'epiestriol':ti,ab,kw OR 'equilenin':ti,ab,kw OR 'equilin':ti,ab,kw OR 'estrane*':ti,ab,kw OR 'estrenolone':ti,ab,kw OR 'estrone':ti,ab,kw OR 'etiocholanolone':ti,ab,kw OR 'folliculin':ti,ab,kw OR 'gestagen*':ti,ab,kw OR 'hermaphrodiol':ti,ab,kw OR 'hydroxyestrone*':ti,ab,kw OR 'hydroxypregnenolone*':ti,ab,kw OR 'hydroxysteroid*':ti,ab,kw OR 'hydroxytestosterone*':ti,ab,kw OR 'isotestosterone':ti,ab,kw OR 'ketosteroid*':ti,ab,kw OR 'medroxyprogesterone':ti,ab,kw OR 'mestranol':ti,ab,kw OR 'methyltestosterone':ti,ab,kw OR 'danazol':ti,ab,kw OR 'nandrolone':ti,ab,kw OR 'nortestosterone':ti,ab,kw OR 'oxosteroid*':ti,ab,kw OR 'pregnenolone*':ti,ab,kw OR 'progestational hormon*':ti,ab,kw OR 'progest*':ti,ab,kw OR 'quinestrol':ti,ab,kw OR 'stanolone':ti,ab,kw OR 'testosterone':ti,ab,kw OR 'dydrogesterone':ti,ab,kw OR 'levonorgestrel':ti,ab,kw OR 'dienogest':ti,ab,kw OR 'norethindrone':ti,ab,kw OR 'norgestimate':ti,ab,kw OR 'drospirenone':ti,ab,kw OR 'desogestrel':ti,ab,kw OR 'etonogestrel':ti,ab,kw OR 'norelgestromin':ti,ab,kw OR 'norgestrel':ti,ab,kw OR 'segesterone':ti,ab,kw OR 'ethynodiol':ti,ab,kw	
#13	('hormon*' NEAR/3 ('replacement' OR 'suppress*' OR 'therap*' OR 'treat*' OR 'cross-sex' OR 'gender-affirming')):ti,ab,kw	113,417
#14	'gender-affirming pharmaceutical*':ti,ab,kw OR 'contraceptive*':ti,ab,kw	73,365
#15	'aromatase inhibitor*':ti,ab,kw OR 'anastrozole':ti,ab,kw OR 'exemestane':ti,ab,kw OR 'letrozole':ti,ab,kw	20,361
#16	'selective estrogen receptor modulator*':ti,ab,kw OR 'serm':ti,ab,kw OR 'antiestrogen*':ti,ab,kw OR 'anti-estrogen*':ti,ab,kw OR 'bazedoxifene':ti,ab,kw OR 'clomiphene':ti,ab,kw OR 'clomifene':ti,ab,kw OR 'ospemifene':ti,ab,kw OR 'raloxifene':ti,ab,kw OR 'tamoxifen':ti,ab,kw OR 'toremifene':ti,ab,kw	59,866
#17	'progestin receptor modulator*':ti,ab,kw OR 'ulipristal':ti,ab,kw OR 'minoxidil':ti,ab,kw	4,123
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,186,884
#19	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,718
#20	'gender dysphor*':ti,ab,kw OR 'gender minorit*':ti,ab,kw OR 'gender divers*':ti,ab,kw OR 'gender identity':ti,ab,kw OR 'gender incongruenc*':ti,ab,kw OR 'gender transition*':ti,ab,kw OR 'trans-female*':ti,ab,kw OR 'transfemale*':ti,ab,kw OR 'trans-feminine':ti,ab,kw OR 'transfeminine':ti,ab,kw OR 'trans-gender*':ti,ab,kw OR 'transgender*':ti,ab,kw OR 'trans-sexual*':ti,ab,kw OR 'transsex*':ti,ab,kw OR 'trans-	24,274

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.21. Free text and controlled vocabulary search of Embase for observational and descriptive studies, May 22, 2023

Search step	Query	Results
	male*':ti,ab,kw OR 'transmale*':ti,ab,kw OR 'trans-masculine':ti,ab,kw OR 'transmasculine':ti,ab,kw OR 'transboy*':ti,ab,kw OR 'transgirl*':ti,ab,kw	
#21	('gender' NEAR/1 ('affirm*' OR 'confirm*' OR 'reassign*')):ti,ab,kw	4,100
#22	(('sex' OR 'medical') NEXT/1 ('reassign*' OR 'transition*')):ti,ab,kw	1,249
#23	#19 OR #20 OR #21 OR #22	42,685
#24	#6 AND #18 AND #23	2,594
#25	#24 NOT (#1 OR #2 OR #3)	1,868
#26	#24 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	1,375
#27	'epidemiology'/de OR 'observational study'/de OR 'clinical study'/exp OR 'cross-sectional study'/exp OR 'seroepidemiology'/exp OR 'national longitudinal study of adolescent health'/de OR 'cohort analysis'/de OR 'longitudinal study'/de OR 'prospective study'/de OR 'follow up'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'quasi experimental study'/de OR 'single-case study'/de OR 'validation study'/de OR 'pilot study'/de OR 'controlled study'/de OR 'pretest posttest control group design'/de OR 'comparative study'/de OR 'comparative effectiveness'/de OR (('observational' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'cohort*':ti,ab,kw OR (('prospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('follow up' OR 'followup') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('longitudinal' OR 'longterm' OR 'long-term') NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data')):ti,ab,kw) OR (('retrospective' NEAR/7 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses' OR 'data' OR 'review')):ti,ab,kw) OR (('case' NEXT/1 'control'):ti,ab,kw) OR (('case' NEXT/1 'comparison'):ti,ab,kw) OR (('case' NEXT/1 'controlled'):ti,ab,kw) OR (('case-referent' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('population' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('descriptive' NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR ((('multidimensional' OR 'multi-dimensional') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('cross-sectional' NEAR/7 ('study' OR 'studies' OR 'design' OR 'research' OR 'analysis' OR 'analyses' OR 'survey' OR 'findings')):ti,ab,kw) OR (('natural' NEXT/1 'experiment'):ti,ab,kw) OR (('natural' NEXT/1 'experiments'):ti,ab,kw) OR (('quasi' NEXT/1 ('experiment' OR 'experiments' OR 'experimental')):ti,ab,kw) OR ((('non experiment' OR 'nonexperiment' OR 'non experimental' OR 'nonexperimental') NEAR/3 ('study' OR 'studies' OR 'design' OR 'analysis' OR 'analyses')):ti,ab,kw) OR (('prevalence' NEAR/3 ('study' OR 'studies' OR 'analysis' OR 'analyses')):ti,ab,kw) OR 'case series':ti,ab,kw OR 'case report'/de OR 'case study'/exp OR (('case' NEAR/3 ('report' OR 'reports' OR 'study' OR 'studies' OR 'histories')):ti,ab,kw) OR 'health services research'/de	19,666,362
#28	#26 AND #27	724

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.22. Free text and controlled vocabulary search of Embase for qualitative studies, June 5, 2023

Search step	Query	Results
#1	'conference abstract'/it OR 'conference review'/it	4,804,537
#2	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	3,133,289
#3	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	7,770,424
#4	'minor (person)'/exp OR 'adolescent'/exp OR 'juvenile'/de OR 'child'/de OR 'pediatrics'/exp OR 'pediatric'/exp OR 'puberty'/exp OR 'sexual development'/exp OR 'adolescence'/exp OR 'preadolescence'/exp	3,438,008
#5	'adolescen*':ti,ab,kw OR 'boy*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'juvenile':ti,ab,kw OR 'minors':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'pre-pubertal':ti,ab,kw OR 'prepubertal':ti,ab,kw OR 'pre-pubesc*':ti,ab,kw OR 'prepubesc*':ti,ab,kw OR 'pubesc*':ti,ab,kw OR 'pubertal':ti,ab,kw OR 'puberty':ti,ab,kw OR 'teen*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'school-aged':ti,ab,kw OR 'adolescen*':jt OR 'child*':jt OR 'paediatr*':jt OR 'pediatr*':jt	3,281,856
#6	#4 OR #5	4,692,643
#7	'sex hormones therapeutic use'/exp OR 'gonadorelin derivative'/exp OR 'sex hormone'/exp OR 'antiandrogen'/exp OR 'steroid 5alpha reductase inhibitor'/exp OR 'gender affirming hormone therapy'/exp OR 'gender affirming care'/exp OR 'hormonal therapy'/exp OR 'puberty suppression'/exp OR 'gender dysphoria'/exp/dm_dt OR 'gender dysphoria'/exp/dm_th	932,377
#8	'gn-rh*':ti,ab,kw OR 'gnrh*':ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR '5-alpha reductase inhibitor*':ti,ab,kw OR '5alpha reductase inhibitor*':ti,ab,kw OR 'goserelin':ti,ab,kw OR 'histrelin':ti,ab,kw OR 'leuprolide':ti,ab,kw OR 'leuprorelin':ti,ab,kw OR 'nafarelin':ti,ab,kw OR 'triptorelin':ti,ab,kw OR 'elagolix':ti,ab,kw OR 'cetrorelix':ti,ab,kw OR 'degarelix':ti,ab,kw OR 'ganirelix':ti,ab,kw OR 'relugolix':ti,ab,kw	46,208
#9	('puberty' NEAR/3 ('inhibit*' OR 'block*' OR 'suppress*')):ti,ab,kw	641
#10	'antiandrogen*':ti,ab,kw OR 'anti-androgen*':ti,ab,kw OR 'bicalutamide':ti,ab,kw OR 'finasteride':ti,ab,kw OR 'dutasteride':ti,ab,kw OR 'spironolactone':ti,ab,kw OR 'flutamide':ti,ab,kw OR 'nilutamide':ti,ab,kw	31,589
#11	('androgen' NEAR/3 ('antagonist*' OR 'inhibit*' OR 'block*')):ti,ab,kw	8,679
#12	'sex hormon*':ti,ab,kw OR 'sex steroid hormon*':ti,ab,kw OR 'gonadal steroid*':ti,ab,kw OR 'androgen*':ti,ab,kw OR 'androst*':ti,ab,kw OR 'estrogen*':ti,ab,kw OR 'oestrogen*':ti,ab,kw OR 'estradiol*':ti,ab,kw OR 'oestradiol*':ti,ab,kw OR	571,157

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.22. Free text and controlled vocabulary search of Embase for qualitative studies, June 5, 2023

Search step	Query	Results
	'dehydroepiandrosterone':ti,ab,kw OR 'prasterone':ti,ab,kw OR 'dhea':ti,ab,kw OR 'dihydrotestosterone':ti,ab,kw OR 'dht':ti,ab,kw OR 'dihydroprogesterone':ti,ab,kw OR 'dihydroepitestosterone':ti,ab,kw OR 'epiandrosterone':ti,ab,kw OR 'epitestosterone':ti,ab,kw OR 'epiestriol':ti,ab,kw OR 'equilenin':ti,ab,kw OR 'equilin':ti,ab,kw OR 'estrane*':ti,ab,kw OR 'estrenolone':ti,ab,kw OR 'estrone':ti,ab,kw OR 'etiocholanolone':ti,ab,kw OR 'folliculin':ti,ab,kw OR 'gestagen*':ti,ab,kw OR 'hermaphrodiol':ti,ab,kw OR 'hydroxyestrone*':ti,ab,kw OR 'hydroxypregnenolone*':ti,ab,kw OR 'hydroxysteroid*':ti,ab,kw OR 'hydroxytestosterone*':ti,ab,kw OR 'isotestosterone':ti,ab,kw OR 'ketosteroid*':ti,ab,kw OR 'medroxyprogesterone':ti,ab,kw OR 'mestranol':ti,ab,kw OR 'methyltestosterone':ti,ab,kw OR 'danazol':ti,ab,kw OR 'nandrolone':ti,ab,kw OR 'nortestosterone':ti,ab,kw OR 'oxosteroid*':ti,ab,kw OR 'pregnenolone*':ti,ab,kw OR 'progestational hormon*':ti,ab,kw OR 'progest*':ti,ab,kw OR 'quinestrol':ti,ab,kw OR 'stanolone':ti,ab,kw OR 'testosterone':ti,ab,kw OR 'dydrogesterone':ti,ab,kw OR 'levonorgestrel':ti,ab,kw OR 'dienogest':ti,ab,kw OR 'norethindrone':ti,ab,kw OR 'norgestimate':ti,ab,kw OR 'drospirenone':ti,ab,kw OR 'desogestrel':ti,ab,kw OR 'etonogestrel':ti,ab,kw OR 'norelgestromin':ti,ab,kw OR 'norgestrel':ti,ab,kw OR 'segesterone':ti,ab,kw OR 'ethynodiol':ti,ab,kw	
#13	('hormon*' NEAR/3 ('replacement' OR 'suppress*' OR 'therap*' OR 'treat*' OR 'cross-sex' OR 'gender-affirming')):ti,ab,kw	113,632
#14	'gender-affirming pharmaceutical*':ti,ab,kw OR 'contraceptive*':ti,ab,kw	73,483
#15	'aromatase inhibitor*':ti,ab,kw OR 'anastrozole':ti,ab,kw OR 'exemestane':ti,ab,kw OR 'letrozole':ti,ab,kw	20,411
#16	'selective estrogen receptor modulator*':ti,ab,kw OR 'serm':ti,ab,kw OR 'antiestrogen*':ti,ab,kw OR 'anti-estrogen*':ti,ab,kw OR 'bazedoxifene':ti,ab,kw OR 'clomiphene':ti,ab,kw OR 'clomifene':ti,ab,kw OR 'ospemifene':ti,ab,kw OR 'raloxifene':ti,ab,kw OR 'tamoxifen':ti,ab,kw OR 'toremifene':ti,ab,kw	59,941
#17	'progestin receptor modulator*':ti,ab,kw OR 'ulipristal':ti,ab,kw OR 'minoxidil':ti,ab,kw	4,137
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,189,104
#19	'gender dysphoria'/exp OR 'gender affirmation'/exp OR 'gender identity'/exp OR 'gender incongruence'/exp OR 'gender nonconformity'/exp OR 'sex reassignment'/exp OR 'gender variance'/exp OR 'transgender and gender nonbinary'/exp OR 'transgender'/exp OR 'transsexuality'/exp	36,860
#20	'gender dysphor*':ti,ab,kw OR 'gender minorit*':ti,ab,kw OR 'gender divers*':ti,ab,kw OR 'gender identity':ti,ab,kw OR 'gender incongruenc*':ti,ab,kw OR 'gender transition*':ti,ab,kw OR 'trans-female*':ti,ab,kw OR 'transfemale*':ti,ab,kw OR 'trans-feminine':ti,ab,kw OR 'transfeminine':ti,ab,kw OR 'trans-gender*':ti,ab,kw OR 'transgender*':ti,ab,kw OR 'trans-sexual*':ti,ab,kw OR 'transsex*':ti,ab,kw OR 'trans-male*':ti,ab,kw OR 'transmale*':ti,ab,kw OR 'trans-masculine':ti,ab,kw OR 'transmasculine':ti,ab,kw OR 'transboy*':ti,ab,kw OR 'transgirl*':ti,ab,kw	24,440
#21	('gender' NEAR/1 ('affirm*' OR 'confirm*' OR 'reassign*')):ti,ab,kw	4,142

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

Table I.B.22. Free text and controlled vocabulary search of Embase for qualitative studies, June 5, 2023

Search step	Query	Results
#22	(('sex' OR 'medical') NEXT/1 ('reassign*' OR 'transition*')):ti,ab,kw	1,251
#23	#19 OR #20 OR #21 OR #22	42,882
#24	#6 AND #18 AND #23	2,604
#25	#24 NOT (#1 OR #2 OR #3)	1,875
#26	#24 NOT (#1 OR #2 OR #3) AND [2010-2023]/py	1,382
#27	'empirical research'/exp OR 'interview'/exp OR 'literature'/exp OR 'focus group'/exp OR 'information processing'/exp OR 'verbal communication'/exp OR 'nursing methodology research'/de OR 'narrative medicine'/de OR 'interview*':ti,ab,kw OR 'qualitative':ti,ab,kw,jt OR 'theme*':ti,ab,kw OR 'thematic':ti,ab,kw OR 'ethnological research':ti,ab,kw OR 'ethnograph*':ti,ab,kw OR 'ethnomedicine':ti,ab,kw OR 'ethnonursing':ti,ab,kw OR 'phenomenol*':ti,ab,kw OR (('grounded' NEXT/1 ('theor*' OR 'study' OR 'studies' OR 'research' OR 'analys?s')):ti,ab,kw) OR 'life stor*':ti,ab,kw OR 'emic':ti,ab,kw OR 'etic':ti,ab,kw OR 'hermeneutic*':ti,ab,kw OR 'heuristic*':ti,ab,kw OR 'semiotic*':ti,ab,kw OR (('data' NEAR/1 'saturat*'):ti,ab,kw) OR 'participant observ*':ti,ab,kw OR 'social construct*':ti,ab,kw OR 'postmodern*':ti,ab,kw OR 'post-structural*':ti,ab,kw OR 'poststructural*':ti,ab,kw OR 'post-modern*':ti,ab,kw OR 'action research':ti,ab,kw OR 'cooperative inquir*':ti,ab,kw OR 'co-operative inquir*':ti,ab,kw OR 'humanistic':ti,ab,kw OR 'existential':ti,ab,kw OR 'experiential':ti,ab,kw OR 'paradigm*':ti,ab,kw OR (('field' NEXT/1 ('study' OR 'studies' OR 'research' OR 'work')):ti,ab,kw) OR 'human science':ti,ab,kw OR 'social science':ti,ab,kw OR 'biographical method':ti,ab,kw OR 'theoretical sampl*':ti,ab,kw OR (('purpos*' NEAR/4 'sampl*'):ti,ab,kw) OR (('focus' NEXT/1 'group*'):ti,ab,kw) OR 'open-ended':ti,ab,kw OR 'narrative*':ti,ab,kw OR 'textual':ti,ab,kw OR 'texts':ti,ab,kw OR 'semi-structured':ti,ab,kw OR 'life-world*':ti,ab,kw OR 'conversation analys?s':ti,ab,kw OR 'personal experience*':ti,ab,kw OR 'theoretical saturation':ti,ab,kw OR ((('lived' OR 'life') NEXT/1 'experience*'):ti,ab,kw) OR 'cluster sampl*':ti,ab,kw OR 'observational method*':ti,ab,kw OR 'content analysis':ti,ab,kw OR (('constant' NEXT/1 ('comparative' OR 'comparison')):ti,ab,kw) OR ((('discourse*' OR 'discurs*') NEAR/3 'analys?s'):ti,ab,kw) OR 'heidegger*':ti,ab,kw OR 'colaizzi*':ti,ab,kw OR 'spiegelberg*':ti,ab,kw OR 'merleau*':ti,ab,kw OR 'husserl*':ti,ab,kw OR 'foucault*':ti,ab,kw OR 'ricoeur':ti,ab,kw OR 'glaser*':ti,ab,kw OR (('van' NEXT/1 'manen*'):ti,ab,kw) OR (('van' NEXT/1 'kaam*'):ti,ab,kw) OR (('corbin*' NEAR/2 'strauss*'):ti,ab,kw)	4,303,354
#28	'questionnaire'/exp OR 'health care survey'/de OR 'self report'/de OR 'questionnaire*':ti,ab,kw OR 'survey*':ti,ab,kw	2,081,019
#29	#27 OR #28	5,833,354
#30	#26 AND #29	380

Table abbreviations: MeSH, medical subject headings (ie, structured vocabulary for Medline); DRRC, Drug Regimen Review Center; SR, systematic review; CADTH, Canada's Drug and Health Technology Agency; RCT, randomized controlled trial; CCT, controlled clinical trial

APPENDIX I.C: STUDIES EXCLUDED AT FULL-TEXT SCREENING, BY CRITERION

Excluded because Wrong Patient Population

Agenor M, Cottrill AA, Kay E, Janiak E, Gordon AR, Potter J. Contraceptive Beliefs, Decision Making and Care Experiences Among Transmasculine Young Adults: A Qualitative Analysis. *Perspect Sex Reprod Health*. 2020;52(1):7-14. doi:10.1363/psrh.12128 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31977155

Ahmad S, Leinung M. The Response of the Menstrual Cycle to Initiation of Hormonal Therapy in Transgender Men. *Transgend Health*. 2017;2(1):176-179. doi:10.1089/trgh.2017.0023 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29159311

Ainsworth AJ, Allyse M, Khan Z. Fertility Preservation for Transgender Individuals: A Review. *Mayo Clin Proc*. 2020;95(4):784-792. doi:10.1016/j.mayocp.2019.10.040 Accessed September 15, 2023. Available at https://www.mayoclinicproceedings.org/article/S0025-6196(19)30947-4/pdf

Alpern S, Yaish I, Wagner-Kolasko G, et al. Why fertility preservation rates of transgender men are much lower than those of transgender women. *Reprod Biomed Online*. 2022;44(5):943-950. doi:10.1016/j.rbmo.2022.01.003 Accessed September 15, 2023. Available at https://www.rbmojournal.com/article/S1472-6483(22)00029-3/fulltext

Amir H, Yaish I, Oren A, Groutz A, Greenman Y, Azem F. Fertility preservation rates among transgender women compared with transgender men receiving comprehensive fertility counselling. *Reprod Biomed Online*. 2020;41(3):546-554. doi:10.1016/j.rbmo.2020.05.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32651108

Anderson WJ, Kolin DL, Neville G, et al. Prostatic Metaplasia of the Vagina and Uterine Cervix: An Androgen-associated Glandular Lesion of Surface Squamous Epithelium. *Am J Surg Pathol*. 2020;44(8):1040-1049. doi:10.1097/PAS.0000000000001486 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32282346

Andrews AR, Kakadekar A, Greene DN, Khalifa MA, Santiago V, Schmidt RL. Histologic Findings in Surgical Pathology Specimens From Individuals Taking Masculinizing Hormone Therapy for the Purpose of Gender Transition. *Arch Pathol Lab Med*. 2022;146(6):766-779. doi:10.5858/arpa.2020-0774-RA Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34559874

Andrzejewski J, Dunville R, Johns MM, Michaels S, Reisner SL. Medical Gender Affirmation and HIV and Sexually Transmitted Disease Prevention in Transgender Youth: Results from the Survey of Today's Adolescent Relationships and Transitions, 2018. *LGBT Health*. 2021;8(3):181-189. doi:10.1089/lgbt.2020.0367 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33566718

Andrzejewski J, Pampati S, Steiner RJ, Boyce L, Johns MM. Perspectives of Transgender Youth on Parental Support: Qualitative Findings From the Resilience and Transgender Youth Study. *Health Educ Behav*. 2021;48(1):74-81. doi:10.1177/1090198120965504 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106050

Return to TOC

Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of antiandrogens and feminization in transgender women. *Clin Endocrinol (Oxf)*. 2021;94(5):743-752. doi:10.1111/cen.14329 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32926454

Aranda G, Fernandez-Rebollo E, Pradas-Juni M, et al. Effects of sex steroids on the pattern of methylation and expression of the promoter region of estrogen and androgen receptors in people with gender dysphoria under cross-sex hormone treatment. *J Steroid Biochem Mol Biol*. 2017;172:20-28. doi:10.1016/j.jsbmb.2017.05.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28539237

Aranda G, Mora M, Hanzu FA, Vera J, Ortega E, Halperin I. Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. *Endocrinol Diabetes Nutr (Engl Ed)*. 2019;66(6):385-392. doi:10.1016/j.endinu.2018.11.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30704917

Araya AC, Warwick R, Shumer D, Selkie E. Romantic relationships in transgender adolescents: A qualitative study. *Pediatrics*. 2021;147(2)doi:10.1542/peds.2020-007906 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2011108095&from=export

Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk Factors for Non-Suicidal Self-Injury Among Trans Youth. *J Sex Med*. 2016;13(3):402-412. doi:10.1016/j.jsxm.2016.01.003 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26944465

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;164(4):635-642. doi:10.1530/EJE-10-1038 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21266549

Atnas C, Milton M, Archer S. Research Paper Making the Decision to Change the experiences of trans men. *Counselling Psychology Review*. 2015;30(1):33-42. doi:10.53841/bpscpr.2015.30.1.33 Accessed June 1, 2023. Available at https://explore.bps.org.uk/content/bpscpr/30/1/33

Auer MK, Fuss J, Hohne N, Stalla GK, Sievers C. Transgender transitioning and change of self-reported sexual orientation. *PLoS One*. 2014;9(10):e110016. doi:10.1371/journal.pone.0110016 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25299675

Auer MK, Fuss J, Nieder TO, et al. Desire to Have Children Among Transgender People in Germany: A Cross-Sectional Multi-Center Study. *J Sex Med*. 2018;15(5):757-767. doi:10.1016/j.jsxm.2018.03.083 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/15/5/757/6980540?redirectedFrom=fulltext

Aziz NA, Mohd Ali MH, Ramli R. Hysterectomy in a phenotypic male with congenital adrenal hyperplasia (CAH). *BMJ Case Rep*. 2022;15(2)doi:10.1136/bcr-2021-246603 Accessed September 15, 2023. Available at https://casereports.bmj.com/content/15/2/e246603

Bartholomaeus C, Riggs DW. Transgender and non-binary Australians' experiences with healthcare professionals in relation to fertility preservation. *Cult Health Sex*. 2020;22(2):129-145.

doi:10.1080/13691058.2019.1580388 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30880612

Becerra-Fernandez A, Perez-Lopez G, Roman MM, et al. Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. *Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion*. 2014;61(7):351-358. doi:10.1016/j.endonu.2014.01.010 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24680383

Beek TF, Kreukels BP, Cohen-Kettenis PT, Steensma TD. Partial Treatment Requests and Underlying Motives of Applicants for Gender Affirming Interventions. *J Sex Med*. 2015;12(11):2201-2205. doi:10.1111/jsm.13033 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26553507

Berookhim BM, Mulhall JP. Outcomes of operative sperm retrieval strategies for fertility preservation among males scheduled to undergo cancer treatment. *Fertil Steril*. 2014;101(3):805-811. doi:10.1016/j.fertnstert.2013.11.122 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24424372

Birenbaum-Carmeli D, Inhorn MC, Patrizio P. Transgender men's fertility preservation: experiences, social support, and the quest for genetic parenthood. *Cult Health Sex*. 2021;23(7):945-960. doi:10.1080/13691058.2020.1743881 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32484394

Borba Soll BM, Robles-Garcia R, Brandelli-Costa A, et al. Gender incongruence: a comparative study using ICD-10 and DSM-5 diagnostic criteria. *Braz J Psychiatry*. 2018;40(2):174-180. doi:10.1590/1516-4446-2016-2224 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28977069

Bosi IM, Holmes-Walker J, Lau NS, et al. Sexual identity in congenital adrenal hyperplasia. *J Paediatr Child Health*. 2021;57(4):581-583. doi:10.1111/jpc.14912 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32468703

Bretherton I, Spanos C, Leemaqz SY, et al. Insulin resistance in transgender individuals correlates with android fat mass. *Ther Adv Endocrinol Metab*. 2021;12:2042018820985681. doi:10.1177/2042018820985681 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33552464

Bui HN, Schagen SE, Klink DT, Delemarre-van de Waal HA, Blankenstein MA, Heijboer AC. Salivary testosterone in female-to-male transgender adolescents during treatment with intra-muscular injectable testosterone esters. *Steroids*. 2013;78(1):91-95. doi:10.1016/j.steroids.2012.10.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23123742

Caanen MR, Soleman RS, Kuijper EA, et al. Antimullerian hormone levels decrease in female-to-male transsexuals using testosterone as cross-sex therapy. *Fertil Steril*. 2015;103(5):1340-1345. doi:10.1016/j.fertnstert.2015.02.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25772768

Carlson KJ, Irwin JA, Dowdall JR, Figy SC, Amoura NJ. Integrated Comprehensive Care for Transcare and Gender Diverse Clinic Patients: An Assessment of Physical, Mental, and Social Needs. *Cureus*.

2021;13(12):e20544. doi:10.7759/cureus.20544 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35070571

Castelo-Branco C, RiberaTorres L, Gomez-Gil E, Uribe C, Canizares S. Psychopathological symptoms in Spanish subjects with gender dysphoria. A cross-sectional study. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*. 2021;37(6):534-540. doi:10.1080/09513590.2021.1913113 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33904350

Chan KJ, Jolly D, Liang JJ, Weinand JD, Safer JD. Estrogen Levels Do Not Rise with Testosterone Treatment for Transgender Men. *Endocr Pract*. 2018;24(4):329-333. doi:10.4158/EP-2017-0203 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29561193

Chan KL, Mok CC. Development of systemic lupus erythematosus in a male-to-female transsexual: The role of sex hormones revisited. *Lupus*. 2013;22(13):1399-1402. doi:10.1177/0961203313500550 Accessed September 15, 2023. Available at https://journals.sagepub.com/doi/10.1177/0961203313500550?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Chen D, Kyweluk MA, Sajwani A, et al. Factors Affecting Fertility Decision-Making Among Transgender Adolescents and Young Adults. *LGBT Health*. 2019;6(3):107-115. doi:10.1089/lgbt.2018.0250 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30985275

Chen S, Loshak H. *Primary Care Initiated Gender-Affirming Therapy for Gender Dysphoria: A Review of Evidence Based Guidelines*. CADTH Rapid Response Report. Canadian Agency for Drugs and Technologies in Health (CADTH); 2020: 14 pages. Last Updated April 21, 2020. Accessed June 1, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33112530

Chuang J, Vallerie A, Breech L, et al. Complexities of gender assignment in 17beta-hydroxysteroid dehydrogenase type 3 deficiency: is there a role for early orchiectomy? *Int J Pediatr Endocrinol*. 2013;2013(1):15. doi:10.1186/1687-9856-2013-15 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24025597

Clark BA, Virani A. “This Wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy. *J Bioeth Inq*. 2021;18(1):151-164. doi:10.1007/s11673-020-10086-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33502682

Cocchetti C, Ristori J, Mazzoli F, et al. 5α-Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature. *J Endocrinol Invest*. 2020;43(8):1131-1136. doi:10.1007/s40618-020-01193-w Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s40618-020-01193-w

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013;10(12):3049-3058. doi:10.1111/jsm.12155 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23574768

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study.

Psychoneuroendocrinology. 2014;39:65-73. doi:10.1016/j.psyneuen.2013.09.029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24275005

Costa C, Castro-Correia C, Mira-Coelho A, et al. The dilemma of the gender assignment in a Portuguese adolescent with disorder of sex development due to 17beta-hydroxysteroid-dehydrogenase type 3 enzyme deficiency. *Endocrinology, diabetes & metabolism case reports*. 2014;2014(101618943):140064. doi:10.1530/EDM-14-0064 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25298885

Costantino A, Cerpolini S, Alvisi S, Morselli PG, Venturoli S, Meriggiola MC. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;39(4):321-335. doi:10.1080/0092623X.2012.736920 https://www.ncbi.nlm.nih.gov/pubmed/23470169

Cupisti S, Giltay EJ, Gooren LJ, et al. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010;94(7):2647-2653. doi:10.1016/j.fertnstert.2010.03.048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20451188

Dabaja AA, Wosnitzer MS, Bolyakov A, Schlegel PN, Paduch DA. When to ask male adolescents to provide semen sample for fertility preservation? *Transl Androl Urol*. 2014;3(1):2-8. doi:10.3978/j.issn.2223-4683.2014.02.01 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26813354

de Blok CJ, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol*. 2021;9(10):663-670. doi:10.1016/S2213-8587(21)00185-6 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34481559

de Blok CJM, Dijkman BAM, Wiepjes CM, et al. Sustained Breast Development and Breast Anthropometric Changes in 3 Years of Gender-Affirming Hormone Treatment. *J Clin Endocrinol Metab*. 2021;106(2):e782-e790. doi:10.1210/clinem/dgaa841 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33206172

de Blok CJM, Staphorsius AS, Wiepjes CM, Smit JM, Nanayakkara PWB, den Heijer M. Frequency, Determinants, and Satisfaction of Breast Augmentation in Trans Women Receiving Hormone Treatment. *J Sex Med*. 2020;17(2):342-348. doi:10.1016/j.jsxm.2019.10.021 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31806494

de Nie I, Meisner A, Kostelijk EH, et al. Impaired semen quality in trans women: prevalence and determinants. *Human reproduction (Oxford, England)*. 2020;35(7):1529-1536. doi:10.1093/humrep/deaa133 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32613241

de Vries ALC. Disorders of Sex Development and Gender Identity Outcome in Adolescence and Adulthood: Understanding Gender Identity Development and its Clinical Implications. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:21-36:chap 2. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

Deeb A, Suwaidi HA, Ibukunoluwa F, Attia S. Phenotype, sex of rearing, gender re-assignment, and response to medical treatment in extended family members with a novel mutation in the SRD5A2 gene. *JCRPE Journal of Clinical Research in Pediatric Endocrinology*. 2016;8(2):236-240. doi:10.4274/jcrpe.2782 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5096483/pdf/JCRPE-8-236.pdf

Demeestere I, Simon P, Dedeken L, et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. *Hum Reprod*. 2015;30(9):2107-2109. doi:10.1093/humrep/dev128 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26062556

Diemer EW, Grant JD, Munn-Chernoff MA, Patterson DA, Duncan AE. Gender Identity, Sexual Orientation, and Eating-Related Pathology in a National Sample of College Students. *J Adolesc Health*. 2015;57(2):144-149. doi:10.1016/j.jadohealth.2015.03.003 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25937471

Dowshen N, Lee S, Franklin J, Castillo M, Barg F. Access to Medical and Mental Health Services Across the HIV Care Continuum Among Young Transgender Women: A Qualitative Study. *Transgend Health*. 2017;2(1):81-90. doi:10.1089/trgh.2016.0046 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28861551

Durand MA, Witt J, Joseph-Williams N, et al. Minimum standards for the certification of patient decision support interventions: feasibility and application. *Patient Educ Couns*. 2015;98(4):462-468. doi:10.1016/j.pec.2014.12.009 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25577469

Durcan E, Turan S, Bircan BE, et al. Fertility Desire and Motivation Among Individuals with Gender Dysphoria: A Comparative Study. *J Sex Marital Ther*. 2022;48(8):789-803. doi:10.1080/0092623X.2022.2053617 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L637611845&from=export

Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010;72(1):1-10. doi:10.1111/j.1365-2265.2009.03632.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19473174

Ellis SJ, Wakefield CE, McLoone JK, Robertson EG, Cohn RJ. Fertility concerns among child and adolescent cancer survivors and their parents: A qualitative analysis. *J Psychosoc Oncol*. 2016;34(5):347-362. doi:10.1080/07347332.2016.1196806 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27269305

Eyssel J, Koehler A, Dekker A, Sehner S, Nieder TO. Needs and concerns of transgender individuals regarding interdisciplinary transgender healthcare: A non-clinical online survey. *PLoS One*. 2017;12(8):e0183014. doi:10.1371/journal.pone.0183014 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28846715

Fein LA, Salgado CJ, Alvarez CV, Estes CM. Transitioning Transgender: Investigating the Important Aspects of the Transition: A Brief Report. *International Journal of Sexual Health*. 2016;29(1):80-88. doi:10.1080/19317611.2016.1227013 Accessed September 15, 2023. Available at https://doi.org/10.1080/19317611.2016.1227013

Ferguson HJ, Brunsdon VEA, Bradford EEF. The developmental trajectories of executive function from adolescence to old age. *Sci Rep*. 2021;11(1):1382. doi:10.1038/s41598-020-80866-1 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33446798

Fernandez JD, Tannock LR. Metabolic Effects of Hormone Therapy in Transgender Patients. *Endocr Pract*. 2016;22(4):383-388. doi:10.4158/EP15950.OR Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26574790

Fisher AD, Castellini G, Ristori J, et al. Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data. *J Clin Endocrinol Metab*. 2016;101(11):4260-4269. doi:10.1210/jc.2016-1276 https://www.ncbi.nlm.nih.gov/pubmed/27700538

Fisher CB, Fried AL, Desmond M, Macapagal K, Mustanski B. Perceived Barriers to HIV Prevention Services for Transgender Youth. *LGBT health*. 2018;5(6):350-358. doi:10.1089/lgbt.2017.0098 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145040/pdf/lgbt.2017.0098.pdf

Flores A, Herman J, Gates G, Brown T. *How Many Adults Identify as Transgender in the United States?* The Williams Institute UCLA School of Law; 2016: 13 pages. Last Updated August 2016. Accessed June 12, 2023. Available at https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-Adults-US-Aug-2016.pdf

Frederick MJ, Berhanu AE, Bartlett R. Chest Surgery in Female to Male Transgender Individuals. *Ann Plast Surg*. 2017;78(3):249-253. doi:10.1097/SAP.0000000000000882 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618622007&from=export

Fuss J, Hellweg R, Van Caenegem E, et al. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). *Eur Neuropsychopharmacol*. 2015;25(1):95-99. doi:10.1016/j.euroneuro.2014.11.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25498415

Gangaher A, Jyotsna VP, Chauhan V, John J, Mehta M. Gender of rearing and psychosocial aspect in 46 XX congenital adrenal hyperplasia. *Indian J Endocrinol Metab*. 2016;20(6):870-877. doi:10.4103/2230-8210.192922 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27867895

Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016;85(2):239-246. doi:10.1111/cen.13050 https://www.ncbi.nlm.nih.gov/pubmed/26932202

Gava G, Mancini I, Cerpolini S, Baldassarre M, Seracchioli R, Meriggiola MC. Testosterone undecanoate and testosterone enanthate injections are both effective and safe in transmen over 5 years of administration. *Clin Endocrinol (Oxf)*. 2018;89(6):878-886. doi:10.1111/cen.13821 https://www.ncbi.nlm.nih.gov/pubmed/30025172

Gavidia R, Whitney DG, Hershner S, Selkie EM, Tauman R, Dunietz GL. Gender identity and transition: relationships with sleep disorders in US youth. *J Clin Sleep Med*. 2022;18(11):2553-2559.

doi:10.5664/jcsm.10158 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35912700

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio IE, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2014;23(2):669-676. doi:10.1007/s11136-013-0497-3 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s11136-013-0497-3

Gomez-Gil E, Zubiaurre-Elorza L, Esteva I, et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;37(5):662-670. doi:10.1016/j.psyneuen.2011.08.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21937168

Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014;46(10):1156-1160. doi:10.1111/and.12208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24329588

Gooren LJ, Sungkaew T, Giltay EJ. Exploration of functional health, mental well-being and cross-sex hormone use in a sample of Thai male-to-female transgendered persons (kathoeys). *Asian J Androl*. 2013;15(2):280-285. doi:10.1038/aja.2012.139 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23353716

Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *J Sex Med*. 2013;10(12):3129-3134. doi:10.1111/jsm.12319 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24010586

Gorin-Lazard A, Baumstarck K, Boyer L, et al. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012;9(2):531-541. doi:10.1111/j.1743-6109.2011.02564.x https://www.ncbi.nlm.nih.gov/pubmed/22145968

Gridley SJ, Crouch JM, Evans Y, et al. Youth and Caregiver Perspectives on Barriers to Gender-Affirming Health Care for Transgender Youth. *J Adolesc Health*. 2016;59(3):254-261. doi:10.1016/j.jadohealth.2016.03.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27235374

Grimstad FW, Fowler KG, New EP, et al. Uterine pathology in transmasculine persons on testosterone: a retrospective multicenter case series. *Am J Obstet Gynecol*. 2019;220(3):257 e251-257 e257. doi:10.1016/j.ajog.2018.12.021 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30579875

Grootens-Wiegers P, Hein IM, van den Broek JM, de Vries MC. Medical decision-making in children and adolescents: developmental and neuroscientific aspects. *BMC Pediatr*. 2017;17(1):120. doi:10.1186/s12887-017-0869-x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28482854

Guaraldi F, Beccuti G, Gori D, Ghizzoni L. MANAGEMENT OF ENDOCRINE DISEASE: Long-term outcomes of the treatment of central precocious puberty. *Eur J Endocrinol*. 2016;174(3):R79-87.

doi:10.1530/EJE-15-0590 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26466612

Haas A, Rodgers P, Herman J. *Suicide Attempts among Transgender and Gender Non-Conforming Adults: Findings of the National Transgender Discrimination Survey*. American Foundation for Suicide Prevention and the UCLA School of Law Williams Institute; 2014: 18 pages. Last Updated January 2014. Accessed June 12, 2023. Available at https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-GNC-Suicide-Attempts-Jan-2014.pdf

Haley SG, Tordoff DM, Kantor AZ, Crouch JM, Ahrens KR. Sex Education for Transgender and Non-Binary Youth: Previous Experiences and Recommended Content. *J Sex Med*. 2019;16(11):1834-1848. doi:10.1016/j.jsxm.2019.08.009 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2003126060&from=export

Halpern JA, Thirumavalavan N, Kohn TP, et al. Distribution of Semen Parameters Among Adolescent Males Undergoing Fertility Preservation in a Multicenter International Cohort. *Urology*. 2019;127:119-123. doi:10.1016/j.urology.2019.01.027 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30771377

Hancock AB, Garabedian LM. Transgender voice and communication treatment: a retrospective chart review of 25 cases. *International journal of language & communication disorders / Royal College of Speech & Language Therapists*. 2013;48(1):54-65. doi:10.1111/j.1460-6984.2012.00185.x Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/10.1111/j.1460-6984.2012.00185.x

Haselbacher G. [Escape from the wrong gender]. *MMW Fortschr Med*. 2014;156(12):38-39. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25369683

Hill WJ, Shapiro MA. Transgender Youth in the Inpatient Psychiatric Setting: A Literature Review and Case Report. *J Psychiatr Pract*. 2017;23(4):290-293. doi:10.1097/PRA.0000000000000244 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28749834

Hisle-Gorman E, Schvey NA, Adirim TA, et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. *J Sex Med*. 2021;18(8):1444-1454. doi:10.1016/j.jsxm.2021.05.014 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/18/8/1444/6956103?redirectedFrom=fulltext

Hughes CK, McGarey P, Morrison D, Gawlik AE, Dominguez L, Dion GR. Vocal Fold Thinning in Transgender Patients. *J Voice*. 2021, 10.1016/j.jvoice.2021.06.026doi:10.1016/j.jvoice.2021.06.026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34452779

Humble RM, Imborek KL, Nisly N, Greene DN, Krasowski MD. Common Hormone Therapies Used to Care for Transgender Patients Influence Laboratory Results. *J Appl Lab Med*. 2019;3(5):799-814. doi:10.1373/jalm.2018.027078 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31639755

Ignacio KHD, Diestro JDB, Espiritu AI, Pineda-Franks MC. Stroke in Male-to-Female Transgenders: A Systematic Review and Meta-Analysis. *Can J Neurol Sci*. 2022;49(1):76-83.

doi:10.1017/cjn.2021.54 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33766179

Imhof RL, Davidge-Pitts CJ, Miest RYN, Nippoldt TB, Tollefson MM. Dermatologic disorders in transgender patients: A retrospective cohort of 442 patients. *J Am Acad Dermatol*. 2020;83(5):1516-1518. doi:10.1016/j.jaad.2020.06.074 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32593637

Jacoby A, Rifkin W, Zhao LC, Bluebond-Langner R. Incidence of Cancer and Premalignant Lesions in Surgical Specimens of Transgender Patients. *Plast Reconstr Surg*. 2021;147(1):194-198. doi:10.1097/PRS.0000000000007452 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L633890506&from=export

Jalowiecka I, Gómez Balaguer M, Cañete San Pastor P, et al. Reproductive desire and gamete preservation in transgender people: Survey on real interest in a cohort from a Spanish tertiary hospital. *Progresos de Obstetricia y Ginecologia*. 2023;66(1):8-13. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2023301187&from=export

Jones BA, Haycraft E, Bouman WP, Brewin N, Claes L, Arcelus J. Risk Factors for Eating Disorder Psychopathology within the Treatment Seeking Transgender Population: The Role of Cross-Sex Hormone Treatment. *Eur Eat Disord Rev*. 2018;26(2):120-128. doi:10.1002/erv.2576 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29318711

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co-morbidities in an irish adult population. *Front Endocrinol (Lausanne)*. 2014;5(JUN):87. doi:10.3389/fendo.2014.00087 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24982651

Karrington B. The Experiences of Transmasculine People with Contraception and Menstruation: A Literature Review of Qualitative and Mixed Method Studies. *Transgend Health*. 2021;6(6):303-314. doi:10.1089/trgh.2020.0047 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993303

Kattari SK, Bakko M, Hecht HK, Kinney MK. Intersecting Experiences of Healthcare Denials Among Transgender and Nonbinary Patients. *Am J Prev Med*. 2020;58(4):506-513. doi:10.1016/j.amepre.2019.11.014 Accessed September 15, 2023. Available at https://www.ajpmonline.org/article/S0749-3797(19)30538-0/fulltext

Katz-Wise SL, Budge SL, Orovecz JJ, Nguyen B, Nava-Coulter B, Thomson K. Imagining the future: Perspectives among youth and caregivers in the trans youth family study. *J Couns Psychol*. 2017;64(1):26-40. doi:10.1037/cou0000186 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5224913/pdf/nihms-828499.pdf

Kearns S, O'Shea D, Neff K. Transgender and non-binary demographics, referrals, and comorbidities among young Irish adults (2014–2020). *Ir J Med Sci*. 2022;192:1679-1685. doi:10.1007/s11845-022-03163-y Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s11845-022-03163-y

Kempf AM, Burns ZT, Guss CE, et al. Clinical outcomes and considerations of gender-affirming care for transgender and gender-diverse pediatric and young adult patients with cancer. *Pediatr Blood Cancer*. 2023;70(1):e29851. doi:10.1002/pbc.29851 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35713118

Keo-Meier CL, Herman LI, Reisner SL, Pardo ST, Sharp C, Babcock JC. Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. *J Consult Clin Psychol*. 2015;83(1):143-156. doi:10.1037/a0037599 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25111431

Ker A, Shaw RM, Byrne J, Veale J. Access to fertility preservation for trans and non-binary people in Aotearoa New Zealand. *Culture, health & sexuality*. 2022;24(9):1273-1288. doi:10.1080/13691058.2021.1944670 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L635611012&from=export

Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol*. 2018;178(2):163-171. doi:10.1530/EJE-17-0496 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29183889

Klein A, Golub SA. Enhancing Gender-Affirming Provider Communication to Increase Health Care Access and Utilization Among Transgender Men and Trans-Masculine Non-Binary Individuals. *LGBT health*. 2020;7(6):292-304. doi:10.1089/lgbt.2019.0294 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7475086/pdf/lgbt.2019.0294.pdf

Klein DA, Ellzy JA, Olson J. Care of a Transgender Adolescent. *Am Fam Physician*. 2015;92(2):142-148. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26176373

Krüger A, Sperandei S, Bermudez XPCD, Merchán-Hamann E. Characteristics of hormone use by travestis and transgender women of the Brazilian Federal District. *Revista brasileira de epidemiologia = Brazilian journal of epidemiology*. 2019;22Suppl 1((Krüger A.; Bermudez X.P.C.D.; Merchán-Hamann E.) Post-Graduate Program in Collective Health, School of Health Sciences, University of Brasília, Brasília (DF), Brazil(Sperandei S.) Institute of Communication and Scientific Information and Technology in He):e190004. doi:10.1590/1980-549720190004.supl.1 Accessed September 15, 2023. Available at https://www.scielo.br/j/rbepid/a/9Cshmsw95pNmdmGtxMZcqYc/?lang=en&format=pdf

Kuper LE, Adams N, Mustanski BS. Exploring Cross-Sectional Predictors of Suicide Ideation, Attempt, and Risk in a Large Online Sample of Transgender and Gender Nonconforming Youth and Young Adults. *LGBT Health*. 2018;5(7):391-400. doi:10.1089/lgbt.2017.0259 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30280981

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-254. doi:10.1080/00224499.2011.596954 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21797716

Lefevor GT, Sprague BM, Boyd-Rogers CC, Smack ACP. How well do various types of support buffer psychological distress among transgender and gender nonconforming students? *Int J Transgend*.

2019;20(1):39-48. doi:10.1080/15532739.2018.1452172 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999593

Lehmann K, Leavey G. Accuracy of psychometric tools in the assessment of personality in adolescents and adults requesting gender-affirming treatments: A systematic review. *Eur Psychiatry*. 2019;62:60-67. doi:10.1016/j.eurpsy.2019.09.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31546228

Lehmann K, Rosato M, McKenna H, Leavey G. Dramaturgical Accounts of Transgender Individuals: Impression Management in the Presentation of Self to Specialist Gender Services. *Arch Sex Behav*. 2021;50(8):3539-3549. doi:10.1007/s10508-021-02028-2 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8604840/pdf/10508_2021_Article_2028.pdf

Lehmann V, Keim MC, Nahata L, et al. Fertility-related knowledge and reproductive goals in childhood cancer survivors: short communication. *Hum Reprod*. 2017;32(11):2250-2253. doi:10.1093/humrep/dex297 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29040512

Leinung MC, Joseph J. Changing Demographics in Transgender Individuals Seeking Hormonal Therapy: Are Trans Women More Common Than Trans Men? *Transgend Health*. 2020;5(4):241-245. doi:10.1089/trgh.2019.0070 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644314

Leung A, Sakkas D, Pang S, Thornton K, Resetkova N. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. *Fertil Steril*. 2019;112(5):858-865. doi:10.1016/j.fertnstert.2019.07.014 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31594633

Levy B, Teplitsky S, Kalaitzoglou E, Kahler S, Matheny JP, Saltzman AF. "Exogenous" 5 Alpha Reductase Deficiency: A Case Report". *Urology*. 2023;178(wsy, 0366151):147-150. doi:10.1016/j.urology.2023.05.001 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37178876

Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstet Gynecol*. 2014;124(6):1120-1127. doi:10.1097/AOG.0000000000000540 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25415163

Littman L. Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners. *Arch Sex Behav*. 2021;50(8):3353-3369. doi:10.1007/s10508-021-02163-w Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34665380

López JLJ, Guzmán MEM, Miranda NJ. Protocol care for patients with gender dysphoria : A case report. *Archivos de Neurociencias*. 2017;22(1):35-40. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L621102318&from=export

Luy SCR, Ho F. A rare case of true hermaphrodite with features of klinefelter syndrome. *Phillippine Journal of Internal Medicine*. 2013;51(4)Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L372245520&from=export

MacDonald T, Noel-Weiss J, West D, et al. Transmasculine individuals' experiences with lactation, chestfeeding, and gender identity: A qualitative study. *BMC Pregnancy Childbirth*. 2016;16(1):106. doi:10.1186/s12884-016-0907-y Accessed September 15, 2023. Available at https://bmcpregnancychildbirth.biomedcentral.com/counter/pdf/10.1186/s12884-016-0907-y.pdf

Makino T, Fujita T, Nakano T. Fatty degeneration of mammary glands in female-to-male transsexuals. *Eur J Plast Surg*. 2017;40(4):309-314. doi:10.1007/s00238-016-1269-4 Accessed June 28, 2023. Available at https://link.springer.com/article/10.1007/s00238-016-1269-4

Manieri C, Castellano E, Crespi C, et al. Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an Italian Public Health Center. *International Journal of Transgenderism*. 2014;15(2):53-65. doi:10.1080/15532739.2014.899174 https://doi.org/10.1080/15532739.2014.899174

Marchiano L. Gender detransition: a case study. *The Journal of analytical psychology*. 2021;66(4):813-832. doi:10.1111/1468-5922.12711 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9298887/pdf/JOAP-66-813.pdf

Marks DH, Hagigeorges D, Manatis-Lornell AJ, Dommasch E, Senna MM. Excess hair, hair removal methods, and barriers to care in gender minority patients: A survey study. *J Cosmet Dermatol*. 2020;19(6):1494-1498. doi:10.1111/jocd.13164 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31553137

Marsh C, McCracken M, Gray M, Nangia A, Gay J, Roby KF. Low total motile sperm in transgender women seeking hormone therapy. *J Assist Reprod Genet*. 2019;36(8):1639-1648. doi:10.1007/s10815-019-01504-y Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708020/pdf/10815_2019_Article_1504.pdf

Mattelin E, Strandell A, Bryman I. Fertility preservation and fertility treatment in transgender adolescents and adults in a Swedish region, 2013-2018. *Human reproduction open*. 2022;2022(2):hoac008. doi:10.1093/hropen/hoac008 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35309678

Mayer TK, Koehler A, Eyssel J, Nieder TO. How Gender Identity and Treatment Progress Impact Decision-Making, Psychotherapy and Aftercare Desires of Trans Persons. *J Clin Med*. 2019;8(5)doi:10.3390/jcm8050749 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31130679

Mehra G, Boskey ER, Peters CJ, Njubigbo C, Charlton BM, Ganor O. Assessing Fertility Intentions in Patients Presenting for Gender-Affirming Surgery. *LGBT health*. 2022;9(5):325-332. doi:10.1089/lgbt.2021.0148 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/lgbt.2021.0148?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Meier SC, Pardo ST, Labuski C, Babcock J. Measures of clinical health among female-to-male transgender persons as a function of sexual orientation. *Arch Sex Behav*. 2013;42(3):463-474. doi:10.1007/s10508-012-0052-2 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s10508-012-0052-2

Meijer JH, Eeckhout GM, van Vlerken RH, de Vries AL. Gender Dysphoria and Co-Existing Psychosis: Review and Four Case Examples of Successful Gender Affirmative Treatment. *LGBT Health*. 2017;4(2):106-114. doi:10.1089/lgbt.2016.0133 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28170299

Menino DD, Katz-Wise SL, Vetters R, Reisner SL. Associations Between the Length of Time from Transgender Identity Recognition to Hormone Initiation and Smoking Among Transgender Youth and Young Adults. *Transgend Health*. 2018;3(1):82-87. doi:10.1089/trgh.2018.0002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29795789

Meyer G, Mayer M, Mondorf A, Flugel AK, Herrmann E, Bojunga J. Safety and rapid efficacy of guideline-based gender-affirming hormone therapy: an analysis of 388 individuals diagnosed with gender dysphoria. *Eur J Endocrinol*. 2020;182(2):149-156. doi:10.1530/EJE-19-0463 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31751300

Meyer G, Mayer M, Mondorf A, Herrmann E, Bojunga J. Increasing normality-persisting barriers: Current socio-demographic characteristics of 350 individuals diagnosed with gender dysphoria. *Clin Endocrinol (Oxf)*. 2020;92(3):241-246. doi:10.1111/cen.14140 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31821578

Millington K, Chan YM. Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. *J Clin Lipidol*. 2021;15(6):840-844. doi:10.1016/j.jacl.2021.09.051 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34657833

Moravek MB, Kinnear HM, George J, et al. Impact of Exogenous Testosterone on Reproduction in Transgender Men. *Endocrinology*. 2020;161(3)doi:10.1210/endocr/bqaa014 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32105330

Motta G, Crespi C, Mineccia V, Brustio PR, Manieri C, Lanfranco F. Does Testosterone Treatment Increase Anger Expression in a Population of Transgender Men? *J Sex Med*. 2018;15(1):94-101. doi:10.1016/j.jsxm.2017.11.004 https://www.ncbi.nlm.nih.gov/pubmed/29175227

Nahata L, Campo-Engelstein LT, Tishelman A, Quinn GP, Lantos JD. Fertility Preservation for a Transgender Teenager. *Pediatrics*. 2018;142(3)doi:10.1542/peds.2017-3142 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30072573

Nguyen HB, Loughead J, Lipner E, Hantsoo L, Kornfield SL, Epperson CN. What has sex got to do with it? The role of hormones in the transgender brain. *Neuropsychopharmacology*. 2019;44(1):22-37. doi:10.1038/s41386-018-0140-7 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30082887

Nikkelen SWC, Kreukels BPC. Sexual Experiences in Transgender People: The Role of Desire for Gender-Confirming Interventions, Psychological Well-Being, and Body Satisfaction. *J Sex Marital Ther*. 2018;44(4):370-381. doi:10.1080/0092623X.2017.1405303 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/pdf/10.1080/0092623X.2017.1405303

Nota NM, Wiepjes CM, de Blok CJM, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. *Brain*. 2018;141(7):2047-2054. doi:10.1093/brain/awy108 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29688280

Oda H, Kinoshita T. Efficacy of hormonal and mental treatments with MMPI in FtM individuals: cross-sectional and longitudinal studies. *BMC Psychiatry*. 2017;17(1):256. doi:10.1186/s12888-017-1423-y Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28716082

Oien RA, Cicchetti DV, Nordahl-Hansen A. Gender Dysphoria, Sexuality and Autism Spectrum Disorders: A Systematic Map Review. *J Autism Dev Disord*. 2018;48(12):4028-4037. doi:10.1007/s10803-018-3686-7 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30019279

Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men. *LGBT Health*. 2014;1(3):165-167. doi:10.1089/lgbt.2014.0018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26789709

Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. *J Adolesc Health*. 2018;62(4):397-401. doi:10.1016/j.jadohealth.2017.08.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29056436

Opsomer D, Gast KM, Ramaut L, et al. Creation of Clitoral Hood and Labia Minora in Penile Inversion Vaginoplasty in Circumcised and Uncircumcised Transwomen. *Plast Reconstr Surg*. 2018;142(5):729e-733e. doi:10.1097/PRS.0000000000004926 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626511517&from=export

Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267-1272. doi:10.1016/j.fertnstert.2008.12.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19200981

Owen-Smith AA, Gerth J, Sineath RC, et al. Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals. *The journal of sexual medicine*. 2018;15(4):591-600. doi:10.1016/j.jsxm.2018.01.017 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463478

Papalini C, Lagi F, Schiaroli E, Sterrantino G, Francisci D. Transgender people living with HIV: characteristics and comparison to homosexual and heterosexual cisgender patients in two Italian teaching hospitals. *Int J STD AIDS*. 2021;32(2):194-198. doi:10.1177/0956462420950573 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33327898

Patel KT, Adeel S, Rodrigues Miragaya J, Tangpricha V. Progestogen Use in Gender-Affirming Hormone Therapy: A Systematic Review. *Endocr Pract*. 2022;28(12):1244-1252. doi:10.1016/j.eprac.2022.08.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36007714

Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;11(12):3002-3011. doi:10.1111/jsm.12698 https://www.ncbi.nlm.nih.gov/pubmed/25250780

Pena ÉD, Westin MR, Duarte MJ, et al. When prevention is the best remedy: HIV pre-exposure prophylaxis (PrEP) among adolescents gays and transgender women in Belo Horizonte, Minas Gerais State, Brazil. *Cad Saude Publica*. 2023;39((Pena É.D., ericadumont@gmail.com) Escola de Enfermagem, Universidade Federal de Minas Gerais, Av. Prof. Alfredo Balena 190, MG, Belo Horizonte, Brazil(Pena É.D., ericadumont@gmail.com) Escola de Enfermagem, Universidade Federal de Minas Gerais, Belo Hori):e00097921. doi:10.1590/0102-311XEN097921 Accessed September 15, 2023. Available at https://www.scielo.br/j/csp/a/jfPMB6tYHHMnJjgsV3ZBgnG/?lang=en&format=pdf

Pivo S, Montes J, Schwartz S, et al. Breast Cancer Risk Assessment and Screening in Transgender Patients. *Clin Breast Cancer*. 2017;17(5):e225-e227. doi:10.1016/j.clbc.2016.08.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28428098

Puckett JA, Cleary P, Rossman K, Newcomb ME, Mustanski B. Barriers to Gender-Affirming Care for Transgender and Gender Nonconforming Individuals. *Sexuality research & social policy : journal of NSRC : SR & SP*. 2018;15(1):48-59. doi:10.1007/s13178-017-0295-8 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29527241

Quinn GP, Tishelman AC, Chen D, Nahata L. Reproductive health risks and clinician practices with gender diverse adolescents and young adults. *Andrology*. 2021;9(6):1689-1697. doi:10.1111/andr.13026 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8566321/pdf/nihms-1701055.pdf

Quinn VP, Nash R, Hunkeler E, et al. Cohort profile: Study of Transition, Outcomes and Gender (STRONG) to assess health status of transgender people. *BMJ Open*. 2017;7(12):e018121. doi:10.1136/bmjopen-2017-018121 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29284718

Quirós C, Patrascioiu I, Mora M, et al. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015;62(5):210-216. doi:10.1016/j.endonu.2015.02.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25790747

Rael CT, Martinez M, Giguere R, et al. Transgender Women's Concerns and Preferences on Potential Future Long-Acting Biomedical HIV Prevention Strategies: The Case of Injections and Implanted Medication Delivery Devices (IMDDs). *AIDS Behav*. 2020;24(5):1452-1462. doi:10.1007/s10461-019-02703-5 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31654172

Rametti G, Carrillo B, Gomez-Gil E, et al. Effects of androgenization on the white matter microstructure of female-to-male transsexuals. A diffusion tensor imaging study. *Psychoneuroendocrinology*. 2012;37(8):1261-1269. doi:10.1016/j.psyneuen.2011.12.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22260939

Reisner SL, Biello KB, White Hughto JM, et al. Psychiatric Diagnoses and Comorbidities in a Diverse, Multicity Cohort of Young Transgender Women: Baseline Findings From Project LifeSkills. *JAMA*

Pediatr. 2016;170(5):481-486. doi:10.1001/jamapediatrics.2016.0067 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26999485

Reisner SL, Vetters R, Leclerc M, et al. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. *J Adolesc Health*. 2015;56(3):274-279. doi:10.1016/j.jadohealth.2014.10.264 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25577670

Reisner SL, Vetters R, White JM, et al. Laboratory-confirmed HIV and sexually transmitted infection seropositivity and risk behavior among sexually active transgender patients at an adolescent and young adult urban community health center. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*. 2015;27(8):1031-1036. doi:10.1080/09540121.2015.1020750 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624263/pdf/nihms731729.pdf

Riggs DW, Bartholomaeus C. Fertility preservation decision making amongst Australian transgender and non-binary adults. *Reprod Health*. 2018;15(1):181. doi:10.1186/s12978-018-0627-z Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30359260

Ristori J, Cocchetti C, Castellini G, et al. Hormonal Treatment Effect on Sexual Distress in Transgender Persons: 2-Year Follow-Up Data. *The journal of sexual medicine*. 2020;17(1):142-151. doi:10.1016/j.jsxm.2019.10.008 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31735612

Robertson BD, Lerner BS, Collen JF, Smith PR. The Effects of Transgender Hormone Therapy on Sleep and Breathing: A Case Series. *J Clin Sleep Med*. 2019;15(10):1529-1533. doi:10.5664/jcsm.7992 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31596219

Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A. Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. *Am J Public Health*. 2013;103(10):1830-1836. doi:10.2105/AJPH.2013.301348 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23948009

Roznovjak D, Petroll AE, Lakatos AEB, Narayan R, Cortina CS. Perceptions of Transgender and Nonbinary Persons Toward Breast and Cervical Cancer Development, Screening, and Potential Impact on Gender-Affirming Hormone Therapy. *JCO oncology practice*. 2023;19(5):e794-e800. doi:10.1200/OP.22.00681 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36800556

Ruppin U, Pfafflin F. Long-Term Follow-Up of Adults with Gender Identity Disorder. *Arch Sex Behav*. 2015;44(5):1321-1329. doi:10.1007/s10508-014-0453-5 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25690443

Sam KQ, Severs FJ, Ebuoma LO, Chandandeep NS, Sedgwick EL. Granulomatous mastitis in a transgender patient. *Journal of Radiology Case Reports*. 2017;11(2):16-22. doi:10.3941/jrcr.v11i2.2934 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443635/pdf/jrcr-11-2-16.pdf

Schultz JJ, Naides AI, Bai D, Shulzhenko NO, Keith JD. Pathological Evaluation of Breast Specimens in Transgender Chest Masculinization: Incidental Findings and Effect of Prior Chest Binding and

Androgen Therapy in 74 Consecutive Patients. *Transgend Health*. 2021;6(6):353-357. doi:10.1089/trgh.2020.0108 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993306

Sequeira GM, Kidd K, El Nokali NE, et al. Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. *J Adolesc Health*. 2019;65(6):818-820. doi:10.1016/j.jadohealth.2019.06.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31543405

She J, McCall J, Pudwell J, Kielly M, Waddington A. An Assessment of the Mental Health History of Patients in a Transgender Clinic in Kingston, Ontario. *Can J Psychiatry*. 2020;65(4):281-283. doi:10.1177/0706743719901245 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31961198

Silveira MT, Knobloch F, Silva Janovsky CCP, Kater CE. Gender Dysphoria in a 62-Year-Old Genetic Female With Congenital Adrenal Hyperplasia. *Arch Sex Behav*. 2016;45(7):1871-1875. doi:10.1007/s10508-016-0750-2 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27270635

Simons L, Schrager SM, Clark LF, Belzer M, Olson J. Parental support and mental health among transgender adolescents. *J Adolesc Health*. 2013;53(6):791-793. doi:10.1016/j.jadohealth.2013.07.019 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24012067

Simonsen R, Hald GM, Giraldi A, Kristensen E. Sociodemographic Study of Danish Individuals Diagnosed with Transsexualism. *Sexual Medicine*. 2015;3(2):109-117. doi:10.1002/sm2.48 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L604885291&from=export

Singh AA. Transgender Youth of Color and Resilience: Negotiating Oppression and Finding Support. *Sex Roles*. 2012;68(11-12):690-702. doi:10.1007/s11199-012-0149-z Accessed June 12, 2023. Available at https://link.springer.com/article/10.1007/s11199-012-0149-z

Singh AA, Meng SE, Hansen AW. "I Am My Own Gender": Resilience Strategies of Trans Youth. *Journal of Counseling & Development*. 2014;92(2):208-218. doi:10.1002/j.1556-6676.2014.00150.x Accessed June 12, 2023. Available at https://onlinelibrary.wiley.com/doi/abs/10.1002/j.1556-6676.2014.00150.x

Singh K, Sung CJ, Lawrence WD, Quddus MR. Testosterone-induced "Virilization" of Mesonephric Duct Remnants and Cervical Squamous Epithelium in Female-to-Male Transgenders: A Report of 3 Cases. *Int J Gynecol Pathol*. 2017;36(4):328-333. doi:10.1097/PGP.0000000000000333 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27571240

Soleman RS, Staphorsius AS, Cohen-Kettenis PT, et al. Oestrogens are Not Related to Emotional Processing: a Study of Regional Brain Activity in Female-to-Male Transsexuals Under Gonadal Suppression. *Cereb Cortex*. 2016;26(2):510-516. doi:10.1093/cercor/bhu201 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25246514

Strandjord SE, Ng H, Rome ES. Effects of treating gender dysphoria and anorexia nervosa in a transgender adolescent: Lessons learned. *Int J Eat Disord*. 2015;48(7):942-945.

doi:10.1002/eat.22438 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26337148

Strauss P, Cook A, Watson V, et al. Mental health difficulties among trans and gender diverse young people with an autism spectrum disorder (ASD): Findings from Trans Pathways. *J Psychiatr Res*. 2021;137:360-367. doi:10.1016/j.jpsychires.2021.03.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33761424

Stuyver I, Somers S, Provoost V, et al. Ten years of fertility treatment experience and reproductive options in transgender men. *Int J Transgend Health*. 2021;22(3):294-303. doi:10.1080/26895269.2020.1827472 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34240072

Sundaram V, Mok-Lin E. Fertility Preservation for the Transgender Individual. *Current Obstetrics and Gynecology Reports*. 2020;9(3):129-137. doi:10.1007/s13669-020-00291-z Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2005392812&from=export

Swendiman RA, Vogiatzi MG, Alter CA, Nance ML. Histrelin implantation in the pediatric population: A 10-year institutional experience. *J Pediatr Surg*. 2019;54(7):1457-1461. doi:10.1016/j.jpedsurg.2018.08.048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30262200

T'Sjoen G, De Cuypere G, Monstrey S, et al. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2011;40(3):635-638. doi:10.1007/s10508-010-9624-1 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L362321508&from=export

Tack LJ, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ*. 2016;7:14. doi:10.1186/s13293-016-0067-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26885361

Tan KKH, Byrne JL, Treharne GJ, Veale JF. Unmet need for gender-affirming care as a social determinant of mental health inequities for transgender youth in Aotearoa/New Zealand. *Journal of public health (Oxford, England)*. 2022;45((Tan K.K.H.; Byrne J.L.; Veale J.F.) Trans Health Research Lab, School of Psychology, University of Waikato, Hamilton, New Zealand(Tan K.K.H.) Faculty of Māori and Indigenous Studies, University of Waikato, Hamilton, New Zealand(Treharne G.J.) Department):e225-e233. doi:10.1093/pubmed/fdac131 Accessed September 15, 2023. Available at https://watermark.silverchair.com/fdac131.pdf

Taziaux M, Swaab DF, Bakker J. Sex differences in the neurokinin B system in the human infundibular nucleus. *J Clin Endocrinol Metab*. 2012;97(12):E2210-E2220. doi:10.1210/jc.2012-1554 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L366220088&from=export

Tomova A, Lalabonova C, Robeva RN, Kumanov PT. Timing of pubertal maturation according to the age at first conscious ejaculation. *Andrologia*. 2011;43(3):163-166. doi:10.1111/j.1439-

0272.2009.01037.x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21486428

Tunas SD, Dinc G, Goker Z, Uneri OS. Gender dysphoria in an adolescent diagnosed with Klinefelter syndrome over a follow-up period. *The European Research Journal*. 2017;4(1):48-51. doi:10.18621/eurj.313304 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626135868&from=export

Turan S, Aksoy Poyraz C, Usta Saglam NG, et al. Alterations in Body Uneasiness, Eating Attitudes, and Psychopathology Before and After Cross-Sex Hormonal Treatment in Patients with Female-to-Male Gender Dysphoria. *Arch Sex Behav*. 2018;47(8):2349-2361. doi:10.1007/s10508-018-1189-4 https://www.ncbi.nlm.nih.gov/pubmed/29594702

van de Grift TC, Pigot GLS, Boudhan S, et al. A Longitudinal Study of Motivations Before and Psychosexual Outcomes After Genital Gender-Confirming Surgery in Transmen. *J Sex Med*. 2017;14(12):1621-1628. doi:10.1016/j.jsxm.2017.10.064 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29128275

van der Miesen AIR, de Vries ALC, Steensma TD, Hartman CA. Autistic Symptoms in Children and Adolescents with Gender Dysphoria. *J Autism Dev Disord*. 2018;48(5):1537-1548. doi:10.1007/s10803-017-3417-5 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L619498209&from=export

van Leerdam TR, Zajac JD, Cheung AS. The Effect of Gender-Affirming Hormones on Gender Dysphoria, Quality of Life, and Psychological Functioning in Transgender Individuals: A Systematic Review. *Transgender Health*. 2023;8(1):6-21. doi:10.1089/trgh.2020.0094 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2022927143&from=export

Vandenbussche E. Detransition-Related Needs and Support: A Cross-Sectional Online Survey. *J Homosex*. 2022;69(9):1602-1620. doi:10.1080/00918369.2021.1919479 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33929297

Vita R, Settineri S, Liotta M, Benvenga S, Trimarchi F. Changes in hormonal and metabolic parameters in transgender subjects on cross-sex hormone therapy: A cohort study. *Maturitas*. 2018;107:92-96. doi:10.1016/j.maturitas.2017.10.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29169588

Vyas N, Douglas CR, Mann C, Weimer AK, Quinn MM. Access, barriers, and decisional regret in pursuit of fertility preservation among transgender and gender-diverse individuals. *Fertil Steril*. 2021;115(4):1029-1034. doi:10.1016/j.fertnstert.2020.09.007 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33276964

Walton E, Abhari S, Tangpricha V, Futral C, Mehta A. Family Planning and Fertility Counseling Perspectives of Gender Diverse Adults and Youth Pursuing or Receiving Gender Affirming Hormone Therapy. *Urology*. 2023;171:244-250. doi:10.1016/j.urology.2022.10.007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36404476

Warrier V, Greenberg DM, Weir E, et al. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. *Nat Commun*. 2020;11(1):3959. doi:10.1038/s41467-020-17794-1 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32770077

Wierckx K, Elaut E, Van Caenegem E, et al. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011;165(2):331-337. doi:10.1530/EJE-11-0250 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21602316

Wierckx K, Van Caenegem E, Elaut E, et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;8(12):3379-3388. doi:10.1111/j.1743-6109.2011.02348.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21699661

Wierckx K, Van Caenegem E, Pennings G, et al. Reproductive wish in transsexual men. *Hum Reprod*. 2012;27(2):483-487. doi:10.1093/humrep/der406 Accessed September 15, 2023. Available at https://watermark.silverchair.com/der406.pdf

Wilson EC, Chen YH, Arayasirikul S, Raymond HF, McFarland W. The Impact of Discrimination on the Mental Health of Trans*Female Youth and the Protective Effect of Parental Support. *AIDS Behav*. 2016;20(10):2203-2211. doi:10.1007/s10461-016-1409-7 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27115401

Witcomb GL, Bouman WP, Claes L, Brewin N, Crawford JR, Arcelus J. Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. *J Affect Disord*. 2018;235:308-315. doi:10.1016/j.jad.2018.02.051 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29665513

Zainuddin AA, Mahdy ZA. The Islamic Perspectives of Gender-Related Issues in the Management of Patients With Disorders of Sex Development. *Arch Sex Behav*. 2017;46(2):353-360. doi:10.1007/s10508-016-0754-y Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618034443&from=export

Zhou Y, Furutani M, Athurupana R, Nakatsuka M. Relation Between Identity Disclosure to Family Members and Mental Health in Japanese Transgender People. *Acta medica Okayama*. 2021;75(5):611-623. doi:10.18926/AMO/62774 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L636627235&from=export

Zhu J, Chan YM. Adult Consequences of Self-Limited Delayed Puberty. *Pediatrics*. 2017;139(6)doi:10.1542/peds.2016-3177 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28562264

Excluded because Wrong Study Design or Publication Type

Fertility 2021 Barriers and breakthroughs 6-10th January 2021 Online. *Hum Fertil (Camb)*. 2021;24(1):46-69. doi:10.1080/14647273.2021.1872160 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33501879

Health Care for Transgender and Gender Diverse Individuals: ACOG Committee Opinion Summary, Number 823. *Obstet Gynecol*. 2021;137(3):554-555. doi:10.1097/AOG.0000000000004296 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33595249

American Psychological A. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol*. 2015;70(9):832-864. doi:10.1037/a0039906 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26653312

American Psychological Association. *APA Guidelines for Psychological Assessment and Evaluation*. Guidelines ATFoPAaE; 2020: 32 pages. Last Updated March 2020. Accessed June 1, 2023. Available at https://www.apa.org/about/policy/guidelines-psychological-assessment-evaluation.pdf

Anderson RA, Wallace WHB, Telfer EE. Ovarian tissue cryopreservation for fertility preservation: clinical and research perspectives. *Hum Reprod Open*. 2017;2017(1):hox001. doi:10.1093/hropen/hox001 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30895221

Ashley F. Homophobia, conversion therapy, and care models for trans youth: defending the gender-affirmative approach. *Journal of LGBT Youth*. 2019;17(4):361-383. doi:10.1080/19361653.2019.1665610 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/full/10.1080/19361653.2019.1665610

Beek TF, Cohen-Kettenis PT, Kreukels BP. Gender incongruence/gender dysphoria and its classification history. *Int Rev Psychiatry*. 2016;28(1):5-12. doi:10.3109/09540261.2015.1091293 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26782319

Benito A, Rodriguez de Fonseca F, Haro G. Sexual Differences in Addictions and Dual Disorders: Importance of Gender Perspective. *Brain Sci*. 2022;12(10)doi:10.3390/brainsci12101346 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36291280

Biggs M. The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence. *J Sex Marital Ther*. 2023;49(4):348-368. doi:10.1080/0092623X.2022.2121238 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/pdf/10.1080/0092623X.2022.2121238

Boekeloo BO. Will you ask? Will they tell you? Are you ready to hear and respond?: barriers to physician-adolescent discussion about sexuality. *JAMA Pediatr*. 2014;168(2):111-113. doi:10.1001/jamapediatrics.2013.4605 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24378601

Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. *Arch Dis Child*. 2018;103(7):631-636. doi:10.1136/archdischild-2018-314992 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29650510

Butler G, Wren B, Carmichael P. Puberty blocking in gender dysphoria: Suitable for all? *Arch Dis Child*. 2019;104(6):509-510. doi:10.1136/archdischild-2018-315984 Accessed September 15, 2023. Available at https://adc.bmj.com/content/104/6/509.long

Carswell JM, Roberts SA. Induction and Maintenance of Amenorrhea in Transmasculine and Nonbinary Adolescents. *Transgend Health*. 2017;2(1):195-201. doi:10.1089/trgh.2017.0021 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29142910

Center of Excellence for Transgender Health. *Guidelines for the Primary and Gender-affirming Care of Transgender and Gender Nonbinary People*. Center of Excellence for Transgender Health University of California San Francisco; 2016: 199 pages. Last Updated June 17, 2016. Accessed June 1, 2023. Available at https://transcare.ucsf.edu/sites/transcare.ucsf.edu/files/Transgender-PGACG-6-17-16.pdf

Chen D, Simons L. Ethical Considerations in Fertility Preservation for Transgender Youth: A Case Illustration. *Clinical practice in pediatric psychology*. 2018;6(1):93-100. doi:10.1037/cpp0000230 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29963344

Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. *Transl Androl Urol*. 2019;8(3):209-218. doi:10.21037/tau.2019.05.09 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31380227

Clayton A. Gender-Affirming Treatment of Gender Dysphoria in Youth: A Perfect Storm Environment for the Placebo Effect-The Implications for Research and Clinical Practice. *Arch Sex Behav*. 2023;52(2):483-494. doi:10.1007/s10508-022-02472-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36376741

Cohen A, Gomez-Lobo V. We Are all Responsible for Transgender Care. *J Clin Endocrinol Metab*. 2022;107(3):E1310-E1311. doi:10.1210/clinem/dgab723 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2017027682&from=export

Cohen-Kettenis PT, Pfafflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010;39(2):499-513. doi:10.1007/s10508-009-9562-y Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19838784

Conway AJ, Hamblin JC, Handelsman DJ. Hormone treatment of gender identity disorder in a cohort of children and adolescents. Comment. *Med J Aust*. 2012;197(5):273; author reply 274. doi:10.5694/mja12.10981 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22938117

Costa R, Carmichael P, Colizzi M. To treat or not to treat: puberty suppression in childhood-onset gender dysphoria. *Nat Rev Urol*. 2016;13(8):456-462. doi:10.1038/nrurol.2016.128 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27431339

d'Abrera JC, D'Angelo R, Halasz G, Prager S, Morris P. Informed consent and childhood gender dysphoria: emerging complexities in diagnosis and treatment. *Australas Psychiatry*. 2020;28(5):536-538. doi:10.1177/1039856220928863 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32469644

D'Angelo R. The complexity of childhood gender dysphoria. *Australas Psychiatry*. 2020;28(5):530-532. doi:10.1177/1039856220917076 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32469645

de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex*. 2012;59(3):301-320. doi:10.1080/00918369.2012.653300 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22455322

de Vries ALC. General Introduction. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:9-20:chap 1. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Summary and General Discussion. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:107-118:chap 8. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Challenges in timing puberty suppression for gender-Nonconforming adolescents. *Pediatrics*. 2020;146(4)doi:10.1542/peds.2020-015974 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2008345978&from=export

de Vries ALC, Richards C, Tishelman AC, et al. Bell v Tavistock and Portman NHS Foundation Trust [2020] EWHC 3274: Weighing current knowledge and uncertainties in decisions about gender-related treatment for transgender adolescents. *Int J Transgend Health*. 2021;22(3):217-224. doi:10.1080/26895269.2021.1904330 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34240066

Drescher J, Cohen-Kettenis PT, Reed GM. Gender incongruence of childhood in the ICD-11: controversies, proposal, and rationale. *Lancet Psychiatry*. 2016;3(3):297-304. doi:10.1016/S2215-0366(15)00586-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26946394

Dubin S, Lane M, Morrison S, et al. Medically assisted gender affirmation: when children and parents disagree. *J Med Ethics*. 2020;46(5):295-299. doi:10.1136/medethics-2019-105567 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31892617

Dyer C. Children are "highly unlikely" to be able to consent to taking puberty blockers, rules High Court. *BMJ*. 2020;371:m4699. doi:10.1136/bmj.m4699 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33262132

Edwards-Leeper L, Spack NP. Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center. *J Homosex*. 2012;59(3):321-336. doi:10.1080/00918369.2012.653302 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22455323

Ehrensaft D, Tishelman AC. Take the T out, put the T in: Gender-affirming hormones in youth. *Andrology*. 2021;9(6):1698-1706. doi:10.1111/andr.13055 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34048640

Transgender Health. Position statement. Endocrine Society and Pediatric Endocrine Society. December 16, 2020. Accessed June 1, 2023. Available at https://www.endocrine.org/advocacy/position-statements/transgender-health

Esteva de Antonio I, Asenjo Araque N, Hurtado Murillo F, et al. Position statement: Gender dysphoria in childhood and adolescence. Working Group on Gender Identity and Sexual Development of the

Spanish Society of Endocrinology and Nutrition (GIDSEEN). *Endocrinol Nutr*. 2015;62(8):380-383. doi:10.1016/j.endonu.2015.03.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25935352

Fisher AD, Ristori J, Bandini E, et al. Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. *J Endocrinol Invest*. 2014;37(7):675-687. doi:10.1007/s40618-014-0077-6 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24862877

Gardner IH, Safer JD. Progress on the road to better medical care for transgender patients. *Curr Opin Endocrinol Diabetes Obes*. 2013;20(6):553-558. doi:10.1097/01.med.0000436188.95351.4d Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24468757

Gava G, Seracchioli R, Meriggiola MC. Therapy with Antiandrogens in Gender Dysphoric Natal Males. In: Simoni M, Huhtaniemi IT, eds. *Endocrinology*. Springer Cham; 2017:1199-1209:chap 42. Accessed September 15, 2023. Available at https://link.springer.com/referenceworkentry/10.1007/978-3-319-44441-3_42

Giordano S, Holm S. Is puberty delaying treatment 'experimental treatment'? *Int J Transgend Health*. 2020;21(2):113-121. doi:10.1080/26895269.2020.1747768 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33015663

Graham P. Transgender children and young people: how the evidence can point the way forward. *BJPsych Bull*. 2023;47(2):98-104. doi:10.1192/bjb.2022.3 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35177147

Hoffman ND, Alderman EM. Improving Our Understanding of Medical Decision-Making Competence in Puberty Suppression. *Pediatrics*. 2021;148(6)doi:10.1542/peds.2021-053451 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34850190

Human Rights Campaign. *Growing Up LGBT in America: HRC Youth Survey Report Key Findings*. Human Rights Campaign; 2017: 36 pages. Last Updated June 7, 2017. Accessed June 12, 2023. Available at https://assets2.hrc.org/files/assets/resources/Growing-Up-LGBT-in-America_Report.pdf

Hyde Z. Comment on: Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust*. 2012;197(5):273-274. doi:10.5694/mja12.10911 Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/10.5694/mja12.10911

Irwig MS. Which reference range should we use for transgender and gender diverse patients? *J Clin Endocrinol Metab*. 2021;106(3):e1479-e1480. doi:10.1210/clinem/dgaa671 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32948869

Jorgensen SCJ, Hunter PK, Regenstreif L, Sinai J, Malone WJ. Puberty blockers for gender dysphoric youth: A lack of sound science. *Jaccp: Journal of the American College of Clinical Pharmacy*. 2022;5(9):1005-1007. doi:10.1002/jac5.1691 Accessed June 28, 2023. Available at https://accpjournals.onlinelibrary.wiley.com/doi/pdfdirect/10.1002/jac5.1691?download=true

Kean AC, Saroufim R, Meininger E, Fuqua JS, Fortenberry JD. Cardiovascular Health of Youth During Gender-Affirming Testosterone Treatment: A Review. *J Adolesc Health*. 2021;69(6):896-904. doi:10.1016/j.jadohealth.2021.08.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34627656

Kelly F, Giordano S, Telfer MM, Pang KC. Parental consent and the treatment of transgender youth: the impact of Re Imogen. *Med J Aust*. 2022;216(5):219-221. doi:10.5694/mja2.51431 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35219281

Kern L, Edmonds P, Perrin EC, Stein MT. An 8-year-old Biological Female Who Identifies Herself as a Boy: Perspectives in Primary Care and from a Parent. *Journal of developmental and behavioral pediatrics : JDBP*. 2017;38:S9-S11. doi:10.1097/DBP.0000000000000057 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L619915671&from=export

Lopez X, Marinkovic M, Eimicke T, Rosenthal SM, Olshan JS. Statement on gender-affirmative approach to care from the pediatric endocrine society special interest group on transgender health. *Curr Opin Pediatr*. 2017;29(4):475-480. doi:10.1097/MOP.0000000000000516 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28562420

Malone W, D'Angelo R, Beck S, Mason J, Evans M. Puberty blockers for gender dysphoria: the science is far from settled. *The Lancet Child and Adolescent Health*. 2021;5(9):e33-e34. doi:10.1016/S2352-4642(21)00235-2 Accessed September 15, 2023. Available at https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00235-2/fulltext

Mason A, Crowe E, Haragan B, Smith S, Kyriakou A. Gender Dysphoria in Young People: A Model of Chronic Stress. *Horm Res Paediatr*. 2023;96(1):54-65. doi:10.1159/000520361 Accessed September 15, 2023. Available at https://karger.com/hrp/article-pdf/96/1/54/3952495/000520361.pdf

Mehringer J, Dowshen NL. Sexual and reproductive health considerations among transgender and gender-expansive youth. *Curr Probl Pediatr Adolesc Health Care*. 2019;49(9):100684. doi:10.1016/j.cppeds.2019.100684 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31735693

Moral-Martos A, Guerrero-Fernandez J, Gomez-Balaguer M, et al. Clinical practice guidelines for transsexual, transgender and gender diverse minors. *An Pediatr (Engl Ed)*. 2022;96(4):349 e341-349 e311. doi:10.1016/j.anpede.2022.02.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35534418

Moravek MB. Fertility preservation options for transgender and gender-nonconforming individuals. *Curr Opin Obstet Gynecol*. 2019;31(3):170-176. doi:10.1097/GCO.0000000000000537 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30870185

Moreno-Perez O, Esteva De Antonio I, Grupo de Identidad y Diferenciacion Sexual de la S. [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012;59(6):367-382. doi:10.1016/j.endonu.2012.02.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22542505

Nakatsuka M. [Puberty-delaying hormone therapy in adolescents with gender identity disorder]. *Seishin Shinkeigaku Zasshi*. 2013;115(3):316-322. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23691819

Oliphant J, Veale J, Macdonald J, et al. Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand. *N Z Med J*. 2018;131(1487):86-96. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30543615

Olson-Kennedy J, Chan YM, Rosenthal S, et al. Creating the Trans Youth Research Network: A Collaborative Research Endeavor. *Transgender Health*. 2019;4(1):304-312. doi:10.1089/trgh.2019.0024 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/pdf/10.1089/trgh.2019.0024?download=true

Özel F, Indremo M, Karamanis G, et al. Exploring gender dysphoria and related outcomes in a prospective cohort study: Protocol for the Swedish Gender Dysphoria Study (SKDS). *BMJ Open*. 2023;13(4):e066571. doi:10.1136/bmjopen-2022-066571 Accessed September 15, 2023. Available at https://bmjopen.bmj.com/content/bmjopen/13/4/e066571.full.pdf

Pang JH, Safer JD. A Beginning in the Investigation of the Metabolic Consequences of Transgender Hormone Treatment on Young People. *J Clin Endocrinol Metab*. 2020;105(3)doi:10.1210/clinem/dgz249 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31803926

Pang KC, Pace CC, Tollit MA, Telfer MM. Everyone agrees transgender children require more science. *Med J Aust*. 2019;211(3):142-142.e141. doi:10.5694/mja2.50237 Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/10.5694/mja2.50237

Pang KC, Peri AJS, Chung HE, et al. Rates of Fertility Preservation Use Among Transgender Adolescents. *JAMA Pediatr*. 2020;174(9):890-891. doi:10.1001/jamapediatrics.2020.0264 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32282014

Paré F. *Outlawing Trans Reparative Therapy*. Thesis. McGill University; 2019. Accessed June 1, 2023. Available at https://escholarship.mcgill.ca/downloads

Position Statement on Genital Surgery in Individuals with Differences of Sex Development (DSD)/Intersex Traits. Position statement. Pediatric Endocrine Society. October 20, 2020. Accessed June 1, 2023. Available at https://pedsendo.org/clinical-resource/position-statement-on-genital-surgery-in-individuals-with-differences-of-sex-development-dsd-intersex-traits/

Pemde HK, Bansal U, Bhattacharya P, et al. Adolescent Health Academy Statement on the Care of Transgender Children, Adolescents, and Youth. *Indian Pediatr*. 2023, ((Pemde H.K.) Department of Pediatrics, Lady Hardinge Medical College, New Delhi, India(Bansal U.) Uttar Pradesh. Correspondence to: Dr Utkarsh Bansal, Professor and Head, Department of Pediatrics, Hind Institute of Medical Sciences, Uttar Pradesh, India(B)Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37179471

Pepper MS. Gender and sexual diversity--changing paradigms in an ever-changing world. *S Afr Med J*. 2015;105(9):746-747. doi:10.7196/SAMJnew.8169 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26428972

Playdon Z. Narrative Matters: A confusion of tongues - trans/historical voices. *Child Adolesc Ment Health*. 2018;23(2):134-135. doi:10.1111/camh.12272 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32677330

Pradhan S, Gomez-Lobo V. Hormonal Contraceptives, Intrauterine Devices, Gonadotropin-releasing Hormone Analogues and Testosterone: Menstrual Suppression in Special Adolescent Populations. *J Pediatr Adolesc Gynecol*. 2019;32(5S):S23-S29. doi:10.1016/j.jpag.2019.04.007 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30980941

Quinn GP, Sampson A, Campo-Englestein L. Familial Discordance Regarding Fertility Preservation for a Transgender Teen: An Ethical Case Study. *The Journal of clinical ethics*. 2018;29(4):261-265. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L625778774&from=export

Radix A, Davis AM. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons. *JAMA*. 2017;318(15):1491-1492. doi:10.1001/jama.2017.13540 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28903155

Reardon S. Transgender youth study kicks off. *Nature*. 2016;531((Reardon S.)):560. doi:10.1038/531560a Accessed September 15, 2023. Available at https://www.nature.com/articles/531560a.pdf

Ristori J, Steensma TD. Gender dysphoria in childhood. *Int Rev Psychiatry*. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26754056

Schardein JN, Hotaling JM. The onset of puberty represents a vulnerable time in the lives of adolescents with gender incongruence. *Fertil Steril*. 2022;118(5):946-947. doi:10.1016/j.fertnstert.2022.09.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36192233

Schmidt L, Levine R. Psychological Outcomes and Reproductive Issues Among Gender Dysphoric Individuals. *Endocrinol Metab Clin North Am*. 2015;44(4):773-785. doi:10.1016/j.ecl.2015.08.001 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26568492

Schwartz AR, Russell K, Gray BA. Approaches to Vaginal Bleeding and Contraceptive Counseling in Transgender and Gender Nonbinary Patients. *Obstet Gynecol*. 2019;134(1):81-90. doi:10.1097/AOG.0000000000003308 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31188325

Skordis N, Butler G, de Vries MC, Main K, Hannema SE. ESPE and PES International Survey of Centers and Clinicians Delivering Specialist Care for Children and Adolescents with Gender Dysphoria. *Horm Res Paediatr*. 2018;90(5):326-331. doi:10.1159/000496115 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30695784

Smith KP, Madison CM, Milne NM. Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. *Pharmacotherapy*. 2014;34(12):1282-1297. doi:10.1002/phar.1487 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25220381

Steensma TD, Kreukels BP, de Vries AL, Cohen-Kettenis PT. Gender identity development in adolescence. *Horm Behav*. 2013;64(2):288-297. doi:10.1016/j.yhbeh.2013.02.020 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23998673

Stevenson MO, Tangpricha V. Osteoporosis and Bone Health in Transgender Persons. *Endocrinol Metab Clin North Am*. 2019;48(2):421-427. doi:10.1016/j.ecl.2019.02.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31027549

Substance Abuse and Mental Health Services Administration (SAMHSA). *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*. SMA15-4928. Substance Abuse and Mental Health Services Administration (SAMHSA); 2015: 76 pages. Last Updated October 20, 2015. Accessed June 1, 2023. Available at https://store.samhsa.gov/product/Ending-Conversion-Therapy-Supporting-and-Affirming-LGBTQ-Youth/SMA15-4928

Taslim N, Canales AD, Alshehab SMT. Gender Dysphoria: A Medical and Ethical Perplexity as Distinct from Reality and the Rational Approach for Muslim Young People. *Psychiatr Danub*. 2021;33(4):475-484. doi:10.24869/psyd.2021.475 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34928894

Taylor J, Vullikanti M, Nelamangala SL, Boguszewski KE, Marshall MF. Sexual & reproductive health information on minor consent forms for pubertal suppression and gender affirming hormones. *Frontiers in reproductive health*. 2023;5(9918230899006676):1071212. doi:10.3389/frph.2023.1071212 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37152482

Telfer MM, Tollit MA, Pace CC, Pang KC. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust*. 2018;209(3):132-136. doi:10.5694/mja17.01044 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29902964

The Lancet. Gender-affirming care needed for transgender children. *Lancet*. 2018;391(10140):2576. doi:10.1016/S0140-6736(18)31429-6 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30070208

Tishelman AC, Kaufman R, Edwards-Leeper L, Mandel FH, Shumer DE, Spack NP. Serving Transgender Youth: Challenges, Dilemmas and Clinical Examples. *Prof Psychol Res Pr*. 2015;46(1):37-45. doi:10.1037/a0037490 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26807001

Turban JL, Ehrensaft D. Research Review: Gender identity in youth: treatment paradigms and controversies. *Journal of child psychology and psychiatry, and allied disciplines*. 2018;59(12):1228-1243. doi:10.1111/jcpp.12833 Accessed September 15, 2023. Available at https://acamh.onlinelibrary.wiley.com/doi/10.1111/jcpp.12833

United Nations Human Rights Council. *Practices of so-called "conversion therapy": Report of the Independent Expert on protection against violence and discrimination based on sexual orientation and gender identity*. A/HRC/44/53. United Nations Independent Expert on Sexual Orientation and Gender Identity (IESOGI); 2020: 22 pages. Last Updated May 1, 2020. Accessed June 1, 2023. Available at https://www.ohchr.org/en/documents/thematic-reports/ahrc4453-practices-so-called-conversion-therapy-report-independent

Warling A, Keuroghlian AS. Clinician-Level Implications of Bans on Gender-Affirming Medical Care for Youth in the US. *JAMA Pediatr*. 2022;176(10):963-964. doi:10.1001/jamapediatrics.2022.2771 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35939318

Wilkes J. Practice guidelines: Gender-dysphoric/gender-incongruent persons: Treatment recommendations from the Endocrine Society. *Am Fam Physician*. 2018;97(9):608-609. Accessed June 28, 2023. Available at https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2018/0501/p608.pdf

Williams DR, Chaves E, Greenwood NE, et al. Care of Gender Diverse Youth with Obesity. *Current Obesity Reports*. 2022;11(4):215-226. doi:10.1007/s13679-022-00480-2 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s13679-022-00480-2

Yager J, Brooks KM, Brothers J, et al. Pharmacokinetics of Emtricitabine/Tenofovir Disoproxil Fumarate Among Transgender Adolescents and Young Adults Without HIV Receiving Gender Affirming Hormones. *AIDS Res Hum Retroviruses*. 2022;38(11):840-846. doi:10.1089/AID.2022.0043 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35943868

Excluded because No Intervention of Interest

Anaya VK. A transgender adolescent with chronic pain, depression, and PTSD. *Current Psychiatry*. 2018;17(12):e1-e3. Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L625666621&from=export

Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018;141(5)doi:10.1542/peds.2017-3845 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29661941

Berrahou IK, Grimes A, Autry AM, Hawkins M. Management of Menstruation in Transgender and Gender Nonbinary Adolescents. *Clin Obstet Gynecol*. 2022;65(4):753-767. doi:10.1097/GRF.0000000000000710 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35467570

Chemas-Velez MM, Bastidas D, Jimenez Fandiño LH. Novel Use of Feminization Laryngoplasty. *J Voice*. 2023;37(2):302.e313-302.e315. doi:10.1016/j.jvoice.2020.12.048 Accessed September 15, 2023. Available at https://www.jvoice.org/article/S0892-1997(21)00013-8/fulltext

Clark TC, Lucassen MF, Bullen P, et al. The health and well-being of transgender high school students: results from the New Zealand adolescent health survey (Youth'12). *J Adolesc Health*. 2014;55(1):93-99. doi:10.1016/j.jadohealth.2013.11.008 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24438852

Conron KJ, Landers SJ, Reisner SL, Sell RL. Sex and gender in the US health surveillance system: a call to action. *Am J Public Health*. 2014;104(6):970-976. doi:10.2105/AJPH.2013.301831 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24825193

Cooney M, Kaufman M, Birken C, Dettmer E, Toulany A. Impact of Adolescent Gender Dysphoria on Treatment Uptake in an Obesity Management Program. *J Pediatr*. 2016;176:207-209. doi:10.1016/j.jpeds.2016.05.028 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27283460

de Vries AL, Kreukels BP, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res*. 2011;186(2-3):414-418.

doi:10.1016/j.psychres.2010.07.033 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20801524

de Vries ALC. Comparing adult and adolescent transsexuals: An MMPI-2 and MMPI-A study. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:37-50:chap 3. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

Erisen Karaca S, Eröz R, Arslanoglu İ. A Rare Cause of Female Gender Dysphoria: Report of Three Cases with Low Percentage of Turner Mosaicism. *Düzce Tıp Fakültesi Dergisi*. 2020;22(3):226-229. doi:10.18678/dtfd.780970 Accessed June 28, 2023. Available at https://dergipark.org.tr/en/download/article-file/1242185

Fisher AD, Ristori J, Castellini G, et al. Psychological characteristics of Italian gender dysphoric adolescents: a case-control study. *J Endocrinol Invest*. 2017;40(9):953-965. doi:10.1007/s40618-017-0647-5 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28357782

Gower AL, Rider GN, Coleman E, Brown C, McMorris BJ, Eisenberg ME. Perceived Gender Presentation Among Transgender and Gender Diverse Youth: Approaches to Analysis and Associations with Bullying Victimization and Emotional Distress. *LGBT Health*. 2018;5(5):312-319. doi:10.1089/lgbt.2017.0176 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29920146

Grimstad FW, Knoll MM, Jacobson JD. Oxandrolone Use in Trans-Masculine Youth Appears to Increase Adult Height: Preliminary Evidence. *LGBT Health*. 2021;8(4):300-306. doi:10.1089/lgbt.2020.0355 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33819432

Grossman AH, Park JY, Frank JA, Russell ST. Parental Responses to Transgender and Gender Nonconforming Youth: Associations with Parent Support, Parental Abuse, and Youths' Psychological Adjustment. *J Homosex*. 2021;68(8):1260-1277. doi:10.1080/00918369.2019.1696103 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31774377

Guss CE, Williams DN, Reisner SL, Austin SB, Katz-Wise SL. Disordered Weight Management Behaviors, Nonprescription Steroid Use, and Weight Perception in Transgender Youth. *J Adolesc Health*. 2017;60(1):17-22. doi:10.1016/j.jadohealth.2016.08.027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28029539

Hagenas I, Jorgensen N, Rechnitzer C, et al. Clinical and biochemical correlates of successful semen collection for cryopreservation from 12-18-year-old patients: a single-center study of 86 adolescents. *Hum Reprod*. 2010;25(8):2031-2038. doi:10.1093/humrep/deq147 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20570975

Hardon A, Idrus NI, Hymans TD. Chemical sexualities: The use of pharmaceutical and cosmetic products by youth in South Sulawesi, Indonesia. *Reproductive Health Matters*. 2013;21(41):214-224. doi:10.1016/S0968-8080(13)41709-3 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/pdf/10.1016/S0968-8080%2813%2941709-3

Havnes IA, Muller AE. Nonprescribed androgen use among women and trans men. *Current Opinion in Endocrinology, Diabetes and Obesity*. 2021;28(6):595-603. doi:10.1097/MED.0000000000000680 Accessed September 15, 2023. Available at https://www.ingentaconnect.com/content/wk/coedo/2021/00000028/00000006/art00008

Hiort O, Marshall L, Birnbaum W, et al. Pubertal Development in 17Beta-Hydroxysteroid Dehydrogenase Type 3 Deficiencyâ. *Horm Res Paediatr*. 2017;87(5):354-358. doi:10.1159/000453613 Accessed September 15, 2023. Available at https://karger.com/hrp/article-abstract/87/5/354/162629/Pubertal-Development-in-17Beta-Hydroxysteroid?redirectedFrom=fulltext

Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: Demographics and associated difficulties. *Clin Child Psychol Psychiatry*. 2016;21(1):108-118. doi:10.1177/1359104514558431 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25431051

Janssen A, Erickson-Schroth L. A new generation of gender: learning patience from our gender nonconforming patients. *J Am Acad Child Adolesc Psychiatry*. 2013;52(10):995-997. doi:10.1016/j.jaac.2013.07.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24074463

Kaltiala-Heino R, Sumia M, Tyolajarvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health*. 2015;9:9. doi:10.1186/s13034-015-0042-y Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25873995

Kaltiala-Heino R, Työläjärvi M, Lindberg N. Sexual experiences of clinically referred adolescents with features of gender dysphoria. *Clin Child Psychol Psychiatry*. 2019;24(2):365-378. doi:10.1177/1359104519827069 Accessed September 15, 2023. Available at https://journals.sagepub.com/doi/10.1177/1359104519827069?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Katz-Wise SL, Budge SL, Fugate E, et al. Transactional Pathways of Transgender Identity Development in Transgender and Gender Nonconforming Youth and Caregivers from the Trans Youth Family Study. *Int J Transgend*. 2017;18(3):243-263. doi:10.1080/15532739.2017.1304312 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29527139

Kwiatkowska A, Kułak K, Wertel I. Gender Dysphoria Disrupting the Course of Treatment of a Recurrent Juvenile Granulosa Cell Tumor in an Adolescent Female: A Case Report. *Case Rep Oncol*. 2020;13(3):1330-1336. doi:10.1159/000510810 Accessed September 15, 2023. Available at https://karger.com/cro/article-pdf/13/3/1330/2522856/000510810.pdf

Maffei SR, Dean A. Strange Behavior in a Transgender Teenager. *Pediatr Rev*. 2021;42(2):100-102. doi:10.1542/pir.2020-001982 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33526577

McConnell EA, Birkett MA, Mustanski B. Typologies of Social Support and Associations with Mental Health Outcomes Among LGBT Youth. *LGBT Health*. 2015;2(1):55-61. doi:10.1089/lgbt.2014.0051 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26790019

Mishra R, Kar SK, Goyal P, Kumar D, Sinha UK, Gupta SK. Gender identity disorder in an adolescent boy: An attribution of adverse childhood experiences! *Journal of Indian Association for Child and Adolescent Mental Health*. 2016;12(4):336-344. Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L612814716&from=export

Morandini JS, Kelly A, de Graaf NM, Carmichael P, Dar-Nimrod I. Shifts in demographics and mental health co-morbidities among gender dysphoric youth referred to a specialist gender dysphoria service. *Clin Child Psychol Psychiatry*. 2022;27(2):480-491. doi:10.1177/13591045211046813 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34689580

Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental Health of Transgender Children Who Are Supported in Their Identities. *Pediatrics*. 2016;137(3):e20153223. doi:10.1542/peds.2015-3223 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26921285

Olson KR, Key AC, Eaton NR. Gender cognition in transgender children. *Psychol Sci*. 2015;26(4):467-474. doi:10.1177/0956797614568156 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25749700

Pakpoor J, Wotton CJ, Schmierer K, Giovannoni G, Goldacre MJ. Gender identity disorders and multiple sclerosis risk: A national record-linkage study. *Mult Scler*. 2016;22(13):1759-1762. doi:10.1177/1352458515627205 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26857201

Pariseau EM, Chevalier L, Long KA, Clapham R, Edwards-Leeper L, Tishelman AC. The relationship between family acceptance-rejection and transgender youth psychosocial functioning. *Clinical Practice in Pediatric Psychology*. 2019;7(3):267-277. doi:10.1037/cpp0000291 Accessed September 15, 2023. Available at

Puri M, Hall EG, Erisman M, Vwich Y. Acting strange after trying to 'get numb'. *Current Psychiatry*. 2014;13(11):50-54. Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L601128088&from=export

Ryan C, Russell ST, Huebner D, Diaz R, Sanchez J. Family acceptance in adolescence and the health of LGBT young adults. *J Child Adolesc Psychiatr Nurs*. 2010;23(4):205-213. doi:10.1111/j.1744-6171.2010.00246.x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21073595

Saleem F, Rizvi SW. Transgender Associations and Possible Etiology: A Literature Review. *Cureus*. 2017;9(12):e1984. doi:10.7759/cureus.1984 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29503778

Shields JP, Cohen R, Glassman JR, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013;52(2):248-250. doi:10.1016/j.jadohealth.2012.06.016 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23332492

Sorbara JC, Ngo HL, Palmert MR. Factors associated with age of presentation to gender-affirming medical care. *Pediatrics*. 2021;147(4)doi:10.1542/peds.2020-026674 Accessed September 15, 2023. Available at

https://www.embase.com/search/results?subaction=viewrecord&id=L2011883932&from=export

Steensma TD, Cohen-Kettenis PT. More than two developmental pathways in children with gender dysphoria? *J Am Acad Child Adolesc Psychiatry*. 2015;54(2):147-148. doi:10.1016/j.jaac.2014.10.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25617255

Sutherland N, Espinel W, Grotzke M, Colonna S. Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. *Journal of genetic counseling*. 2020;29(4):625-633. doi:10.1002/jgc4.1278 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L631570158&from=export

Tack LJW, Craen M, Lapauw B, et al. Proandrogenic and Antiandrogenic Progestins in Transgender Youth: Differential Effects on Body Composition and Bone Metabolism. *J Clin Endocrinol Metab*. 2018;103(6):2147-2156. doi:10.1210/jc.2017-02316 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29672753

Turban JL, Dolotina B, King D, Keuroghlian AS. Sex Assigned at Birth Ratio Among Transgender and Gender Diverse Adolescents in the United States. *Pediatrics*. 2022;150(3)doi:10.1542/peds.2022-056567 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35918512

VanderLaan DP, Postema L, Wood H, et al. Do children with gender dysphoria have intense/obsessional interests? *J Sex Res*. 2015;52(2):213-219. doi:10.1080/00224499.2013.860073 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24558954

Vinay B, Krishna Prasad M, Kumar S, Bharath S. Transsexualism in the Indian context. *Journal of Indian Association for Child and Adolescent Mental Health*. 2010;6(2):44-46. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L362913526&from=export

Weinhardt LS, Stevens P, Xie H, et al. Transgender and Gender Nonconforming Youths' Public Facilities Use and Psychological Well-Being: A Mixed-Method Study. *Transgend Health*. 2017;2(1):140-150. doi:10.1089/trgh.2017.0020 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29159308

Zucker KJ, Bradley SJ, Owen-Anderson A, et al. Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *J Sex Marital Ther*. 2012;38(2):151-189. doi:10.1080/0092623X.2011.611219 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22390530

Excluded because Article Withdrawn or Outdated

Committee Opinion No. 685: Care for Transgender Adolescents. *Obstet Gynecol*. 2017;129(1):e11-e16. doi:10.1097/AOG.0000000000001861 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28002311

Coleman E, Bockting W, Botzer M, et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. *International Journal of Transgenderism*. 2012;13(4):165-232. doi:10.1080/15532739.2011.700873 Accessed September 15, 2023. Available at https://doi.org/10.1080/15532739.2011.700873

APPENDIX I.D: CLINICAL PRACTICE GUIDELINE DATA EXTRACTION TABLES

Return to TOC

Table I.D.1. Overview of development methodology and level of evidence (LOE) for recommendations by guidelines or position statements addressing gender-affirming hormonal therapies (GAHT)

Guideline/Statement Name	Organization; publication year	Overview of Development Methods and LOE Rating
Standards of Care for the Health of Transgender and Gender Diverse People, Version 8[39]	World Professional Association for Transgender Health (WPATH); 2022	***Guideline Development Methodology:*** Formal recommendations were informed by a systematic review of the evidence performed by expert methodologists and expert opinion. Methodologists evaluated the risk of bias of included evidence and graded the evidence using the GRADE system. A multidisciplinary guideline team of experts who completed COI statements and were not compensated for their service defined guideline questions, drafted chapters, and voted on recommendations using Delphi-consensus (requiring that ≥ 75% of voters agreed). Guideline development was funded by a grant by the Tawani Foundation and WPATH. ***LOE Ratings:*** Formal recommendations were not assigned a specific LOE. The recommendations strengths (strong or weak) correlate with the LOE. ***Strength of recommendations:*** • Strong, worded as "we recommend": Formal recommendations supported by (1) high evidence quality; (2) high certainty of effectiveness; (3) comparatively few risks; and (4) high acceptance by the community. • Weak, worded as "we suggest": Formal recommendations supported or limited by (1) evidence with weaknesses; (2) doubt about effectiveness in regular care; (3) requirement for careful balance of the risks vs benefits; and (4) acceptance by the community varies.
Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons[42]	Endocrine Society (ES); 2017	***Guideline Development Methodology:*** The guideline was developed by experts, a medical writer, and a methodologist. Guideline developer's COI were declared. Guideline development was funded by the ES. Two systematic reviews were commissioned for the guideline; these reviews addressed the effects of sex steroid hormonal therapy on (1) cardiovascular and lipid outcomes or (2) bone health in transgender people. Recommendations were based on "…the best available research evidence" (page 3872) and were assigned strength of recommendation and quality of evidence using the GRADE approach.[408] ***LOE Ratings:*** Very-low quality: primarily based one unsystematic observations or indirect evidence; low quality: evidence from flawed RCTs or observational studies, or indirect evidence; moderate quality: RCT-level evidence with limitations or strong observational study evidence lacking bias; high quality: evidence from good-quality RCTs or very strong observational studies lacking bias.[409] ***Strength of recommendations:*** • Strong, worded as "we recommend": Most patients will receive greater benefits than harms by following this recommendation. • Weak, worded as "we suggest": Determine whether to follow this recommendation by considering each patient's unique values and circumstances. • Other, "Ungraded Good Practice Statement": These are basic principles; evidence for the statement was either lacking, or outside the scope of the guideline.
Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction[41]	European Society for Sexual Medicine Position Statement (ESSM); 2020	***Guideline Development Methodology:*** An interdisciplinary team of 7 experts with clinical or research experience on transgender patient healthcare (ie, including areas of endocrinology, psychology, psychiatry, surgery, sociology) developed consensus-based recommendations informed by a systematic literature review. COI were disclosed, and the guideline was developed with funding from the European Society of Sexual Medicine. Experts voted on "General Statements" pertaining to transgender healthcare, revising statements until they achieved 100% consensus. It was described that "The available literature for a direct recommendation was limited, and most of the literature was used as background or indirect evidence" (page 572). ***LOE Ratings:*** No formal LOE ratings provided for each recommendation. Recommendations are consensus-based with inference from the literature. ***Strength of recommendations:*** No rating strength provided. Recommendation statements include "We advise…"
General Approaches to Medical Management of Menstrual Suppression[40]	The American College of Obstetricians and Gynecologists (ACOG); 2022	***Guideline Development Methodology:*** The guideline is consensus-based, informed by a systematic review of the literature using a hierarchy-of-evidence approach with an emphasis on systematic reviews, randomized controlled trials, and observational studies. No risk of bias assessment or LOE rating was performed. The committee of about 20 ACOG members including members with subspecialty expertise (eg, adolescents) reviewed compiled literature and voted on consensus statements informed by the literature, or based on expert opinion if evidence was limited. Included recommendation statements required at least 75% agreement among voting committee members. Committee members were required to disclose COI; no information about funding was provided in the guideline publication. ***LOE Ratings:*** No LOE ratings performed or provided for each recommendation. Recommendations are consensus-based with inference from the literature. ***Strength of recommendations:*** No rating strength provided.

Table abbreviations: ACOG, American College of Obstetricians and Gynecologists; COI, conflict of interest; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; LOE, level of evidence; WPATH, World Professional Association for Transgender Health.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
Guidelines	
Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (2022); World Professional Association for Transgender Health (WPATH)[39]	
• **Target population:** All persons with a gender identity differing from the identity typically associated with the gender assigned at birth. This includes transgender and gender-diverse persons, including but not limiting to the following: gender nonconforming, nonbinary, and identities or expressions not typically recognized by Western culture. • **Adolescents:** People who have reached puberty and who are < 18 years old (or age of majority). • **Children:** People who are pre-pubescent.	
Adolescents should meet ALL OF THE FOLLOWING criteria to receive gender-affirming medical treatments (rated together as strong): • "The adolescent meets the diagnostic criteria for gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care…" (page S48) • "The experience of gender diversity/incongruence is marked and sustained over time" (page S48) • "The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment" (page S48) • "The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed" (page S48) • "The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development" (page S48) • "The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated" (page S48) • "The adolescent had at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated" (page S48)[39]	**General Treatment Recommendation for all age groups:** • "We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people" (page S16).[39] (strong) **Hormonal therapy recommendations for children:** • Hormone or hormone-blocking treatments are not recommended before puberty (ie, before Tanner Stage 2) (non-graded). **Recommendations for when to begin hormonal therapies in eligible adolescents for pubertal suppression or CSHT:** • May begin pubertal hormonal suppression after reaching Tanner stage 2 (strong) ○ Use of GnRH analog for pubertal suppression is only considered for Tanner stage 1 (pre-pubescent youth) if the youth is also experiencing constitutional delay of growth. Youth with constitutional delay of growth eligible for hormonal therapy may start CSHT with GnRH analog therapy. (non-graded) • GnRH analog is suggested if the adolescent is developed beyond Tanner stage 3, and there is a desire to delay sex hormone replacement (weak). • May begin sex hormone replacement therapy (CSHT) if ≥ Tanner stage 2; parental involvement is recommended unless it is considered detrimental or unnecessary (strong) **The following hormonal treatments are suggested or recommended as part of pubertal suppression or CSHT for eligible TBNB people:** • GnRH analogs recommended for adolescents when puberty suppression is indicated (strong)

[a] *Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.*

[b] *Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).*

[c] *Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.*

[d] *Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
Recommendation for assessment of adolescents for hormonal therapies (strong): "We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiations, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated through the course of treatment until the transition is made to adult care" (page S56).[39]	○ Progestins (oral or injectable depot) are an alternative for puberty suppression in youth when GnRH analogs are not accessible (weak). There is a lack of information about the safety (for bone development) of treatment with GnRH analog *monotherapy* after age 14 (non-graded), which is potentially another reason to consider alternative pubertal suppression therapies. • Feminizing CSHT for people with testes: ○ 17-β-estradiol recommended for pubertal induction in adolescents with testes (non-graded) ○ Transdermal estrogen for adults/adolescents receiving GAET at higher risk for VTE (eg, age > 45 years or a history of VTE) (weak) ○ Testosterone-lowering therapies (cyproterone acetate, spironolactone, or GnRH analog) for adults/adolescents desiring sex hormone levels like cisgender women (strong) • Masculinizing CSHT for people with ovaries: ○ Testosterone-ester injection is often recommended by experts for pubertal induction in adolescents due to availability and history of use (non-graded) **The following hormonal therapies are NOT recommended as part of CSHT for eligible adults or adolescents:** • Ethinyl estradiol (strong) (17-β-estradiol is a preferred option due to lower thromboembolism risk [non-graded]) • Conjugated estrogen if estradiol is available (weak) • Progestins (other than cyproterone acetate) for feminizing treatment (eg, additional breast development) are not suggested for most adults/adolescents since there is a lack of evidence of benefits and a potential for harm. Evaluate response within 1 year if used. (non-graded) • Bicalutamide (an anti-androgen) or 5α-reductase inhibitors (except for treating alopecia associated with high dihydrotestosterone levels) are not recommended for "routine use" page S124 (non-graded) **Menstrual cycle suppression for eligible adolescents:** • Menstrual suppression agents (progestogens or GnRH analogs) are recommended for people with a uterus not receiving testosterone, or in the case of breakthrough bleeding with testosterone therapy alone. Menstrual suppression may reduce menstruation-related gender dysphoria (strong). ○ Progestins, or GnRH analogs in youth meeting criteria for puberty suppression, are options for primary or adjunctive menstrual suppression to testosterone (non-graded) **Recommendations for continuation of hormonal therapies for eligible TGNB people:** • Due to potential adverse effects on bone health, the duration of GnRH analog monotherapy in adolescents should be decided based on various clinical factors (eg, bone mass, bone age, pubertal stage) and psychosocial factors (eg, maturity, and development relative to peers). (non-graded)

[a] *Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.*

[b] *Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).*

[c] *Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.*

[d] *Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
	• Generally, GnRH analogs may be continued in adolescents with ovaries who started them until testosterone levels are sufficient to suppress estrogen (non-graded). For adolescents with testes, GnRH analogs (or an alternative testosterone-blocking therapy) should be continued until gonadectomy (if indicated). (non-graded) • Testosterone-lowing therapies (including GnRH analogs or other agents) are usually continued in people with testes until gonadectomy, if desired (non-graded) • After gonadectomy, it is important to continue sex hormone replacement therapy for bone and mental health (non-graded) • Initiate and continue CSHT for eligible adolescents/adults "…due to demonstrated improvement in psychosocial functioning and quality of life," page S126[39] (strong) • Continue hormonal therapy for eligible adolescents/adults if "…mental health deteriorates and assess the reason for the deterioration, unless contraindicated," page S126[39] (strong)
Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons (2017); Endocrine Society (ES)[42]	
Target population: Individuals with gender dysphoria (ie, meeting the DSM-5 definition) or gender incongruence (people identifying as a gender or with gender expression different from the natal gender)	

Criteria for Adolescents to Receive GnRH analog treatment (non-graded; copied by ES from 2017 WPATH SOC):
• "A qualified MHP has confirmed that:"
  ○ "the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed)"
  ○ "gender dysphoria worsened with the onset of puberty,"
  ○ "any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such as that the adolescent's situation and functioning are stable enough to start treatment,"
  ○ "the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment"
• "And the adolescent:"
	Hormonal therapy recommendations for children:
	• Hormone or hormone-blocking treatments for pubertal suppression for gender-affirming treatment are not recommended before puberty (Strong; low LOE).
	Recommendations for when to begin hormonal therapies in eligible adolescents:
	• Pubertal suppression is suggested as the initial treatment (Weak, Low LOE)
	• Suggest beginning pubertal suppression after exhibiting initial signs of puberty (ie, Tanner stages G2/B2) (Weak, Low LOE)
	  ○ Authors considered early puberty (Tanner stage 2) to be the optimal time to initiate pubertal suppression. Pubertal suppression can be initiated in later stages of puberty for menstrual suppression and prevention of facial hair growth. (non-graded)
	• Sex hormone replacement therapy (CSHT) may be initiated at a low dose and up titrated once the adolescent has capacity to give informed consent (as confirmed by a multidisciplinary care team); in most cases, capacity is reached by age 16 (Strong, Low LOE)
	• Sex hormone replacement therapy (CSHT) may be started before age 16 (although there is little data for starting earlier than 13.5-14 years) under compelling circumstances when managed by multidisciplinary care team (Strong, Very Low LOE)

[a] *Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.*

[b] *Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).*

[c] *Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.*

[d] *Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
○ "has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility," ○ "has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation), the parents and other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process" • "And a pediatric endocrinologist or other clinician experienced in pubertal assessment" ○ "agrees with the indication for GnRH analog treatment," ○ "has confirmed that puberty has started in the adolescent (Tanner stage ≥ G2/B2)," ○ "has confirmed that there are no medical contraindications to GnRH analog treatment" (page 3878)[42] • **Criteria for Adolescents to Receive Sex Hormone Replacement (non-graded; copied by ES from 2017 WPATH SOC):** • "A qualified MHP has confirmed:" ○ "the persistence of gender dysphoria," ○ "any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment," ○ "the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) reversible treatment," • "And the adolescent: ○ "has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility), ○ "has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depend on applicable legislation) the parents and other caretakers or guardians	○ Specific criteria for "compelling cases" are not provided; potential examples listed for special cases are when there may be harm from delaying sex hormone therapy (eg, bone harm due to starting GnRH analogs at a very early age, or psychological harm from delayed growth relative to peers) **The following hormonal treatments are suggested or recommended for eligible adolescents:** • GnRH analogs are the recommended agents for pubertal suppression (Strong, Low LOE) • Long-acting GnRH analogs preferred to GnRH antagonists due to less evidence for use of antagonists use in adolescents (non-graded) • Oral or depot progestins, or an anti-androgen in transgender female patients, are alternatives if GnRH analogs are inaccessible (non-graded) • Suggested feminizing hormones include oral or transdermal 17-β-estradiol (non-graded) • Suggested masculinizing hormones include intramuscular or subcutaneous testosterone esters (non-graded) **Recommendations for continuation of hormonal therapies in eligible adolescents:** • Continue GnRH analogs after starting CSHT, until gonadectomy. Alternatively for transgender male patients, the GnRH analogs may be continued until reaching an adult testosterone dose; a progestin may be added for breakthrough menstrual bleeding. Transgender female patients wishing to stop GnRH analogs may consider starting an anti-androgen instead. (non-graded) • Adults/adolescents who undergo gonadectomy require chronic hormone replacement or surveillance to prevent adverse effects from sex hormone deficiency (non-graded)

[a] *Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.*

[b] *Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).*

[c] *Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.*

[d] *Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
have consented to the treatment and are involved in supporting the adolescent through the treatment process," • "And a pediatric endocrinologist or other clinicians experienced in pubertal induction:" ○ "agrees with the indication for sex hormone treatment," ○ "has confirmed that there are no medical contraindications to sex hormone treatment." (page 3878)[42]	
Assessment and Hormonal Management in Adolescent and Adult Trans People, with Attention for Sexual Function and Satisfaction (2020); European Society for Sexual Medicine[41]	
Target population: People with a gender identity differing from their natal sex; the term "trans" was used broadly to recognize diverse gender identities, including people identifying as female, male, nonbinary, agender or other.	
Hormone-therapy Related Assessment Statements for Gender Diverse Adolescents: • For pubertal adolescents: HCPs should "…inform and explore all nonmedical and medical options, including the effect that GAMIs [gender-affirming medical interventions] (puberty blockers, hormones as well as surgical) may have on sexuality and fertility and if indicated, facilitate GAMIs [gender-affirming medical interventions]" (page 573)[41] (formal consensus) ○ Supporting information (informal) about assessment criteria for pubertal adolescents used in effectiveness studies evaluating puberal suppression therapies (page 573)[41]: ▪ "(i) the adolescents show a persistent and long-lasting GIC [gender incongruence] that usually intensified or began around the start of puberty (and did not remit), ▪ (ii) the adolescents' co-occurring psychosocial difficulties should not interfere or hamper assessment or treatment, ▪ (iii) the adolescent understands the pros and cons of [gender-affirming medical intervention] and has sufficient capacity to give informed consent, ▪ (iv) the adolescent has sufficient family or other social support to pursue [gender-affirming medical intervention], and	**Hormonal therapy recommendations for children:** • No information was provided about pharmacologic treatment of children. However, recommendations for puberty suppression and CSHT were for "adolescents" specifically. **Recommendations for beginning hormone therapy in adolescents (formal consensus):** • Hormonal puberty suppression suggested after Tanner stage G2 when adolescents may give consent and after addressing other assessment criteria (ie, assessment of gender identity and managing other psychosocial challenges when possible) • Puberty induction with CSHT is advised for adolescents desiring masculinizing or feminizing therapy, respectively, once the individual can give informed consent **The following hormonal treatments are suggested or recommended for eligible adolescents or adults:** • GnRH analogs are options for adolescent pubertal suppression (informal information) • Pubertal induction with testosterone (with gradual dose up-titration) advised for interested trans adolescents AFAB when the adolescent can give informed consent (formal consensus) ○ Examples of suggested hormone treatment options for people AFAB (listed without regarded to age) (informal information): ▪ Progestins: oral lynestrenol or medroxyprogesterone; parenteral medroxyprogesterone

[a] Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.

[b] Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).

[c] Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.

[d] Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
▪ (v) the adolescent has actually experienced of the first physical puberal changes (Tanner stage G2) because blocking is not necessary before that time and the experience of puberty is deemed important for gender identity development."	▪ Testosterone: intramuscular testosterone esters or testosterone undecanoate; subcutaneous testosterone esters; transdermal androgen gel; oral testosterone undecanoate • Feminizing hormone therapy as pubertal induction with 17-β-estradiol (with gradual dose up-titration) advised for interested adolescents AMAB when the adolescent can give informed consent. Feminizing therapy with estrogens and/or anti-androgens is suggested without specifying a target age. (both formal consensus statements). ○ Examples of suggested hormonal treatment options for people AMAB (listed without regarded to age) (informal information): ▪ Estrogens: oral estradiol (17-β-estradiol valerate); intramuscular estradiol valerate or estradiol cypionate; or transferal estradiol patch or gel. Guideline authors consider oral or transdermal 17-β-estradiol to be the treatment of choice. ▪ Anti-androgens: spironolactone, cyproterone acetate ▪ GnRH analog: intramuscular or subcutaneous triptorelin **Menstrual suppression for AFAB (informal information):** • During later adolescent puberty, a progestin is usually used (inferred that this is in place of GnRH analogs due to potential AEs from GnRH analogs) • "If induction of amenorrhea is desired and does not occur with testosterone treatment alone, the addition of a pregestational agent or GnRH analog may be considered"[41] (page 577; provided without regard to age) **Continuation of therapy recommendations for eligible adolescents and/or adults (informal information):** • Therapies for menstrual suppression can be stopped after hysteron-oophorectomy • "If started, GnRH analogs are advised to be continued at least until the maintenance dosage of testosterone is reached and to be continued until gonadectomy" (page 576).[41] • For people AFAB, testosterone therapy is usually life-long • For people AMAB, estrogen should be continued after gonadectomy. There is a lack of consensus in the medical literature about whether estrogen should be stopped at ages matching postmenopausal ages in cisgender women.

[a] Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.

[b] Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).

[c] Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.

[d] Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.2. Guideline recommendations for use of gender-affirming hormonal or hormone-blocking therapy (GAHT) in TGNB youth

Eligibility or Assessment Criteria for Youth to Receive Gender-affirming Hormone or Hormone-Blocking Therapy (GAHT)[a,b] (Strength/LOE)[c]	Recommendations for Gender-Affirming Hormone or Hormone-blocking Therapy (GAHT)[a,d] in Youth (Strength/LOE)[c]
General Approaches to Medical Management of Menstrual Suppression (2022); The American College of Obstetricians and Gynecologists[40]	
Target population: All people desiring menstrual suppression, including a special section on transgender or gender-diverse people. Only recommendations for unique considerations for transgender people were extracted.	
Not addressed	**General menstrual suppression recommendation for transgender or gender diverse people, without specified age (formal consensus):** • "Transgender and gender-diverse individuals may benefit from menstrual suppression to decrease gender dysphoria associated with menses" (page 536)[41] **Agents recommended for menstrual suppression therapy that would not be used by cisgender women (formal consensus):** • Testosterone therapy as part of CSHT is an option for amenorrhea

[a] *Extracted information from guidelines is focused on eligibility criteria for children or adolescents to receive hormonal or hormone-blocking GAHT (left column) and information about initiation or cessation of GAHT, including preferences for particular GAHT (right column). Depending on the structure of the guideline, information about GAHT (right column) was extracted from the adolescent section or from a combined hormonal therapy section non-specific to age. If recommendations did not specify an age or were not from a text section on adolescents only, we indicated the recommendation may apply to either adolescents or adults.*

[b] *Although not an explicit eligibility criterion by all guidelines, youth should also not have a contraindication to receiving a given hormonal therapy. Refer to prescribing information for each treatment for contraindications. WPATH explicitly states that co-treatment with antiretroviral medications is not a contraindication to GAHT (strong recommendation). Additionally, WPATH recommends screening for conditions which may be worsened during GAHT therapy before treatment (for example, to assist with lowering the risk for adverse events).*

[c] *Guidelines used different approaches for rating recommendations or statements. 'Formal' recommendations include those assigned a ROB rating, LOE rating, or formed by consensus vote. In contrast, 'non-graded' or 'informal' statements were not formally evaluated to form official statements but were typically provided as supportive text elaborating on formal recommendations. Non-graded/informal information was extracted when it answered questions of adolescent eligibility, or which and when hormonal treatments are recommended.*

[d] *Refer to Appendix I.A for a list of medications belonging to each drug class. This report uses hormone terminology consistent with each guideline; in some cases, multiple words are used to refer to similar medications. For example, progestins are a synthetic subtype of progestogens.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; COI, conflict of interest; CSHT, cross-sex hormonal therapy; GAET, gender-affirming estrogen treatment; GAHT, gender-affirming hormonal therapy; GnRH, gonadotropin releasing hormone; HCPs, healthcare professionals; ICD, International Classification of Diseases; LOE, level of evidence; MHP, mental health professional; ROB, risk of bias; SOC, standard of care; TGNB, transgender, non-binary or gender diverse; VTE, venous thromboembolism.

Return to TOC

Table I.D.3. Overview of GAHT monitoring addressed by guidelines or position statements [a]

Guideline/Statement Name	Organization (publication year)	Hormonal Therapy Monitoring Addressed	Target Population(s) for Statement[b]
Standards of Care for the Health of Transgender and Gender Diverse People, Version 8[39]	World Professional Association for Transgender Health (WPATH); 2022	• Measurement of sex hormone levels during treatment • Monitoring for physical and laboratory adverse effects • Hematocrit (or hemoglobin) monitoring	• Everyone receiving sex hormone replacement • Everyone receiving sex hormone replacement • Everyone receiving testosterone replacement
Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons[42]	Endocrine Society (ES); 2017	• Monitoring parameters and monitoring frequency during pubertal suppression treatment (eg, BP, height, weight, hormonal levels, vitamin D level, bone density) • Monitoring parameters and monitoring frequency during sex hormone (ie, puberty induction) treatment (eg, BP, height, weight, hormone-specific laboratory parameters, bone density) • Monitoring for physical and laboratory adverse effects from sex hormones • Laboratory monitoring parameters for spironolactone	• Adolescents receiving puberty suppression therapy • Adolescents receiving puberty induction therapy • Everyone receiving sex hormone therapy • Everyone receiving spironolactone therapy
Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction[41]	European Society for Sexual Medicine (ESSM); 2020	• Measurement of sex hormone levels during treatment • Monitoring for desired effects of sex hormone therapies (ie, virilization with testosterone, feminization for estrogens and/or anti-androgen therapy) • Laboratory monitoring of hematocrit • Osteoporosis screening	• Everyone receiving sex hormone replacement • Everyone receiving sex hormone replacement • Everyone receiving testosterone replacement • People AFAB who stop testosterone therapy and have other risk factors for bone loss
General Approaches to Medical Management of Menstrual Suppression[40]	The American College of Obstetricians and Gynecologists (ACOG); 2022	None specific to gender diverse people	Not applicable

[a] *Extracted information is very general, with a focus on the nature of hormone/hormone-blocking therapy monitoring recommendations. Refer to guidelines for details about the 'how' and 'when' of monitoring recommendations.*

[b] *Statements in the right column are matched for the type of monitoring addressed in same row of the left-adjacent column. For example, measuring sex hormone levels is recommended by WPATH for everyone receiving puberty suppression and/or sex hormone therapy replacement.*

Table abbreviations: AFAB, assigned female at birth; BP, blood pressure.

Return to TOC

APPENDIX I.E: SYSTEMATIC REVIEW DATA EXTRACTION TABLES

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)[43]**	
Baker (2021)[46] **Type**: Systematic review, narrative synthesis **Databases**: PubMed, Embase, PsycINFO **Search dates**: Through October 2018 through June 10, 2020	1. Yes	**Purpose well-specified?** Population, intervention, comparators, and outcomes were well-specified.
	2. Yes	***A priori* protocol?** Protocol published on PROSPERO (CRD42018115379)
	3. No	**Study designs justified?** Case reports were excluded without justification.
	4. No	**Comprehensive search strategy?** Authors searched 3 bibliographic databases and gray-literature sources without publication and language restrictions. They also searched reference lists of relevant studies. They did not describe consulting with experts or searching trial registries. They did not publish search strategies or terms in either the publication or protocol.
	5. Yes	**Performed study selection in duplicate?** Duplicate screening was described.
	6. Yes	**Performed data extraction in duplicate?** ROB assessment of primary studies was conducted in duplicate; data collection was conducted by a single reviewer with a second reviewer checking accuracy.
	7. No	**List of excluded studies?** No list of excluded studies was provided.
	8. Yes	**Detailed description of included studies?** Authors described populations (with key details), interventions and comparators (with key details), outcomes, research designs, settings, and timeframe for follow-up.
	9. Yes	**Assessed study-level ROB?** Authors used the revised Cochrane risk-of-bias tool for RCTs and ROBINS-I for NRSIs.
	10. No	**Described funding sources for primary sources?** No funding sources were described.
	11. N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12. Yes	**Impact of ROB on results assessed?** Authors assessed the impact of primary-study ROB on their findings.
	13. Yes	**Impact of ROB on results discussed?** Authors discussed the impact of primary-study ROB on their findings.
	14. N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15. N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16. Yes	**Potential review author conflicts of interest addressed?** Authors stated that the work was funded by WPATH.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)**[43]	
Chew (2018)[47] **Type**: Systematic review, narrative synthesis; a quantitative synthesis was planned, but there were too few studies. **Databases**: Medline, Embase, PubMed **Search dates**: 1946 through June 10, 2017	1. Yes	**Purpose well-specified?** Populations, interventions, outcomes, and study designs were well-specified in the protocol. Comparators were not defined in advance because all were considered.
	2. Yes	***A priori* protocol?** Protocol published on PROSPERO (42017056670).
	3. No	**Study designs justified?** No justification for including all study designs was provided.
	4. Partial yes	**Comprehensive search strategy?** Authors searched 2 bibliographic databases (counting Medline and PubMed as one) without language restrictions and provided search terms. They also conducted the search within 24 months of publication. They also searched reference lists of relevant studies. However, authors did not justify exclusion of unpublished studies, search in registries or other grey literature sources, or consult experts.
	5. Yes	**Performed study selection in duplicate?** Duplicate screening was described.
	6. Yes	**Performed data extraction in duplicate?** Duplicate data extraction was described.
	7. No	**List of excluded studies?** No list of excluded studies was provided.
	8. Partial yes	**Detailed description of included studies?** Authors described populations, interventions, comparators, outcomes, research designs, and timeframe for follow-up. They left out settings and key details of the population, interventions, and comparators.
	9. Unclear	**Assessed study-level ROB?** Authors used a modified QUIPS, an ROB tool for prognostic studies
	10. No	**Described funding sources for primary sources?** No funding sources were described.
	11. N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12. Yes	**Impact of ROB on results assessed?** Authors did not assess the impact of primary-study ROB on their findings.
	13. Yes	**Impact of ROB on results discussed?** Authors did not discuss the impact of primary-study ROB on their findings.
	14. N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15. N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16. Yes	**Potential review author conflicts of interest addressed?** The work was funded by the Royal Children's Hospital Foundation, the Melbourne Children's Clinician Scientist Fellowship Scheme, the Apex Foundation for Research into Intellectual Disability, and the William Collie Trust at the University of Melbourne. They reported no conflicts of interest.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)**[43]	
D'hoore (2022)[48] **Type**: Systematic review, narrative synthesis **Databases**: PubMed Medline and Embase **Search dates**: 2015 through April 16, 2021	1. Yes	**Purpose well-specified?** Population, outcomes, and study designs were well-specified. interventions and comparators were not defined in advance.
	2. No	***A priori* protocol?** Protocol not mentioned.
	3. No	**Study designs justified?** No justification for including only cohort or cross-sectional studies and RCTs.
	4. No	**Comprehensive search strategy?** Authors searched 2+ bibliographic databases (Medline and Embase) and provided both search terms. They also conducted the search within 24 months of publication. However, authors did not justify publication and language restrictions (they included only English-language studies and excluded studies not available in full text at their institution). The made no mention of searching reference lists of relevant studies or in registries or other grey literature sources, or consulting experts.
	5. Yes	**Performed study selection in duplicate?** Duplicate screening was described.
	6. No	**Performed data extraction in duplicate?** Data extraction was performed by a single author.
	7. No	**List of excluded studies?** No list of excluded studies was provided.
	8. No	**Detailed description of included studies?** Authors did not describe populations, interventions, comparators, outcomes, research designs, settings, or timeframe for follow-up.
	9. No	**Assessed study-level ROB?** Authors did not describe any ROB assessment method.
	10. No	**Described funding sources for primary sources?** No funding sources were described.
	11. N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12. No	**Impact of ROB on results assessed?** Authors did not assess the impact of primary-study ROB on their findings.
	13. No	**Impact of ROB on results discussed?** Authors did not discuss the impact of primary-study ROB on their findings.
	14. N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15. N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16. Yes	**Potential review author conflicts of interest addressed?** The authors reported no conflicts in this work.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)[43]**		
Ludvigsson (2023)[49] **Type**: Systematic review, narrative synthesis **Databases**: CINAHL, Cochrane, EMBASE, PsycINFO, PubMed, Scopus, SocINDEX, Campbell Library, Epistemonikos, Evidence Search, International HTA database, Database of Abstracts of Reviews of Effects (DARE), Health and Technology Assessment (HTA), NHS Economic Evaluation Database (EED), PROSPERO **Search dates**: Through November 9, 2021	1.	Yes	**Purpose well-specified?** Population, intervention, outcomes, and study designs were well-specified. Comparators were not defined in advance because all were accepted.
	2.	Yes	***A priori* protocol?** *A priori* protocol was published on the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) website.[410]
	3.	No	**Study designs justified?** No justification for including both RCTs and NRSIs was provided.
	4.	Partial yes	**Comprehensive search strategy?** Authors searched 13 bibliographic databases (CINAHL, Cochrane Library, EMBASE, PsycINFO, PubMed, Scopus, SocINDEX, Campbell Library, Epistemonikos, Evidence Search, International HTA database, Database of Abstracts of Reviews of Effects (DARE), Health and Technology Assessment (HTA), NHS Economic Evaluation Database (EED), and PROSPERO) and provided complete search strategies.[411] They also conducted the search within 24 months of publication. However, authors did not justify language restrictions (they included only English-language studies). The made no mention of searching reference lists of relevant studies or in registries or other grey literature sources, or consulting experts. However, while their search strategy was robust, they used an arbitrary threshold on their study-level ROB assessment to exclude a third of the studies retrieved, which goes against best practices.[30,43,412]
	5.	Yes	**Performed study selection in duplicate?** Duplicate screening was described.
	6.	Unclear	**Performed data extraction in duplicate?** Data extraction was performed by 2 authors, but it was unclear whether the 2 authors performed extraction in duplicate.
	7.	No	**List of excluded studies?** Authors stated that they provided a list of 12 studies that were excluded due to a high risk of bias on the SBU website.[54] However, the list only included 11 studies. In addition, authors also failed to provide a list of 159 studies examined in full text and subsequently excluded.
	8.	No	**Detailed description of included studies?** Authors described populations, interventions, comparators, outcomes, research designs, and timeframe for follow-up, but they did not describe settings, nor did they describe the populations, interventions, and comparators in detail. They did not describe study-level findings.
	9.	Yes	**Assessed study-level ROB?** The authors used ROBINS-I to assess study-level ROB.[413] ROBINS-I addresses all 4 required ROB domains and several more that are not included in the AMSTAR-2 tool. Notably, the authors excluded studies that had a high ROB according to ROBINS-I, which means that some studies may have been excluded because they had a high ROB on dimensions not considered key domains in the AMSTAR-2.
	10.	No	**Described funding sources for primary sources?** No funding sources were described.
	11.	N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12.	No	**Impact of ROB on results assessed?** Authors did not assess the impact of primary-study ROB on their findings. Rather, they simply excluded studies that had a high ROB according to ROBINS-I.
	13.	No	**Impact of ROB on results discussed?** Authors did not discuss the impact of primary-study ROB on their findings. Authors excluded studies with a high ROB.
	14.	N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15.	N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16.	Yes	**Potential review author conflicts of interest addressed?** The authors reported that their work was funded by the Swedish Agency for Health Technology Assessment and Assessment of Social Services.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)[43]**		
Mahfouda (2019)[50] **Type**: Systematic review, narrative synthesis **Databases**: Medline and Embase **Search dates**: Through June 9, 2018	1.	No	**Purpose well-specified?** Population and outcomes were well-specified. Comparators were described as "gender-affirming CSHs," but were not listed by name. In fact, authors ended up also including GnRH analogs, which are not considered CHST. Outcomes were described in categories (eg, "mental health" and "physical effects," but were not well-described in advance. Comparators were not specified in advance.
	2.	No	***A priori* protocol?** No explicit statement was made that the protocol was written in advance.
	3.	No	**Study designs justified?** All explanatory studies were potentially eligible; case studies were excluded. No justification was given
	4.	Partial yes	**Comprehensive search strategy?** Authors searched 2 bibliographic databases (Medline and Embase) and they provided keyword search terms. They also conducted the search within 24 months of publication, without language restrictions, and searched the references of relevant studies. They did not describing having searched in registries or other grey literature sources.
	5.	No	**Performed study selection in duplicate?** No mention of duplicate eligibility screening.
	6.	No	**Performed data extraction in duplicate?** No mention of duplicate data extraction.
	7.	No	**List of excluded studies?** No list of excluded studies was provided.
	8.	Partial yes	**Detailed description of included studies?** Authors described populations (with details), interventions (with details), outcomes, research designs, settings, and time frames for follow-up. Their report lacked key details about comparators (when between-group comparisons were made).
	9.	No	**Assessed study-level ROB?** Authors did not describe ROB assessment using any ROB measurement tool that addresses key bias domains.
	10.	No	**Described funding sources for primary sources?** No funding sources were described.
	11.	N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12.	No	**Impact of ROB on results assessed?** Authors did not describe the impact of primary-study ROB on their findings.
	13.	No	**Impact of ROB on results discussed?** Authors did not discuss the impact of primary-study ROB on their findings.
	14.	N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15.	N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16.	Yes	**Potential review author conflicts of interest addressed?** Authors declared no conflicts of interest, and reported that the work was funded by University of Western Australia, Perth Children's Hospital Fund, Raine Medical Foundation, and Australian National Health and Medical Research Council.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)[43]**		
Ramos (2021)[51] **Type**: Systematic review, narrative synthesis **Databases**: Medline and Embase: Medline and Embase **Search dates**: 2009-2019	1.	Yes	**Purpose well-specified?** Population and interventions were well-specified. Comparators and outcomes were not defined in advance because all were accepted.
	2.	No	***A priori* protocol?** No explicit statement was made that the protocol was written in advance.
	3.	No	**Study designs justified?** All experimental and non-experimental studies were potentially eligible, but no justification was provided..
	4.	Partial yes	**Comprehensive search strategy?** Authors searched 2+ bibliographic databases (Medline and Embase) and they provided keyword search terms. They also conducted the search within 24 months of publication without language restrictions However, authors did not justify publication restrictions (they included only published studies), and they did not search in registries or other grey literature sources. It was unclear if they searched the reference lists of published studies or if they consulted experts.
	5.	No	**Performed study selection in duplicate?** No mention of duplicate eligibility screening.
	6.	Yes	**Performed data extraction in duplicate?** 2 reviewers extracted data and resolved discrepancies..
	7.	No	**List of excluded studies?** No list of excluded studies was provided.
	8.	Partial yes	**Detailed description of included studies?** Authors described populations (with details), interventions, outcomes, research designs, and settings. Their report lacked key details about the interventions, and comparators were not described in adequate detail. The timeframe for follow-up was not described. .
	9.	Yes	**Assessed study-level ROB?** Authors used the Cochrane ROB tool for observational and intervention studies, which addresses selection bias, performance bias, selective outcome reporting, detection bias, attrition bias, and potential confounding.
	10.	No	**Described funding sources for primary sources?** No funding sources were described.
	11.	N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12.	Yes	**Impact of ROB on results assessed?** Authors described the impact of primary-study ROB on their findings.
	13.	Yes	**Impact of ROB on results discussed?** Authors discuss the impact of primary-study ROB on their findings.
	14.	Partial yes	**Impact of heterogeneity explained and discussed?** Although no quantitative pooled synthesis was conducted, authors describe the potential impact of heterogeneity on review findings.
	15.	N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16.	Yes	**Potential review author conflicts of interest addressed?** No conflicts to report; no funding.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.1. ROB, purpose, and search details for relevant first-corpus systematic reviews addressing included outcomes associated with medical treatments of TGNB adolescents

First author (Year) **Search details**	**ROB assessment (AMSTAR-2)[43]**		
Rew (2021)[52] **Type**: Systematic review, narrative synthesis **Databases**: PubMed and Embase **Search dates**: 2009-2/6/2019	1.	Partial yes	**Purpose well-specified?** Population was well-specified. Intervention (GnRH analogs) were specified by class only. All study designs were listed. No comparators or outcomes were specified *a priori*. study designs were well-specified. Comparators (ie, specific GnRH analogs) and outcomes were not defined in advance because all were accepted.
	2.	No	***A priori* protocol?** Protocol not mentioned
	3.	No	**Study designs justified?** Authors did not justify their choice to include all study designs, but all study designs were included.
	4.	Partial yes	**Comprehensive search strategy?** Authors searched 2 bibliographic databases without restricting by language, provided search terms and a complete search strategy, and published within 2 years of conducting the search. However, authors neither searched reference lists of relevant studies nor did they search in registries or other grey literature sources, search within 24 months of publication.
	5.	No	**Performed study selection in duplicate?** Duplicate screening was not described.
	6.	Unclear	**Performed data extraction in duplicate?** There is no mention of duplicate data extraction in the applicable section; there is a statement that data extraction was performed in duplicate in the section that describes ROB assessment, but it is unclear whether that statement applies to all data extraction or to ROB assessment only.
	7.	No	**List of excluded studies?** No list of excluded studies was provided.
	8.	No	**Detailed description of included studies?** Authors did not include study details in a tabular format; some study details were described in the narrative, but not uniformly.
	9.	Yes	**Assessed study-level ROB?** Authors used the Cochrane ROB tool.
	10.	No	**Described funding sources for primary sources?** No funding sources were described.
	11.	N/A	**Appropriate meta-analytic methods?** No quantitative pooled synthesis was conducted.
	12.	No	**Impact of ROB on results assessed?** Authors did not assess the impact of primary-study ROB on their findings.
	13.	No	**Impact of ROB on results discussed?** Authors did not discuss the impact of primary-study ROB on their findings.
	14.	N/A	**Impact of heterogeneity explained and discussed?** No pooled synthesis was conducted.
	15.	N/A	**Small-study effects (eg, publication bias) examined and discussed?** No pooled synthesis was conducted.
	16.	Yes	**Potential review author conflicts of interest addressed?** Authors reported that the work was unfunded and that there were no conflicts of interest.

Table abbreviations: TGNB; transgender, nonbinary, or other gender diverse; ROB, risk of bias; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GAHT, gender-affirming hormone therapy including testosterone in transgender males, estrogen or anti-androgens in transgender females, or GnRH analogs in all TGNB individuals; WPATH, World Professional Association for Transgender Health; GnRH, gonadotropin releasing hormone; RCT, randomized controlled trial; ROBINS-I, Cochrane risk-of-bias tool for NRSIs; NRSI; non-randomized studies of interventions

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Achille (2020)[55] Prospective, longitudinal, pre-post study found in bibliographic database searches (second-corpus); included in evidence tables for longitudinal, pre-post, within-group and between-TGNB-group comparisons.	Mental health Psychosocial outcomes						
Asscheman (2011)[414] Found in first-corpus bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Asscheman (1989)[415] Not found in bibliographic database searches; categorically excluded from consideration (publication year <2010).	Mental health						
Auer (2018)[416] NCT01072825 Prospective cohort study cited in Clinicaltrials.gov;[417] not found in bibliographic database searches; excluded from eligibility during title-abstract screening (wrong population).	Not specified (metabolic changes)						
Becerra-Culqui (2018)[418] Not found in bibliographic database searches; excluded at full-text screening (no intervention of interest).			Mental health				
Becker (2018)[103] Cohort study found in bibliographic database searches (second corpus); included in evidence tables for between-TGNB group comparisons.			Psychosocial outcomes				
Becker-Hebly (2021)[72] Cohort study found in bibliographic database searches (first corpus); included in evidence tables for between-TGNB group and longitudinal, pre-post, within-group comparisons.				Mental health			
Bultynck (2017)[419] NCT01072825 Prospective cohort study cited in Clinicaltrials.gov;[417] found in bibliographic database searches (second corpus); excluded from eligibility during title-abstract screening (wrong population).	Not specified (Psychosocial)						
Burke (2016)[130] Cohort study found in bibliographic database searches (first corpus); included in evidence tables for TGNB/cisgender peer group comparisons.		Psychosocial outcomes			Psychosocial outcomes Other		

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Cantu (2020)[74] Descriptive study found in bibliographic database searches (second corpus); included in evidence tables for between-TGNB group comparisons and longitudinal, pre-post, within-group comparisons.				Mental health			
Carmichael (2021)[73] Descriptive study found in bibliographic database searches (first-corpus); included in evidence tables for longitudinal, pre-post, within-group and between-TGNB group comparisons.			Mental health Bone health	Mental health			
Cohen-Kettenis (2011)[168] Case report found in bibliographic database searches (first corpus); excluded from data extraction due to a lack of high-priority comparison types.							Body changes Metabolic changes
Colizzi (2014)[10] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Costantino (2013)[420] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Costa (2015)[77] Cohort study found in bibliographic database searches (first corpus); included in evidence tables for between-TGNB-group, TGNB/cisgender peer group, and longitudinal, pre-post, within-group comparisons.		Psychosocial outcomes	Psychosocial outcomes	Mental health		Psychosocial outcomes	
de Vries (2011)[57] Descriptive study found in bibliographic database searches (first corpus); included in longitudinal, pre-post, within-group, and between-TGNB-group results.	Mental health	Mental health Psychosocial outcomes				Body changes Psychosocial outcomes	Mental health Psychosocial outcomes
de Vries (2014)[79] Cohort study found in bibliographic database searches (first corpus); included in between-TGNB and longitudinal, pre-post, within-group comparisons.	Mental health	Mental health Psychosocial outcomes		Mental health	Psychosocial outcomes		
de Vries (2016)[107] Cross-sectional study not found in bibliographic database searches; included in evidence tables for between-TGNB group comparisons.			Mental health				
Defreyne (2018)[421] Cohort study found in bibliographic database searches (first-corpus); excluded at title/abstract screening (irrelevant).	Mental health						

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Delemarre-van de Waal (2006)[422] Not found in bibliographic database searches; categorically excluded from consideration (publication year <2010).		Body changes Bone health Metabolic changes					
Fisher (2016)[423] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Fisher (2017)[424] Found in bibliographic database searches (second corpus); excluded at title/abstract screening (no interventions of interest).			Mental health Psychosocial outcomes				
Fuss (2015)[425] Cohort study found in bibliographic database searches (first-corpus); excluded at full-text screening (wrong population).	Mental health						
Gava (2016)[426] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health Psychosocial outcomes						
Gava (2018)[427] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Psychosocial outcomes						
Giovanardi (2019)[428] Qualitative descriptive study found in bibliographic database searches (first corpus); excluded at title-abstract screening (wrong population).						Other	
Gómez-Gil (2012)[429] Cross-sectional study found in bibliographic database searches (second-corpus); excluded at full-text screening (wrong population).	Mental health						
Gorin-Lazard (2012)[430] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Guss (2017)[431] Found in bibliographic database searches (first corpus); excluded at title/abstract screening (no intervention of interest).							

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Hannema (2017)[59] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			Body changes CV risk factors		Other		
Hisle-Gorman (2021)[432] Cohort study found in bibliographic database searches (second-corpus); excluded at full-text screening (wrong population).				Mental health			
Jarin (2017)[136] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.		Body changes CV risk factors Metabolic changes	CV risk factors	CV risk factors	CV risk factors Metabolic changes		
Joseph (2019)[137] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.				Bone health			
Khatchadourian (2014)[82] Cohort study found in bibliographic database searches (second corpus); included in evidence tables for between-TGNB group comparisons.						Mental health Safety Other	Mental health Other
Klaver (2018)[83] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group, and between-TGNB group comparisons.			Body changes	Body changes	Body changes	Body changes	Body changes
Klaver (2020)[139] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			CV risk factors	Body changes Metabolic changes CV risk factors			
Klink (2013)[433] Descriptive study not found in bibliographic database searches; excluded from consideration due to publication type (abstract only).						Bone health	
Klink (2015)[140] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.		Body changes Bone health	Bone health	Bone health	Bone health	Bone health	
Kuper (2020)[141] Descriptive study found in bibliographic database searches (second-corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			Mental health Psychosocial outcomes				

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Leavitt (1980)[434] Not found in bibliographic database searches; categorically excluded from consideration (publication year <2010).	Mental health						
Lee (2020)[85] Cohort study found in bibliographic database searches (second-corpus); included in evidence tables for between-TGNB group comparisons.				Bone health			
Lopez (2018)[435] Descriptive study found in bibliographic database searches (first corpus); included in bibliography only due to a lack of high-priority group comparisons.						Other	
López de Lara (2020)[62] Likely-relevant, non-English study found in bibliographic database searches (first-corpus; included in bibliography only.	Mental health						
Manieri (2014)[436] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Psychosocial outcomes						
Metzger (2019)[437] Cohort study found in bibliographic database searches (first-corpus); excluded at title/abstract screening (irrelevant).	Mental health						
Motta (2018)[438] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Mueller (2005)[439] Not found in bibliographic database searches; categorically excluded from consideration (publication year <2010).							
Mullins (2021)[91] Cohort study found in bibliographic database searches (first-corpus); included in evidence tables for between-TGNB group comparisons.				CV risk factors			
Nahata (2017)[115] Cross-sectional study found in bibliographic database searches (second corpus); included in evidence tables for between-TGNB group comparisons.							Other

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Navabi (2021)[92] Cohort study found in bibliographic database searches (first corpus); included in evidence tables for between-TGNB group and longitudinal, pre-post, within-group comparisons.				Bone health			
Nokoff (2020)[131] Prospective cohort study found in bibliographic database searches (second corpus); included in evidence tables for TGNB/cisgender peer group comparisons.			Body changes	Body changes Metabolic changes			
Olson (2014)[440] Descriptive study found in bibliographic database searches (second corpus); excluded at full-text screening (wrong population).		Body changes Metabolic changes					
Olson-Kennedy (2018)[143] Descriptive study found in bibliographic database searches (first corpus); excluded at full-text screening (wrong population).					Metabolic parameters?		
Pelusi (2014)[441] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Psychosocial outcomes						
Perl (2020)[144] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			CV risk factors	Body changes CV risk factors			
Schagen (2016)[148] Descriptive study found in bibliographic database searches (second corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.		Body changes Metabolic changes	Body changes	Body changes Metabolic changes		Body changes	Body changes Metabolic changes
Schagen (2020)[94] Prospective cohort study found in bibliographic database searches (first corpus); included in evidence tables for between-TGNB-group and longitudinal, pre-post, within-group comparisons.			Bone health	Bone health			
Schneider (2017)[442] Case report found in bibliographic database searches (second corpus); included in bibliography only due to a lack of high-priority group comparisons.							Psychosocial outcomes
Schulmeister (2022)[95] Prospective cohort study found in bibliographic database searches (first corpus); included in evidence table between-TGNB group and TGNB/cisgender peer group comparisons.				Body changes			

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Sequeira (2017)[443] Not found in bibliographic database searches; categorically excluded from eligibility due to publication type (abstract only).					Psychosocial outcomes		
Shadid (2020)[444] NCT01072825 Prospective cohort study cited in clinicaltrials.gov;[417] was not found in bibliographic database searches; excluded from eligibility during title-abstract screening (wrong population).	Not specified (metabolic changes)						
Staphorsius (2015)[119] Prospective cohort study found in bibliographic database searches (first-corpus); included in evidence tables for between-TGNB-group and longitudinal, pre-post, within-group comparisons.		Psychosocial outcomes		Mental health			
Smith (2001)[445] Not found in bibliographic database searches; categorically excluded from consideration (publication year <2010).					Psychosocial outcomes		
Stoffers (2019)[149] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			Bone health	Bone health			
Tack (2016)[446] Descriptive study found in bibliographic database searches (second-corpus); excluded at full-text screening (wrong population) because treatments were initiated at ages 18+.		Body changes CV risk factors Metabolic changes		Body changes CV risk factors Mental health	CV risk factors Metabolic changes Other		
Tack (2017)[150] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.		Body changes CV risk factors Metabolic change	Body changes		CV risk factors Metabolic changes		
Tack (2018)[447] Observational study found in bibliographic database searches (second corpus); excluded at full-text screening (wrong interventions) for evaluating only interventions not approved for use in the US (cyproterone and lynestrenol).			Body changes Bone health				
Tankersley (2021)[448] SR not found in bibliographic database searches; included in bibliography only (wrong outcomes).							
Trotman (2014)[449] Not found in bibliographic database searches; categorically excluded from consideration due to publication type (abstract only).					CV risk factors Metabolic changes		

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.2. Disposition of primary studies included in first-corpus SRs examining high-priority outcomes associated with GD treatments in TGNB children/adolescents

First author (year) Disposition in this DRRC review	Systematic reviews						
	Baker (2021)[46]	Chew (2018)[47]	D'hoore (2022)[48]	Ludvigsson (2023)[49]	Mahfouda (2019)[50]	Ramos (2021)[51]	Rew (2021)[52]
Turan (2018)[450] Not found in bibliographic database searches; excluded at full-text screening (wrong population).	Mental health						
Turban (2020)[121] Cross-sectional study found in bibliographic database searches (first corpus); included in evidence tables for between-TGNB group comparisons.							Mental health
van der Loos (2021)[69] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group comparisons.			Bone health	Bone health			
van der Miesen (2020)[124] Cohort study found in bibliographic database searches (second corpus); included in evidence tables for between-TGNB group and TGNB/cisgender peer group comparisons.			Mental health Psychosocial functioning				
Vlot (2017)[99] Descriptive study found in bibliographic database searches (first corpus); included in evidence tables for longitudinal, pre-post, within-group, and between-TGNB group comparisons.		Bone health Body changes	Bone health	Bone health	Bone health	Bone health	Bone health
Vrouenraets (2016)[451] Descriptive study found in bibliographic database searches (first corpus); included in bibliography only due to a lack of high-priority group comparisons.						Other	
Warrier (2020)[452] Not found in bibliographic database searches; excluded at full-text screening (wrong population).							
Wierckx (2011)[453] Cross-sectional study found in bibliographic database searches (second corpus); excluded at full-text screening (wrong population).	Mental health						

Table abbreviations: SR, systematic review; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse;

Return to TOC

Table I.E.3. Systematic reviews examining mental health outcomes (eg, anxiety, depression, suicidality) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings from primary studies**
Baker (2021)[46] **Primary studies**: Mental health outcomes were assessed in 4 primary studies of 3 TGNB adolescent cohorts. **Conclusions:** Hormone therapy may decrease depression and anxiety in TGNB adolescents; no conclusions can be drawn about suicidality.	**Anxiety** *TGNB patients, pre-post: GnRH analogs with or without CSHT were associated with a statistically significant decrease in mean anxiety scores versus baseline in 1 out of 3 primary studies; any changes were nonsignificant in 2 others. No study found that hormone therapy increased anxiety. Authors concluded that hormone therapy may decrease anxiety in TGNB adolescents.* • GnRH analog therapy for puberty suppression for an average of 1.88 years had no significant effect on STAI trait subscale scores in N=41 treatment-naïve, Danish TGNB adolescents with a mean age of 14.8 years (p=NS) in de Vries (2011).[57] ○ In a subset of N=32 patients (mean age 14.8 years) who went on to receive CSHT for an average duration of 5.9 years, there was no significant change in STAI trait subscale scores versus baseline in de Vries (2014).[79] • GnRH analog therapy plus CSHT for a treatment duration of 12 months was associated with a decrease in mean (SD) STAI trait subscale score from 33.0 (7.2) to 18.5 (8.4) in N=38 Spanish, TGNB adolescents with a mean age of 16 years (p<0.001)) in López de Lara (2020).[62] **Depression** *TGNB patients, pre-post: GnRH analogs with or without CSHT were associated with a statistically significant decrease in mean depression scores versus baseline in 3 out of 4 primary studies; any change was nonsignificant in 1 other. No study found that hormone therapy increased depression. Authors concluded that hormone therapy may decrease depression in TGNB adolescents.* • GnRH analog therapy for puberty suppression for an average of 1.88 years was associated with decrease in mean (SD) BDI score from 8.31 (7.12) to 4.95 (6.72) in N=41 treatment-naïve, Danish TGNB adolescents with a mean age of 14.8 years (p=0.004) in de Vries (2011).[57] ○ In a subset of N=32 patients who went on to receive CSHT for an average duration of 5.9 years, there was no significant differences in BDI score (mean age 14.8 years) in de Vries (2014).[79] • GnRH analog therapy plus CSHT for a treatment duration of 12 months was associated with a decrease in mean CESD-R decrease from 21.4 to 13.9 (p<0.001) in N=47 US-based, TGNB adolescents with a mean age of 16.2 years. (A score of 16 indicates no clinical depression.) Mean PHQ-9 score decreased from 9.0 to 5.4 over the same period (p<0.001) in Achille (2020).[55] • GnRH analog therapy plus CSHT for a treatment duration of 12 months was associated with a decrease in mean (SD) BDI score from 19.3 (5.5) to 9.7 (3.9) in N=38 Spanish, TGNB adolescents with a mean age of 16 years (p<0.001) in López de Lara (2020).[62] **Suicide** *Investigators looked for but did not find primary studies that addressed suicide-related outcomes in TGNB adolescents.*
Chew (2018)[46] **Primary studies**: Mental health outcomes were assessed in 1 primary study including TGNB adolescents. **Authors conclusions** GnRH analogs were associated with improvements in depression, but impact on anxiety remains unclear. No research was found examining the effects of progestin, antiandrogens, estrogens, and testosterone.	**Anxiety** *TGNB patients, pre-post: GnRH analogs were associated with a nonsignificant decrease in anxiety and anger versus baseline in 1 primary study that examined it.* • GnRH analog therapy for puberty suppression for an average (SD) of 1.88 (1.05) years was associated with a nonsignificant decrease in a composite of depression and anxiety among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (p=NS) in de Vries (2011).[57] **Depression** *TGNB patients, pre-post: GnRH analogs were associated with a statistically significant decrease in mean depression scores versus baseline in 1 primary study that examined it.* • GnRH analog therapy for puberty suppression for an average (SD) of 1.88 (1.05) years was associated with significant decrease in depression among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (p<0.05) in de Vries (2011).[57]
D'hoore (2022)	**ADHD**

Table abbreviations: GAHT, gender-affirming hormone therapy; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; BDI, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; PHQ-9, Patient Health Questionnaire Modified for Teens; STAI, State-Trait Anxiety Inventory; US, United States;

Return to TOC

Table I.E.3. Systematic reviews examining mental health outcomes (eg, anxiety, depression, suicidality) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings from primary studies**
Primary studies: Mental health outcomes were assessed in 5 primary studies including TGNB adolescents.	*TGNB patients vs cisgender peers: Untreated TGNB youth have higher rates of ADHD compared to cisgender peer groups in 1 primary study.* • No treatment was associated with higher rates of ADHD (15% in transfeminine and 16% in transmasculine patients compared to age-matched cisgender peer groups in Becerra-Culqui et al (2018).[418] **Anxiety** *TGNB patients, pre-post: GAHT was associated with improved anxiety in 1 primary study.* • GAHT was associated with improvements in anxiety among TGNB patients (mean age 14.9) in Kuper (2020).[141] **Depression** *TGNB patients vs cisgender peers: Untreated TGNB youth had higher rates of depression than cisgender peers in 1 primary study.* • No treatment was associated with higher rates of depressive disorders (49% in transfeminine and 62% in transmasculine adolescents) compared to age-matched cisgender peer groups in Becerra-Culqui et al (2018).[418] *TGNB patients, pre-post: GAHT was associated with improved depression in 1 primary study.* • GAHT was associated with improvements in depression among TGNB patients (mean age 14.9) in Kuper (2020).[141] **Psychological functioning** *TGNB vs cisgender peers: Untreated TGNB patients had worse psychological functioning compared to cisgender peers in 1 primary study; GAHT was associated with psychosocial functioning that was similar to or better than that of peers in another.* • No treatment was associated with worse psychological functioning compared to a cisgender peer group in Fisher (2017).[424] • GAHT was associated with psychosocial functioning was that was similar to or better than that of peers in van der Miesen (2020).[124] *TGNB patients, pre-post: GAHT was associated with improved mental health outcomes in 2 primary studies.* • GAHT was associated with improved mental health problems among London trans adolescents (mean age 13.6) Carmichael (2021).[73] • Puberty blockers were associated with improvements in behavioral and emotional problems in van der Miesen (2020).[124] **Suicide ideation/behavior** *TGNB patients vs cisgender peers: Untreated TGNB youth have higher rates suicidal ideation compared to cisgender peer groups in 1 primary study.* • No treatment was associated with higher rates of lifetime suicidal ideation (7.5% in transfeminine and 10.4% in transmasculine adolescents) among n = 1388 TGNB youth ages 3-17 years (588 transfeminine and 745 transmasculine, ages 3-17 years) compared to age-matched cisgender peer groups in Becerra-Culqui et al (2018).[418]
Ludvigsson (2023)[49] **Primary studies:** Mental health outcomes were assessed in 5 primary studies out of 24 included by review authors. Authors drew conclusions about mental health outcomes based on 3 primary studies,	**Anxiety** *TGNB patients, pre-post: Authors concluded from 2 primary studies that GAHT was associated with no changes in anxiety.* • GnRH analogs for 1 year followed by subsequent CSHT for 4 years were assessed for changes/differences anxiety (STAI) among N=196 TGNB patients (mean age 13.6 years) in de Vries (2014).[79] • GnRH analogs followed by subsequent CSHT were assessed for changes/differences in anxiety (GAD-7) among N=80 TGNB patients (mean age 15 years) in Cantu (2020).[74a] **Depression** *TGNB patients, pre-post: Review authors concluded from 2 primary studies that GAHT was associated with no changes in depression.* • GnRH analogs for 1 year followed by subsequent CSHT for 4 years were assessed for changes/differences in depression (BDI) among N=196 TGNB patients (mean age 13.6 years) in de Vries (2014).[79] • GnRH analogs followed by subsequent CSHT were assessed for changes/differences in acute distress and suicidality among N=80 TGNB patients (mean age 15 years) in Cantu (2020).[74b] **Suicide ideation** *TGNB patients, pre-post: Review authors concluded from 1 primary study that GAHT was associated with no changes in suicide ideation; authors omitted 1 included study that also addressed suicidality.*

[a] *Publication year was erroneously listed as 2019 in the review authors' reference lists.*
[b] *Publication year was erroneously listed as 2019 in the review authors' reference lists.*

Table abbreviations: GAHT, gender-affirming hormone therapy; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; BDI, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; PHQ-9, Patient Health Questionnaire Modified for Teens; STAI, State-Trait Anxiety Inventory; US, United States;

Return to TOC

Table I.E.3. Systematic reviews examining mental health outcomes (eg, anxiety, depression, suicidality) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings from primary studies**
omitting any findings from 2. **Author conclusions:** GnRH analogs have no effect on depression, anxiety, or suicide ideation.	• GnRH analogs followed by subsequent CSHT were assessed for changes/differences in suicidality among N=80 TGNB patients (mean age 15 years) in Cantu (2020).[74c] *1 other included primary study that assessed suicidality was omitted by review authors when drawing their conclusions.* • CSHT for a mean of 12 months were assessed for changes/differences in height, weight, and BMI, triglycerides, cholesterol, suicide, and side effects among N=43 TGNB adolescents (ages 15-17 years at start of treatment) in Tack (2016).[446]
Ramos (2021)[51] **Primary studies**: Mental health outcomes were assessed in 2 primary studies including TGNB adolescents.	**Suicide behaviors** *TGNB patients, pre-post: GnRH analog therapy for puberty suppression was associated with a decrease in suicidality in 1 primary study.* • GnRH analog therapy for puberty suppression or monitoring in a GD clinic was associated with a decline in suicide attempts from 12% to 5% among N=84 TGNB youths in Khatchadourian et al (2014).[82] **General mental health** *TGNB patients, pre-post: GnRH analog therapy for puberty suppression was associated with improved mental health in 1 primary study.* • GnRH analogs for puberty suppression were associated with significant improvement in mental health in N=70 TGNB youths who received in de Vries et al (2011).[57]
Rew (2021)[52] **Primary studies:** Mental health was examined in 4 out of 9 primary studies addressing TGNB adolescents.	**Anxiety** *AFAB vs AMAB transgender adolescents: 1 primary study showed that AFAB patients had more anxiety than AMAB patients who received GnRH analogs.* • AFAB patients who received unspecified GnRH analogs had more anxiety compared to AMAB who received them among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69] **Depression** *TGNB patients, pre-post: 1 primary study showed decreased depressive symptoms associated with GnRH analogs.* • GnRH analogs were associated with decreases in depressive symptoms in both AMAB and AFAB patients among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69] **Mood and affect** *Case findings: Leuprorelin was associated with improved affect in one case; another patient case had to discontinue due to mood swings and emotional liability.* • 1 patient who received GnRH analogs followed discontinued due to mood swings and emotional lability among N=84 TGNB adolescents (age between 11.4-19.8 years) in Khatchadourian (2014).[82] • Leuprorelin was associated with improvement in affective and social life in N=1 TGNB patient in Schneider (2017).[442] *TGNB patients, pre-post: 1 primary study showed decreased psychological distress in patients who started puberty suppression between ages 9 and 16 years.* • Unspecified puberty blockers were associated with reduced past-month psychological distress among N=89 TGNB patients who started treatment between ages 9 and 16 in Turban (2020).[121] • • Suicide ideation *TGNB patients, pre-post: 1 primary study showed reduced suicide ideation in patients who started puberty suppression between ages 9 and 16 years.* • Unspecified puberty blockers were associated with decreased lifetime suicide ideation in N=89 TGNB adolescents who started treatment between ages 9 and 16 in Turban (2020).[121]

[c] *Publication year was erroneously listed as 2019 in the review authors' reference lists.*

Table abbreviations: GAHT, gender-affirming hormone therapy; GD, gender dysphoria; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; BDI, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; PHQ-9, Patient Health Questionnaire Modified for Teens; STAI, State-Trait Anxiety Inventory; US, United States;

Return to TOC

Table I.E.4. Systematic reviews examining psychosocial outcomes (eg, QOL, behavioral/social functioning, GD, body image) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
Baker (2021)[46] **Primary studies** Psychosocial and emotional outcomes were assessed in 1 primary study of TGNB adolescents. **Authors conclusions** Hormone therapy was associated with improved QOL.	**QOL** *TGNB patients, pre-post: No change in QOL from baseline in 1 primary study; no study found that hormone therapy decreased QOL.* • GnRH analog therapy plus CSHT for a treatment duration of 12 months was associated no change from baseline in mean Q-LES-Q-SF in N=38 Spanish, TGNB adolescents with a mean age of 16 years (*p*=NS) in López de Lara (2020).[62]
Chew (2018)[47] **Primary studies**: Psychosocial and emotional outcomes were assessed in 4 primary studies among 3 cohorts of TGNB adolescents. **Authors conclusions** GnRH analogs significantly improve global functioning and behavioral/emotional problems. The effects on anger remain unclear. Treatment had no significant effect on GD and body image. No research was found examining the effects of progestin, antiandrogens, estrogens, and testosterone.	**Anger** *TGNB patients, pre-post: GnRH analogs were associated with a nonsignificant decrease in anger and anxiety in 1 primary study.* • GnRH analog therapy for puberty suppression for an average (SD) of 1.88 (1.05) years was associated with a nonsignificant decrease in a composite of anger and depression among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (*p*=NS) in de Vries (2011).[57] **Behavioral and emotional outcomes** *TGNB patients, pre-post: GnRH analogs were associated with significant improvement in total and internalizing and externalizing CBCL and YSR scores in 1 primary study, and nonsignificant improvements in another primary study that included a subset of the patients included in the first.* • GnRH analog therapy for puberty suppression over an average (SD) of 1.88 (1.05) years was associated with a statistically significant decreases (improvements) in CBCL *total and internalizing* scores (*p*<0.05) and *externalizing* scores (*p*<0.05) among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (*p*<0.05). It was also associated with statistically significant decreases (improvements) in YSR *total and internalizing* scores (*p*<0.05) and *externalizing* scores (*p*<0.05) in de Vries (2011).[57] ○ In a subset of the same cohort who went on to receive CSHT, GnRH analog therapy for puberty suppression over an average (SD) of 1.88 (1.05) years was associated with nonsignificant decreases (improvements) in CBCL *externalizing* scores (P=NS) as well as in YSR *externalizing* scores among N=55 Danish TGNB adolescents with a mean (SD) age of 14.75 (1.92) years (*p*=NS) in de Vries (2014).[79] **Gender dysphoria and body image** *TGNB patients, pre-post: There was no significant improvement in body image in 1 primary study, but the assessment tool was not designed to assess changes related to unwanted secondary sex characteristics.* • GnRH analog therapy for puberty suppression over an average (SD) of 1.88 (1.05) years was associated with no significant changes in GD and body image among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (*p*=NS) in de Vries (2011).[57] **Global functioning** *TGNB patients, pre-post: GnRH analogs were associated with significant improvement in global functioning in 1 primary study, and nonsignificant improvement in another primary study. A third primary study reported improvement but did not report significance.* • GnRH analog therapy for puberty suppression over an average (SD) of 1.88 (1.05) years was associated with a statistically significant increase in global functioning among N=70 Danish TGNB adolescents with a mean (SD) age of 13.65 (1.85) years (*p*<0.05) in de Vries (2011).[57] ○ In a subset of the same cohort who went on to receive CSHT, GnRH analog therapy for puberty suppression over an average (SD) of 1.88 (1.05) years was associated with nonsignificant improvement in global functioning among N=55 Danish TGNB adolescents with a mean (SD) age of 14.75 (1.92) years (*p*=NS) in de Vries (2014).[79] • GnRH analog therapy for puberty suppression over an average (SD) duration of 0.75 (0.59) years was associated with improvement in global functioning among N=201 TGNB adolescents with a mean (SD) age of 15.52 (1.41) years (*p*=N/R) in Costa (2015).[77]
D'hoore (2022)[48]	**Body image**

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.4. Systematic reviews examining psychosocial outcomes (eg, QOL, behavioral/social functioning, GD, body image) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
Primary studies: Mental health outcomes in TGNB adolescents were assessed in 5 primary studies out of 91 that addressed a variety of outcomes in TGNB populations.	*TGNB patients, pre-post: GAHT was associated with improved body image in 2 primary studies.* • GAHT was associated with improvements in body dissatisfaction among TGNB adolescents (mean age 14.9) in Kuper (2020).[141] • GAHT was associated with significant improvement in body image in treated adolescents in Becker (2018).[103] *TGNB patients vs cisgender peers: Untreated TGNB patients had worse body image compared to cisgender peers in 1 primary study.* • No treatment was associated with significantly higher levels of body uneasiness among N = 46 Italian TGNB patients (mean age = 16.0 ± 1.49) compared to a cisgender peer group in Fisher (2017).[424] **Global/psychosocial functioning** *TGNB patients, pre-post: GnRH analogs were associated with improved global functioning in 1 primary study.* • Puberty suppression with GnRH analogs was associated with improved global functioning in n = 201 UK patients in Costa (2015).[77] *TGNB patients vs cisgender peers: Untreated TGNB patients had worse psychosocial functioning vs cisgender peers; after starting GAHT, they had comparable or better psychosocial functioning in 1 primary study.* • Untreated TGNB patients had worse psychosocial functioning vs cisgender peers; after starting GAHT psychosocial functioning was similar or better than that of peers in van der Miesen (2020).[124]
Ludvigsson (2023)[49] **Primary studies:** Psychosocial outcomes were assessed in 7 primary studies out of 24 included by review authors. Review authors based their conclusions about psychosocial outcomes on only 5 primary studies, omitting any results from 2. **Authors conclusions** GnRH analogs improve global function, but have no effect on cognition. They also improve quality of life.	**Cognition** *Authors concluded from 1 primary study that GAHT was associated with no change in cognition.* • GnRH analogs for a mean of 1.6 years were assessed for changes/differences in cognitive function (executive function task test) among N=41 patients (ages 12+ years) in Staphorsius (2015).[119] **Gender dysphoria** *Authors concluded from 2 primary studies that GAHT was associated with no change in GD as assessed with UGDS; authors omitted 1 included study that also looked at GD using UGDS.* • GnRH analogs for 1 year were assessed for changes/differences in GD among N=436 TGNB patients (mean age 15.5 years) in Costa (2015).[77] • GnRH analogs for a mean of 31 months were assessed for changes/differences in GD among N=44 TGNB patients (mean age 13.6 years) in Carmichael (2021).[73] *Other included studies that also looked at GD:* • GnRH analogs for 1 year followed by subsequent CSHT for 4 years were assessed for changes/differences in depression (BDI), anxiety (STAI), GD (UGDS), global functioning (CGAS), anger (TPI) among N=196 TGNB patients (mean age 13.6 years) in de Vries (2014).[79] **Global/psychosocial function** *Authors concluded from 4 primary studies that GAHT was associated with improved global functioning as assessed with CGAS. Authors omitted 1 primary study that assessed psychosocial functioning with other measures.* • GnRH analogs for 1 year followed by subsequent CSHT for 4 years were assessed for changes/differences in global/psychosocial functioning among N=196 TGNB patients (mean age 13.6 years) in de Vries (2014).[79] • GnRH analogs for 1 year were assessed for changes/differences in global/psychosocial functioning among N=436 TGNB patients (mean age 15.5 years) in Costa (2015).[77] • GnRH analogs for a mean of 31 months were assessed for changes/differences in global/psychosocial functioning among N=44 TGNB patients (mean age 13.6 years) in Carmichael (2021).[73] • GnRH analogs for 0.5-4 years followed by CSHT for 0.5-0.4 years were assessed for changes/differences global/psychosocial functioning among N=434 TGNB patients (mean age 15.5 years) in Becker-Hebly (2020).[72] *Other included primary studies that assessed suicide ideation that the authors omitted when drawing their conclusions:* • GnRH analogs followed by subsequent CSHT were assessed for changes/differences in psychosocial functioning (PHQ-9), anxiety (GAD-7), acute distress, suicidality, among N=80 TGNB patients (mean age 15 years) in Cantu (2020).[d74] **QOL** *Authors concluded from 2 primary studies that GAHT was associated with improved of QOL.* • GnRH analogs for a mean of 31 months were assessed for changes/differences in HRQOL (Kidscreen52) among N=44 TGNB patients (mean age 13.6 years) in Carmichael (2021).[73] • GnRH analogs for 0.5-4 years followed by CSHT for 0.5-0.4 years were assessed for changes/differences in global functioning (CGAS), psychosocial function (YSR/ASR) among N=434 TGNB patients (mean age 15.5 years) in Becker-Hebly (2020).[72]

[d] *Publication year was erroneously listed as 2019 in the review authors' reference lists.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.4. Systematic reviews examining psychosocial outcomes (eg, QOL, behavioral/social functioning, GD, body image) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
Mahfouda (2019)[50] **Primary studies**: Psychosocial outcomes were examined in 3 out of 12 primary studies that addressed TGNB adolescents.	**Body dissatisfaction** *TGNB patients, pre-post: 1 primary study found improvements in body dissatisfaction associated with unspecified GAHT.* • Unspecified GAHT was associated with improvements in body dissatisfaction among N=50 TGNB adolescents (mean ages 14.3 years for transgender males and 15.7 years for transgender females) in Sequeira (2017).[443] **Cognitive functioning** *TGNB patients vs cisgender peers: 1 primary study found no differences in cognitive function associated with GnRH analogs and subsequent CSHT.* • Puberty suppression with GnRH analogs followed by CSHT was associated with no difference in cognitive function among N=21 transgender males (mean age at baseline 16.1 years) vs N=20 age-matched cisgender males and N=21 age-matched cisgender females in Burke (2016).[130] **Disordered eating** *TGNB patients, pre-post: 1 primary study found improvements in disordered eating associated with unspecified GAHT.* • Unspecified GAHT was associated with improvements in body dissatisfaction among N=50 TGNB adolescents (mean ages 14.3 years for transgender males and 15.7 years for transgender females) in Sequeira (2017).[443] **Gender dysphoria** *TGNB patients, pre-post: 1 primary study found improvements in GD associated with GnRH analogs and subsequent CSHT.* • GnRH analogs for puberty suppression and unspecified CSHT was associated with reduced GD among N=55 transgender males (mean age 13.7 years at baseline) and N=22 transgender females (mean age 13.6 years at baseline) in de Vries (2014).[79] **Global functioning** *TGNB patients, pre-post: 1 primary study found improvements in global functioning associated with GnRH analogs and subsequent CSHT.* • GnRH analogs for puberty suppression and unspecified CSHT was associated with reduced global functioning among N=55 transgender males and N=22 transgender females in de Vries (2014).[79]
Ramos (2021)[51] **Primary studies**: Psychosocial outcomes were examined in 2 primary studies that included adolescents.	**Psychosocial outcomes:** *Transgender males versus females: One primary study found AFAB patients were less satisfied with secondary sex characteristic changes associated with GnRH analogs vs AMAB patients.* • De Vries et al (2011)[57] found AFAB patients who received **GnRH analog** puberty suppression were less satisfied with secondary sex characteristics than AMAB patients who received the same treatments in N=70 TGNB youths.[57] *TGNB patients, pre-post: One primary study found no difference in GD and body image scales associated with GnRH analogs; another found improvements in psychosocial functioning when the treatment was accompanied by psychological support.* • De Vries et al (2011)[57] found no differences in GD and body image scales vs baseline in N=70 patients who received **GnRH analog** puberty suppression.[57] • Costa et al (2015)[77] found improvements in psychosocial functioning in N≈200 TGNB adolescents undergoing **GnRH analog** puberty suppression along with psychological support.[77]
Rew (2021)[52] **Primary studies:** Psychosocial outcomes were examined in 3 out of 9 primary studies addressing TGNB adolescents.	**Gender dysphoria** *AMAB vs AFAB TGNB patients: 1 primary study showed that AFAB patients who received GnRH analogs had more problem behaviors than AMAB patients who received them.* • AFAB patients who received unspecified GnRH analogs had more problem behaviors vs AMAB patients among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69] *TGNB patients, pre-post: 1 primary study showed no change in GD associated with GnRH analogs.* • GnRH analogs were associated with no change in GD among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69] **Emotional and behavior problems** *TGNB patients, pre-post: 1 primary study showed that GnRH analogs were associated with fewer emotional and behavior problems.* • GnRH analogs were associated with significantly fewer emotional and behavior problems among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69] **Global functioning** *TGNB patients, pre-post: 1 primary study showed GnRH analogs were associated with improved global functioning.* • GnRH analogs were associated with increases in global functioning among N=70 TGNB adolescents (mean age 13.6 years) in de Vries (2011).[69]

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.4. Systematic reviews examining psychosocial outcomes (eg, QOL, behavioral/social functioning, GD, body image) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	Global IQ *Case findings: 1 patient experienced a decrease in global IQ after starting leuprorelin.* • Leuprorelin was associated with a decrease in global IQ in N=1 TGNB patient in Schneider (2017).[442] **Social functioning** *Case findings: Leuprorelin was associated with improved social life in 1 case report.* • Leuprorelin was associated with improved social life in N=1 TGNB patient in Schneider (2017).[442] **Substance abuse** *TGNB patients, pre-post: Puberty suppression was associated with decreases in binge drinking and illicit drug use in 1 primary study.* • Unspecified puberty blockers were associated with decreased past-month binge drinking and lower lifetime illicit drug use in N=89 TGNB patients who started treatments between ages 9 and 16 years in Turban (2020).[121]

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.5. Systematic reviews addressing body changes (eg, endogenous hormones, growth, fat/lean/body mass, breast development, testicular volume) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
Chew (2018)[47] **Primary studies**: Body changes were assessed in 7 primary studies, including 1 for which only the transgender female adolescents met our eligibility criteria. One primary study that included young adults was excluded. **Authors conclusions** GnRH analogs were associated with decreased growth velocity, increased body fat percentage, increased BMI, and decreased lean body mass. Lynestrenol significantly increases weight and BMI. Cyproterone decreases growth velocity without affecting body weight and BMI after 12 months. Estrogen in combination with cyproterone resulted in reduced growth and increases in total BMI. Testosterone monotherapy increased growth velocity and increased BMI.	**Endogenous hormone levels** *TGNB patients, pre-post: GnRH analogs, which are used for puberty suppression, tended to suppress gonadotropin hormone, LH, FSH, and sex hormones (testosterone and estrogen) in 3 out of 3 primary studies, although 1 study showed a decrease in testosterone levels for transgender females but not transgender males. CSHT tended to produce changes in endogenous hormone levels that were consistent with that of the affirmed gender in 3 out of 3 primary studies.* Studies in transgender females: • GnRH analog therapy for puberty suppression over 2+ years was associated with decreases in gonadotropin (p=N/R) and testosterone levels (p=N/R) among N=10 transgender females (mean age not given) in Delemarre-van de Waal (2006).[422] • GnRH analog therapy for puberty suppression over a mean of 1.3 years was associated with a statistically significant decrease in testosterone (p<0.05), LH (p<0.05), and FSH (p<0.05), and a nonsignificant decrease in androstenedione (p=NS) in N=15 transgender female adolescents with a mean (SD) age of 14.9 (1.9) years in Klink (2015).[140] • GnRH analog therapy for puberty suppression over at least 3 months was associated with nonsignificant decreases in gonadotropin (p=NS), estradiol (p=NS), testosterone (p=NS), LH (p=NS), and FSH (p=NS) among N=49 transgender female adolescents with a mean (SD) age of 13.6 years (p=NS) in Schagen (2016).[148] • Estrogen in combination with cyproterone[e] over a mean of 1.3 years was associated with a statistically significant decrease in testosterone (p<0.05), fT (p<0.05), LH (p<0.05), a statistically significant increase in estradiol (p<0.05) and SHBG (p<0.05), a nonsignificant decrease in FSH (p=NS), and no significant change in DHEA (p=NS) among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Studies in transgender males • GnRH analog therapy for puberty suppression over a mean of 1.5 years was associated with statistically significant decreases in estradiol (p<0.05), LH (p<0.05), and FSH (p<0.05), and a non-significant decrease in androstenedione (p=NS), but no change in testosterone levels (p=NS) in N=19 transgender male adolescents with a mean (SD) age of 15.0 (2.0) years in Klink (2015).[140] • Testosterone in combination with lynestrenol[f] over a mean of 0.95 years was associated with a statistically significant decrease in LH and FSH (p<0.05) and increase in testosterone and fT (p<0.05), a nonsignificant decrease in SHBG (p=NS), and a nonsignificant increase in estradiol (p=*NS)* among N=38 transgender male adolescents with a mean age of 15.8 years in Tack (2016).[446] • Testosterone over 1-3 months was associated with a nonsignificant increase in testosterone (p=NS) and a nonsignificant decrease in estradiol (p=NS) among N=transgender male adolescents with a mean age of 16 years in Jarin (2017).[136] **Body composition** *TGNB patients, pre-post: GnRH analogs increased fat mass and decreased lean mass in both transgender males (1 out of 1 primary study) and females (2 out of 2 primary studies).* Studies transgender females: • GnRH analog therapy for puberty suppression over 2+ years was associated with increased fat mass percentage (p=N/R) and decreased lean body mass percentage (p=N/R) among N=10 transgender females (mean age not given) in Delemarre-van de Waal (2006).[422] • GnRH analog therapy for puberty suppression over at least 3 months was associated with a statistically significant increase in fat percentage (p<0.05) and a decrease in lean mass percentage (p<0.05) N=49 transgender female adolescents with a mean (SD) age of 13.6 years (p=NS in Schagen (2016).[148] Studies in transgender males: • GnRH analog therapy for puberty suppression over at least 3 months was associated with a statistically significant increase in fat percentage (p<0.05) and a decrease in lean mass percentage (p<0.05) among N=49 transgender female adolescents with a mean (SD) age of 13.6 years (p=NS) in Schagen (2016).[148] **Growth** *TGNB patients, pre-post: GnRH analogs therapy tended to decrease growth velocity in transgender males and females compared with age- and puberty-matched peers. CSHT tended to accelerate growth in both transgender males and females. No studies showed whether in individuals who received GnRH analogs would achieve their predicted final height after starting CSHT.* Studies transgender females:

[e] *Cyproterone is an antiandrogen not available in the US.*

[f] *Lynestrenol is an androgenic progesterone not available in the US.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.5. Systematic reviews addressing body changes (eg, endogenous hormones, growth, fat/lean/body mass, breast development, testicular volume) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	• GnRH analog therapy for puberty suppression over 2+ years was associated with decreases in height velocity (*p*=N/R) and height variance (*p*=N/R) among N=10transgender females (mean age not given) in Delemarre-van de Waal (2006).[422] • GnRH analog therapy for puberty suppression over a mean of 1.3 years was associated with a statistically significant increase in height (*p*<0.05), weight (*p*<0.05), and BMI (*p*<0.05), and a significant decrease in standardized height for trans female adolescents (*p*<0.05) as well as a nonsignificant change in BMI variance (*p*=NS) among N=15 transgender female adolescents with a mean (SD) age of 14.9 (1.9) years in Klink (2015).[140] • GnRH analog therapy for puberty suppression over at least 3 months was associated with a statistically significant increase in height (*p*<0.05), weight (*p*<0.05), BMI (*p*<0.05), and BMI variance (*p*<0.05), and a significant decrease in height variance (*p*<0.05) and among N=49 transgender female adolescents with a mean (SD) age of 13.6 years (*p*=NS) in Schagen (2016).[148] • GnRH analog therapy for puberty suppression over an unspecified duration was associated with an increase in height (*p*=N/R) and weight (*p*=N/R) among N=28 transgender female adolescents with a mean age of 13.5 years in Vlot (2017).[99] • Estrogen CSHT for an unspecified duration was associated with increases in height (*p*=N/R) among N=28 transgender female adolescents with a mean age at start of CSHT of 16.0 years in Vlot (2017).[99] • Estrogen in combination with cyproterone[g] over a mean of 1.3 years was associated with a statistically significant increase in height (*p*<0.05), a decrease in height relative to male peers (*p*<0.05), and an increase in BMI after 6-12 months (*p*<0.05), though BMI was still lower than that of Flemish male peers, among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Studies in transgender males: • GnRH analog therapy for puberty suppression over a mean of 1.5 years was associated with a statistically significant increase in height (*p*<0.05), weight (*p*<0.05),), and BMI (*p*<0.05), and a nonsignificant decrease in standardized height (*p*=NS) as well as a nonsignificant change in BMI variance (*p*=NS) for transgender male adolescents among N=19transgender male adolescents with a mean (SD) age of 15.0 (2.0) years in Klink (2015).[140] • GnRH analog therapy for puberty suppression over at least 3 months was associated with a statistically significant increase in height (*p*<0.05), weight (*p*<0.05), BMI (*p*<0.05), and BMI variance (*p*<0.05), and a nonsignificant decrease in standardized height (*p*=NS) among N=67 transgender male adolescents with a mean (SD) age of 14.2 years in Schagen (2016).[148] • GnRH analog therapy for puberty suppression over an unspecified duration was associated with an increase in height (*p*=N/R) and weight (*p*=N/R) among N=42 transgender male adolescents with a mean age of 15.1 years in Vlot (2017).[99] • Testosterone in combination with lynestrenol[h] over a mean of 0.95 years was associated with an increase in height (*p*=N/R) and statistically significant increases in weight (*p*<0.05) and BMI (*p*<0.05) among N=38 male adolescents with a mean age of 15.8 years in Tack (2016).[446] • Testosterone CSHT over an unspecified duration was associated with an increase in height (*p*=N/R) and weight (*p*=N/R) among N=42 transgender male adolescents with a mean age at the start of CSHT of 16.3 years in Vlot (2017).[99] • Testosterone over 1-3 months was associated with a nonsignificant increase in BMI (*p*=NS) among N=72 transgender male adolescents with a mean age of 16 years in Jarin (2017).[136] **Secondary sex characteristics** *TGNB patients, pre-post: GnRH analogs tended to decrease unwanted secondary sex characteristics in 3 out of 3 primary studies. Estrogen produced changes in transgender females that were consistent with the affirmed sex.* Testicular volume: • GnRH analog therapy for puberty suppression over 2+ years was associated with decreases in testicular volume (*p*=N/R) in N=10 transgender females (mean age not given) in Delemarre-van de Waal (2006).[422] • GnRH analog therapy for puberty suppression over a mean of 1.3 years was associated with a statistically significant decrease in testicular volume in N=15 transgender female adolescents with a mean (SD) age of 14.9 (1.9) years in Klink (2015).[140] Feminization: • Estrogen in combination with cyproterone[i] over a mean of 1.3 years was associated with a decreased need for shaving in 71.4% (*p*=N/R), breast development at Tanner stage B3 in 66.7% or B4 in 9.5% (*p*=N/R), breast tenderness in 57.1%, emotionality in 28.6%, and hot flashes in 14.3% among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Virilization

[g] *Cyproterone is an antiandrogen not available in the US.*

[h] *Lynestrenol is an androgenic progesterone not available in the US.*

[i] *Cyproterone is an antiandrogen not available in the US.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.5. Systematic reviews addressing body changes (eg, endogenous hormones, growth, fat/lean/body mass, breast development, testicular volume) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	• GnRH analog therapy for puberty suppression over at least 3 months was associated with a cessation of menses in N=67 transgender male adolescents with a mean (SD) age of 14.2 years in Schagen (2016).[148]
D'hoore (2022)[48] **Primary studies**: Body changes in TGNB adolescents were assessed in 6 studies out of 22 that addressed adolescent TGNB populations. **Authors conclusions**	**Body composition** *TGNB patients, pre-post: GnRH puberty suppression (1 primary study), progestins (2 primary studies), and cross-sex hormone treatments (3 primary studies) were effective in producing body changes consistent with the affirmed gender in 6 primary studies.* • GnRH analog monotherapy in trans girls (n = 49, median age = 13.6) and trans boys (n = 67, median age = 14.2) was associated with increased height, weight, fat mass, and BMI, and decreased lean body mass in the first year of treatment in Schagen (2016).[148] • Progestins in late-pubertal adolescents were associated with reduced endogenous hormone effects in Tack (2017).[150] • Progestins for a mean <12 months were associated with increased lean mass and grip strength among n = 44 Belgian trans boys. Similarly, progestins decreased lean mass and grip strength and increased fat mass in n = 21 trans girls in Tack (2018).[447] • Estradiol led to breast development within 3 months in 83% of trans girls (n = 22). At 3 years, 86% had Tanner breast stage 4-5. Hip circumference increased and waist-to-hip ratio decreased in Hannema (2017).[59] • In n = 121 trans boys and n = 71 trans girls who started GAHT at age 16 years, waist-to-hip ratio and body composition changed toward the affirmed sex by age 22. In trans girls, total body fat increased, and lean body mass and waist-to-hip ratio decreased. In trans boys, total body fat decreased, and lean body mass and waist-to-hip ratio increased in Klaver (2018).[83] • In n = 19 Colorado trans boys (mean age 17), 3+ months of testosterone resulted in body composition changes consistent with the affirmed gender, and no difference in insulin sensitivity versus cis controls. in n = 14 trans girls (mean age 16.3), 3+ months of estradiol also produced the desired body composition changes, but trans girls became more insulin resistant than cis boys in Nokoff (2020).[131]
Ludvigsson (2023)[49] **Primary studies:** Body changes were assessed in 13 primary studies out of 24 included primary studies that addressed TGNB adolescents. Authors drew conclusions about body changes based on only 4 included primary studies, omitting any results from 9. **Author conclusions** GnRH analogs were associated with increased weight and BMI as well as decreased lean body mass and growth velocity.	**Anthropometric measurements** *Weight and BMI: Authors concluded from 1 primary study that GnRH analogs were associated with increases in weight and BMI. Authors omitted from their conclusions 6 other included primary studies that also looked at weight and/or BMI. Authors did not draw separate conclusions for AFAB vs AMAB adolescents, who would be expected to respond differently to the treatments.* • GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.9 years were assessed for changes/differences in weight and BMI by age 22 years among N=192 TGNB adolescents (mean age 15 years at start of treatment) in Klaver (2018).[454] *Other included primary studies that assessed weight and/or BMI in patients who received GnRH analogs that were omitted by the authors when drawing their conclusions:* • GnRH analogs for 1+ years were assessed for changes/differences weight and BMI among N=70 TGNB adolescents (mean age 13 years at start of treatment) in Joseph (2019).[137] • GnRH analogs for 3-12 were assessed for changes/differences in weight and BMI among N=138 TGNB adolescents (mean age 14 years at start of treatment) in Schagen (2016).[148] • GnRH analogs for 10-14 months were assessed for changes/differences in BMI among N=92 TGNB adolescents (mean age 11.5 years at start of treatment) in Schulmeister (2022).[j95] • GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.5 years were assessed for changes/differences in BMI by age 22 years among N=192 TGNB adolescents (mean age 14.9 years at start of treatment) in Klaver (2020).[139] • GnRH analogs for 2-4 months followed by CSHT for 2-6 months were assessed for changes/differences in BMI among N=48 TGNB adolescents (mean age 14 years at start of treatment) in Perl (2020).[144] • GnRH analogs followed by CSHT were assessed for changes/differences in BMI among N=116 TGNB adolescents (ages 10+ years at start of treatment) after an average follow-up for 2 years in Jarin (2017).[136] **Body composition** *Lean body mass: Authors concluded from 3 primary studies that GnRH analogs were associated with decreased lean body mass. Authors did not report findings separately for AFAB and AMAB youth, who would be expected to respond differently to treatments. Authors did not draw conclusions about other measures of body composition, such as fat mass and WHR, which were addressed in X of their included primary studies.* • GnRH analogs for 3-12 were assessed for changes/differences in lean mass among N=138 TGNB adolescents (mean age 14 years at start of treatment) in Schagen (2016).[148] • GnRH analogs for 0.5-5.8 years were assessed for changes/differences in % lean mass among N=17 TGNB adolescents (mean age 12 years at start of treatment) in Nokoff (2020).[k131]

[j] *Publication year is erroneously listed as 2021 in Ludvigsson's results tables, but actual publication year is 2022.*
[k] *Publication year is erroneously listed as 2021 in Ludvigsson tables, but actual publication year is 2020.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.5. Systematic reviews addressing body changes (eg, endogenous hormones, growth, fat/lean/body mass, breast development, testicular volume) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	• GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.9 years were assessed for changes/differences in total body % by age 22 years among N=192 TGNB adolescents (mean age 15 years at start of treatment) in Klaver (2018).[454] *Other body composition measures that were addressed in 2 included primary studies were ignored by review authors when they drew their conclusions:* • GnRH analogs for 0.5-5.8 years were assessed for changes/differences in insulin, glucose, HbA1c, HOMA-IR, body fat, % lean mass among N=17 TGNB adolescents (mean age 12 years at start of treatment) in Nokoff (2020). [l131] • GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.9 years were assessed for changes/differences in weight, BMI, total body %, WHR by age 22 years among N=192 TGNB adolescents (mean age 15 years at start of treatment) in Klaver (2018).[454] **Growth velocity** *Authors concluded from 1 primary study that GnRH analogs were associated with reduced growth velocity.* • GnRH analogs for 10-14 months were assessed for changes/differences in height velocity among N=92 TGNB adolescents (mean age 11.5 years at start of treatment) in Schulmeister (2022). [m95]
Mahfouda (2019)[50] **Primary studies**: Body changes were examined in 1 out of 12 primary studies that addressed TGNB adolescents.	**Body composition changes** *TGNB patients, pre-post: 1 primary study found GnRH analogs and subsequent CSHT were associated with changes towards the affirmed gender. .* • Puberty suppression with GnRH analogs and CSHT were associated with body changes towards the affirmed gender by age 22 years among N=192 TGNB patients (mean ages at start of treatment were 15.3 years for transgender male sand 14.5 years for transgender females); this was characterized by increased fat mass, decreased lean mass, and decreased waist-to-hip ratio in transgender males, and decreased fat mass, increased lean mass, and increased waist-to-hip ratio in transgender females in Klaver (2018).[83]
Ramos (2021)[51] Primary studies: Body changes were assessed in 2 primary studies that assessed it out of 3 studies/4 publications that addressed adolescent TGNB patients.	**Body composition changes:** *TGNB patients, pre-post: One primary study found all body composition changes were more like the affirmed gender in transgender women who underwent GnRH analog therapy followed by CSHT. Transgender men experienced increases in mass and waist to hip ration, but body composition was more like that of cisgender women than cisgender men. Earlier initiation of therapy improved outcomes in transgender men.* Studies in transgender women • GnRH analog puberty suppression followed by CSHT given during adolescence was associated with an increase in body fat and a decline in lean mass and waist-hip ratio among N=71 transgender women assessed at age 22 years, resulting in a body composition that was similar to that of cisgender women in Klaver (2018).[83] Studies in transgender men • GnRH analog puberty suppression followed by CSHT given during adolescence was associated with increases in lean mass and waist-hip ratio among N=121 transgender men, but body composition at age 22 was more similar to that of cisgender women than cisgender men. In a subset of transgender men who initiated treatment earlier, body composition at age 22 was more similar to that of cisgender men in Klaver (2018).[83] **Endogenous hormone changes:** *TGNB patients, pre-post: One primary study found endogenous hormone changes during GnRH analog therapy along with adequate puberty suppression.* • GnRH analog puberty suppression for between 3 months and 3 years was associated with endogenous gonadotropin decreases in the first 3 months of treatment, after which there were no more changes. Testosterone and estradiol decreased after 3 months of treatment, with no signs of insufficient puberty suppression among TGNB patients in Schagen (2016).[148]
Rew (2021)[52] **Primary studies:** Body changes were examined in 3 primary studies out of 9	**Anthropometric measurements** *Case findings: Triptorelin at age 13.7 years followed by testosterone and subsequent gonadectomy were associated with normal anthropometric measurements at 35 years in 1 case report.* • Triptorelin at age 13.7 years, testosterone at 18.6 years, and subsequent gonadectomy were associated normal anthropometric measurements at age 35 years in N=1 AFAB patient in Cohen-Kettenis (2011).[168] **Body composition**

[l] *Publication year is erroneously listed as 2021 in Ludvigsson tables, but actual publication year is 2020.*
[m] *Publication year is erroneously listed as 2021 in Ludvigsson's results tables, but actual publication year is 2022.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.5. Systematic reviews addressing body changes (eg, endogenous hormones, growth, fat/lean/body mass, breast development, testicular volume) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
addressing TGNB adolescents.	*TGNB patients vs cisgender peers: GnRH analogs and subsequent CSHT were associated with changes consistent with the affirmed gender in 1 primary study.* • GnRH analogs followed by CSHT were associated with higher body fat in MTF and lower body fat in FTM patients compared to cisgender peers among N=192 TGNB adolescents who started puberty suppression before age 16 years in Klaver (2018).[83] *TGNB patients, pre-post: Triptorelin was associated with decreased average lean mass and increased average fat mass in 1 primary study, but review authors did not report findings separately for AMAB and AFAB youth, which makes these findings difficult to interpret.* • Triptorelin was associated with decreased lean mass and increased fat mass among N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148] **Endogenous hormone levels** *Case findings: 21 years after starting treatment, a patient who had received triptorelin followed by subsequent testosterone and gonadectomy had elevated endogenous hormone levels in 1 primary study.* • Triptorelin at age 13.7 years, testosterone at 18.6 years, and subsequent gonadectomy were associated with elevated FSHS and LH at age 35 years in N=1 AFAB patient in Cohen-Kettenis (2011).[168] *TGNB patients, pre-post: Triptorelin suppressed endogenous hormone levels in 1 primary study.* • Triptorelin was associated with suppressed gonadotropin and sex steroid levels among N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148] **Growth** *TGNB patients, pre-post: Triptorelin was associated with slower growth in 1 primary study, but findings were not summarized separately for AMAB and AFAB youth.* • Triptorelin was associated with decreased height velocity among N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148] **Menstruation** *TGNB patients, pre-post: Triptorelin was associated with cessation of menses in 1 primary study.* • Triptorelin was associated with cessation of menses volume in the FTM subset of N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148] **Testicular volume** *TGNB patients, pre-post: Triptorelin was associated with decreased testicular volume in 1 primary study.* • Triptorelin was associated with decreased testicular volume in the MTF subset of N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148]

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.6. Systematic reviews examining bone health (eg, bone density, bone turnover measures) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
Chew (2018)[47] **Primary studies**: Bone changes were assessed in 3 primary studies out of 11 that addressed TGNB adolescents. **Authors conclusions** GnRH analogs resulted in no changes in carbohydrate or lipid metabolism or cholesterol levels. It may affect LFTs. Progestins adversely affect lipid profile, but have no effect on glucose metabolism. LFTs resulted in non-clinically-significant changes. Cyproterone reduced triglycerides but did not affect other lipids; it had no effect on LFTs. Estrogen and testosterone had no effect on carbohydrate or lipid metabolism or LFTs.	**BMD** *TGNB patients, pre-post: GnRH analog therapy was associated with no change or nonsignificant decreases in BMD among transgender females in 2 out of 2 primary studies. In transgender males, GnRH analog therapy was associated with a mix of significant and nonsignificant decreases in 2 out of 2 primary studies. CSHT was associated with statistically increases in BMD among both transgender males and females in 1 out of 1 primary study.* Studies in transgender females • GnRH analog therapy for puberty suppression over 2+ years was associated with no change in BMD values (p=N/R), and a decrease in BMD z scores (p=N/R) among N=10 transgender females (mean age not given) in Delemarre-van de Waal (2006).[422] • GnRH analog therapy for puberty suppression over a mean of 1.3 years was associated with no significant change in BMD value (p=NS) and a nonsignificant decrease in BMD z score (p=NS) at the lumbar spine among N=15 transgender female adolescents with a mean (SD) age of 14.9 (1.9) years; it was also associated with nonsignificant decreases in both BMD values and z scores at the nondominant femur (p=NS) in Klink (2015).[140] • Estrogen CSHT for an unspecified duration was associated statistically significant increases in BMD values (p<0.05) and BMD z scores (p<0.05) at the lumbar spine among N=28 transgender female adolescents with a mean age at start of CSHT of 16.0 years; it was also associated with no significant changes in hip bone density (p=N/R) in Vlot (2017).[99] Studies in transgender males • GnRH analog therapy for puberty suppression over a mean of 1.5 years was associated with a nonsignificant decrease in BMD values (p=NS) and a statistically significant decrease (p<0.05) in z score at the lumbar spine among transgender male adolescents among N=19 transgender male adolescents with a mean (SD) age of 15.0 (2.0) years; it was also associated with nonsignificant decreases both BMD values and z scores and the nondominant femur (p=NS) in Klink (2015).[140] • GnRH analog therapy for puberty suppression over an unspecified duration was associated with statistically significant decreases in BMD values (p<0.05) and z scores (p<0.05) at the hip for older bone age among N=42 transgender male adolescents with a mean age of 15.1 years; it was also associated with statistically significant decreases in BMD values (p<0.05) and z scores (p<0.05) at the lumbar spine for older bone age, and statistically significant decreases in BMD values (p<0.05) and z scores (p<0.05) at the lumbar spine for younger bone age in Vlot (2017).[99] • Testosterone CSHT over an unspecified duration was associated with statistically significant increases in bone density values (p<0.05) and z scores (p<0.05) at the hip and in bone density values (p<0.05) and z scores (p<0.05) at the lumbar spine among N=42 transgender male adolescents with a mean age at the start of CSHT of 16.3 years in Vlot (2017).[99]
D'hoore (2022)[48] **Primary studies**: Bone health outcomes in TGNB adolescents were assessed in 6 studies out of 22 that addressed TGNB populations.	**Bone health:** *TNGB patients, pre-post: GnRH analog therapy was associated with no (2 studies) or nonsignificant (4 studies) decreases in bone growth; GAHT was associated with significant increases in 3 primary studies, but 1 study showed bone density at age 22 was nonsignificantly lower compared to pretreatment levels.* *Primary studies* • GnRH analog monotherapy was associated with no change in 12-month LS BMD among n = 44 London transgender adolescents with persistent, severe GD (ages 12-15-years). At 24 months, LS bone mineral content and BMD were higher versus baseline. No change from baseline in TH BMD at 34 and 36 months in Carmichael (2021).[73] • GnRH analog monotherapy showed that BMAD stabilized or showed a nonsignificant decrease in n = 121 transgender adolescents (51 trans girls and 70 trans boys), but Z-scores (and bone markers) decreased in all groups. GnRH analog/GAHT combination therapy was associated with significant BMAD increases over 3 years, but Z-scores remained lower in trans girls and normalized in trans boys in Schagen (2020).[94] • Cyproterone[n] monotherapy was associated with limited normal bone expansion and pubertal bone mass accrual at the LS during a mean of 10.6 months (range 5–31) in n = 21 trans girls in Tack (2018).[447]

[n] *Cyproterone is an antiandrogen not available in the US.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.6. Systematic reviews examining bone health (eg, bone density, bone turnover measures) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	• GnRH analog monotherapy was associated with nonsignificant Z-score decreases (−0.8 to −1.4) among n = 15 trans girls (median age 14.9); during CSHT, absolute LS BMD increased in these patients, but mean *Z*-score at age 22 was nonsignificantly decreased compared to pre-treatment. GnRH analog monotherapy was associated with nonsignificant decreases in both LS and FN BMD (Z-scores +0.2 to −0.3) among n = 19 trans boys (median age 15.0); CSHT showed increases by age 22, but LS BMD Z-scores were nonsignificantly lower compared pre-treatment levels. Notably, the pretreatment LS BMD Z-score in trans women was below the population mean at the start of the treatment in Klink (2015).[140] • 24 months of GnRH analog monotherapy was associated with decreased bone turnover markers (P1NP and 1CTP) in younger transgender adolescents (<14 years) and decreased LS BMAD Z- scores. Subsequent CSHT was associated with further bone turnover markers decreased further in all groups except for trans boys >14 years old, but the BMAD increased and Z-scores returned to normal, especially at the LS among n = 56 Amsterdam transgender adolescents (34 transmasculine [median age 15.1] and 22 transfeminine individuals [median age 13.5]) in Vlot (2017).[99] *Between-TGNB group comparisons: Earlier initiation of GnRH puberty suppression was associated with bone changes that were more consistent with the affirmed gender in 1 primary study.* • In 2+ years of GnRH and subsequent CSHT, earlier (vs later) treatment initiation was associated with measures of bone growth (sub-periosteal width and endocortical diameter) that were more similar to the affirmed gender; participants who started treatment later remained within the reference curve of the natal sex among n = 322 transgender adolescents (106 trans girls and 216 trans boys) in van der Loos (2021).[69] ○ Similarly, pretreatment bone density in n = 62 trans boys was also lower than the population mean in Stoffers (2019).[149] Authors attributed it to lower participation in sports activities among trans girls, which negatively impacted mechanical loading, and lower vitamin D levels in the sample.
Ludvigsson (2023)[49] **Primary studies:** Bone health was assessed in 9 primary studies out of 24 included studies addressing TGNB adolescents. Authors drew conclusions about bone effects based on only 6 primary studies, omitting any results from 3. **Authors conclusions** Bone density remains unchanged during puberty blocking, but is decreased over time relative to cisgender peers. Bone density after CSHT is recovered in the hip but not at the LS.	**Bone mineral density** *Puberty blockers: Authors concluded from 5 primary studies that puberty suppression was associated with no change in bone density. Patients in 4 out of the 5 primary studies also received CSHT, which is expected to build bone more rapidly in AMAB patients (versus AFAB); authors did not draw separate conclusions by sex. Authors omitted from their conclusions 2 included primary studies that also examined BMD.* • GnRH analogs for 1.5-4 years followed by CSHT for 3 years were assessed for changes/differences in BMAD among N=127 TGNB adolescents (mean age 14 at start of treatment) in Schagen (2020).[94] • GnRH analogs for 0.25-8 years followed by CSHT for up to 8 years were assessed for changes/differences BMD, BMAD among N=34 adolescents by age 22 (mean age 15 years at start of treatment) in Klink (2015).[140] • GnRH analogs for 1+ years followed by CSHT were assessed for changes/differences in BMAD among N=213 TGNB adolescents (mean age 14 years at start of treatment) in Vlot (2017).[99] • GnRH analogs for 1+ years were assessed for changes/differences BMD and BMAD among N=70 TGNB adolescents (mean age 13 years at start of treatment) in Joseph (2019).[137] • GnRH analogs for 3 months-3 years followed by CSHT for 5 months-3 years were assessed for changes/differences in BMD among N=64 transgender males (mean age 16 years at start of treatment) in Stoffers (2019).[149] *Other primary studies that also evaluated BMD or BMAD* • GnRH analogs for 0.5-2 years followed by CSHT were assessed for changes/differences in BMD, BMAD, and Z-score (hip, LS) among N=193 TGNB adolescents (mean age 15 years at start of treatment) in Navabi (2021).[92] • GnRH analogs for 2 months were assessed for changes/differences in BMD, BMAD, and Z-score (hip, LS) among N=95 TGNB adolescents (mean age 11.5 years at start of treatment) in Lee (2020).[85] **BMD Z-scores (ie, relative to reference mean)** *Puberty blockers: Authors concluded from 5 primary studies that puberty suppression was associated with decreases in bone density relative to the reference population. Patients in 4 out of the 5 primary studies also received CSHT, which is expected to build bone more rapidly in AMAB patients (versus AFAB); authors did not draw separate conclusions by sex. Authors omitted from their conclusions 3 other studies that examined Z-scores in patients who had received GnRH analogs.* • GnRH analogs for 0.25-8 years followed by CSHT for up to 8 years were assessed for changes/differences in Z-score among N=34 adolescents by age 22 (mean age 15 years at start of treatment) in Klink (2015).[140] • GnRH analogs for 1+ years followed by CSHT were assessed for changes/differences in Z-score among N=213 TGNB adolescents (mean age 14 years at start of treatment) in Vlot (2017).[99] • GnRH analogs for 1+ years were assessed for changes/differences in Z-score (hip, spine) among N=70 TGNB adolescents (mean age 13 years at start of treatment) in Joseph (2019).[137] • GnRH analogs for 3 months-3 years followed by CSHT for 5 months-3 years were assessed for changes/differences in Z-score (FN, LS) among N=64 transgender males (mean age 16 years at start of treatment) in Stoffers (2019).[149] • GnRH analogs for 0.5-2 years followed by CSHT were assessed for changes/differences in Z-score (hip, LS) among N=193 TGNB adolescents (mean age 15 years at start of treatment) in Navabi (2021).[92] *Puberty blockers: 3 others of their included primary studies that also examined BMD Z-score changes associated with GnRH analogs were omitted from their conclusions.* • GnRH analogs for 1.5-4 years followed by CSHT for 3 years were assessed for changes/differences in aBMD and Z-score (hip) among N=127 TGNB adolescents (mean age 14 at start of treatment) in Schagen (2020).[94] • GnRH analogs for 2 months were assessed for changes/differences in BMD, aBMAD, and Z-score (hip, LS) among N=95 TGNB adolescents (mean age 11.5 years at start of treatment) in Lee (2020).[85]

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.6. Systematic reviews examining bone health (eg, bone density, bone turnover measures) associated with GD treatments in TGNB children/adolescents

First author (Year) **Primary studies**	**Findings**
	• GnRH analogs for 10-14 months were assessed for changes/differences in height velocity, BMI, Z-score N=92 TGNB adolescents (mean age 11.5 years at start of treatment) in Schulmeister (2022). [o][95]
	CSHT: Authors concluded from 3 primary studies that CSHT was associated with recovered bone density at the hip but not the LS, according to Z-scores. Authors did not draw conclusions separately by sex. Authors omitted 3 other included studies that examined Z-scores that examined Z-scores in patients who had received CSHT.
	• GnRH analogs for 0.25-8 years followed by CSHT for up to 8 years were assessed for changes/differences in Z-score among N=34 adolescents by age 22 (mean age 15 years at start of treatment) in Klink (2015).[140] • GnRH analogs for 3 months-3 years followed by CSHT for 5 months-3 years were assessed for changes/differences in Z-score (FN, LS) among N=64 transgender males (mean age 16 years at start of treatment) in Stoffers (2019).[149] • GnRH analogs for 0.5-2 years followed by CSHT were assessed for changes/differences in Z-score (hip, LS) among N=193 TGNB adolescents (mean age 15 years at start of treatment) in Navabi (2021).[92]
	CSHT: 3 others of their included primary studies also examined BMD Z-score changes associated with CSHT were omitted from their conclusions.
	• GnRH analogs for 1+ years followed by CSHT were assessed for changes/differences in height, BMAD, Z-score (hip, LS), bone markers (P1NP, OC, ICTP) among N=213 TGNB adolescents (mean age 14 years at start of treatment) in Vlot (2017).[99] • GnRH analogs for 0.5-2 years followed by CSHT were assessed for changes/differences in BMD, aBMAD, and Z-score (hip, LS) among N=193 TGNB adolescents (mean age 15 years at start of treatment) in Navabi (2021).[92] • GnRH analogs for 1.5-4 years followed by CSHT for 3 years were assessed for changes/differences in aBMD and Z-score (hip) among N=127 TGNB adolescents (mean age 14 at start of treatment) in Schagen (2020).[94]
Mahfouda (2019)[50] **Primary studies**: Bone health was examined in 2 out of 12 primary studies that addressed TGNB adolescents.	**Bone health** *TGNB patients, pre-post: 1 primary study found increases in bone density associated with CSHT; another found average BMD was below pretreatment potential after GnRH analogs and subsequent CSHT; in the latter study, review authors did not report findings separately for transgender males and transgender females, so it is difficult to interpret this finding.* • Puberty suppression with GnRH analogs and subsequent CSHT were associated with changes in BMD among N=34 TGNB adolescents (mean ages at start of treatment 15.0 years for transgender males and 14.9 years for transgender females); this was characterized by either delayed attainment of peak bone mass, or by attenuation of peak bone mass in Klink (2015).[140] • CSHT was associated with increases in BMAD and BMAD Z-scores at the LS, and decreases in bone turnover markers at 24 months among N=70 TGNB adolescents (mean age at baseline 13.5 years for transgender females and 15.1 years for transgender males) in Vlot (2017).[99]
Ramos (2021)[51] **Primary studies**: Bone health was assessed in 3 primary studies out of 3 reviewed studies/4 reviewed publications that addressed adolescent TGNB patients.	**Bone health:** *Transgender women versus cisgender men: One primary study showed no significant difference in BMD at age 22 after GnRH analog puberty suppression and CSHT.* • GnRH analog puberty suppression with triptorelin in early adolescence followed by CSHT in later adolescence were associated with no effect on BMD changes in N=16 transgender women vs N=19 cisgender men at age 22 years in Klink (2013).[433] *TGNB patients, pre-post: 1 primary study showed a decline in BMD associated with GnRH analogs followed by CSHT in both TGNB males and females; another primary showed declining bone turnover markers during GnRH analog therapy with no change in BMAD, which was followed by a return to normal after initiating CSHT.* • GnRH analog puberty suppression with triptorelin in early adolescence followed by CSHT was associated with a decline in Z-scores from - 0.8 to - 1.4 among transgender women and a decline from 0.2 to - 0.3 in transgender men. Authors concluded that BMD was below pre-treatment potential at age 22 years in both groups in Klink (2015).[140] • GnRH analog therapy was associated with a decrease in bone turnover markers among N=28 transgender women and N=42 transgender men, with no change in BMAD; subsequent CSHT was associated with increased BMAD and Z-scores among both groups in Vlot (2017).[99]
Rew (2021)[52] **Primary studies:** Bone health was examined in 1 primary study out of 9 that addressed TGNB adolescents.	**Bone turnover markers** *TGNB patients, pre-post: Triptorelin and subsequent CSHT were associated with decreases in bone turnover markers in 1 primary study.* • Triptorelin puberty suppression followed by CSHT with testosterone or estradiol was associated with decreases in ICTP and P1NP among N=70 TGNB adolescents in Vlot (2017).[99] **Bone mineral density** *TGNB patients, pre-post: Triptorelin and subsequent CSHT were associated with decreases in LS BMAD Z scores in 1 primary study; findings were not separated out for AMAB vs AFAB youth.* • Triptorelin puberty suppression followed by CSHT with testosterone or estradiol was associated with decreases in LS BMAD Z scores among N=70 TGNB adolescents; pretreatment Z scores in most patients had not fully recovered after 24 months on CSHT in Vlot (2017).[99]

[o] *Publication year is erroneously listed as 2021 in Ludvigsson's results tables, but actual publication year is 2022.*

Table abbreviations: GD, gender dysphoria; QOL, quality of life; TGNB; transgender, nonbinary, or other gender diverse; GnRH, gonadotropin-releasing hormone; CSHT, cross-sex hormone therapy (ie, testosterone in transgender males, estrogen in transgender females; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; CBCL, Child Behavior Checklist; YSR, Youth Self Report; NS, nonsignificant; SD, standard deviation; NR, not reported; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;

Return to TOC

Table I.E.7. Systematic reviews addressing cardiovascular/metabolic risk factors (eg, thrombotic/thromboembolic, insulin sensitivity, blood pressure, cholesterol, liver, and kidney outcomes) in TGNB adolescents who receive GnRH analogs for puberty suppression

First author (Year) **Primary studies**	**Findings**
Chew (2018)[47] **Primary studies:** Cardiovascular and metabolic outcomes were assessed in 3 out of 11 primary studies that addressed TGNB adolescents.	**Cholesterol** *TNGB patients, pre-post: Estrogen CSHT was associated with no changes in cholesterol and TG levels in transgender females in 1 out of 1 primary study. Testosterone was associated with no significant changes in TC, LDL, or TG in 2 out of 2 primary studies, but HDL was significantly decrease in 1 out of 2 primary studies.* Studies in transgender females • Estrogen in combination with cyproterone[p] over a mean of 1.3 years was associated with no significant changes in TC (*p*=NS), LDL (*p*=NS), HDL (*p*=NS), or TG (*p*=NS) levels among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Studies in transgender males • Testosterone in combination with lynestrenol[q] over a mean of 0.95 years was associated with no significant changes in TC (*p*=NS), TG (*p*=NS), HDL (*p*=NS), or LDL (*p*=NS) among N=38 transgender male adolescents with a mean age of 15.8 years in Tack (2016).[446] • Testosterone over 1-3 months was associated with no significant changes in TC (*p*=NS), LDL (*p*=NS), TG (*p*=NS), TG-to-HDL ratio (*p*=NS), and a statistically significant decrease in HDL (*p*=<0.05) among N=72 transgender male adolescents with a mean age of 16 years in Jarin (2017).[136] **Liver and kidney effects** *TGNB patients, pre-post:* Studies in transgender females • GnRH analog therapy for puberty suppression over at least 3 months was associated no significant changes in GGT (*p*=NS), AST (*p*=NS), or ALT (*p*=NS), and a statistically significant decrease in ALP (*p*<0.05) among N=49 transgender female adolescents with a mean (SD) age of 13.6 years (*p*=NS) in Schagen (2016).[148] • Estrogen in combination with cyproterone[r] over a mean of 1.3 years was associated with no significant changes in creatinine (*p*=NS), AST (*p*=NS), or ALT (*p*=NS) among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Studies in transgender males • GnRH analog therapy for puberty suppression over at least 3 months was associated with a statistically significant decrease in creatinine (*p*=<0.05), no significant change in GGT (*p*=NS), AST (*p*=NS), or ALT (*p*=NS), and a statistically significant decrease in AP (*p*<0.05) among N=67 transgender male adolescents with a mean (SD) age of 14.2 years in Schagen (2016).[148] • Testosterone in combination with lynestrenol[s] over a mean of 0.95 years was associated with statistically significant increases in creatinine (*p*<0.05) and in ALT (*p*<0.05) and AST (*p*<0.05), though both of the latter remained in the normal range for males, among N=38 transgender male adolescents with a mean age of 15.8 years in Tack (2016).[446] • Testosterone over 1-3 months was associated with no significant changes in creatinine (*p*=NS), prolactin (*p*=NS), or AST (*p*=NS), and a nonsignificant decrease in ALT (*p*=<0.05), which returned to baseline after 4-6 months, among N=72 transgender male adolescents with a mean age of 16 years in Jarin (2017).[136] **Thrombotic changes:** *TGNB patients, pre-post:* Studies in transgender females: • Estrogen in combination with cyproterone[t] over a mean of 1.3 years was associated with no significant changes in Hb (*p*=NS) or HCT (*p*=NS) among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150]

[p] *Cyproterone is an antiandrogen not available in the US.*
[q] *Lynestrenol is an androgenic progesterone not available in the US.*
[r] *Cyproterone is an antiandrogen not available in the US.*
[s] *Lynestrenol is an androgenic progesterone not available in the US.*
[t] *Cyproterone is an antiandrogen not available in the US.*

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.E.7. Systematic reviews addressing cardiovascular/metabolic risk factors (eg, thrombotic/thromboembolic, insulin sensitivity, blood pressure, cholesterol, liver, and kidney outcomes) in TGNB adolescents who receive GnRH analogs for puberty suppression

First author (Year) **Primary studies**	**Findings**
	Studies in transgender males: • Testosterone in combination with lynestrenol[u] over a mean of 0.95 years was associated with statistically significant increases in HB (p<0.05) and HCT levels among N=38 transgender male adolescents with a mean age of 15.8 years in Tack (2016).[446] • Testosterone over 1-3 months was associated with statistically significant increases in Hb (p<0.05) and HCT (p<0.05) among N=72 transgender male adolescents with a mean age of 16 years in Jarin (2017).[136] **Thyroid changes:** Studies in transgender females: • Estrogen in combination with cyproterone[v] over a mean of 1.3 years was associated with no significant changes in thyrotropin (p=NS) and free thyroxin (p=NS), and a statistically significant decrease in prolactin (p=NS) among N=27 Danish transgender female adolescents with a mean age of 16.5 years at the start of GnRH analog treatment and 17.6 years at the start of CSHT in Tack (2017).[150] Studies in transgender males: • Testosterone in combination with lynestrenol[w] over a mean of 0.95 years was associated with a nonsignificant decrease thyroxine (p=NS) and a statistically significant decrease in fT4 (p<0.05) among N=38 transgender male adolescents with a mean age of 15.8 years in Tack (2016).[446]
D'hoore (2022)[48] [x] **Primary studies**: Cardiovascular risk factor outcomes were assessed in 4 out of 22 studies that addressed TGNB populations.	**Cardiovascular and thromboembolic safety** *TGNB patients, pre-post: CSHT (ie, oral estrogen) was associated with no BP changes in 2 primary studies. Transmasculine individuals in 1 primary study who received androgenic progestins with or without testosterone experienced a significant decrease in HDL; the lipid profile was worse in those who received androgenic progestin monotherapy versus those who received progestin/testosterone combination therapy. Transmasculine adolescents who received testosterone also experienced significant increases in hemoglobin/hematocrit in 1 primary study. Transfeminine individuals who received estrogen experienced no changes in HDL, hemoglobin, or hematocrit in 1 primary study.* • 12+ months of oral estrogen in n = 28 transfeminine individuals was associated with no significant changes in blood pressure in Hannema (2017).[59] • No changes in blood pressure were observed with GnRH analog therapy in n = 19 transfeminine individuals, or with estrogen in n = 15 who continued with estrogen treatment in Perl (2020)[144] • GAHT was associated with a significant decrease in mean HDL-cholesterol level (from 50.2 to 45.0 mg/dl) in n = 72 transmasculine adolescents (mean age 16); in the subset who were received androgenic progestin monotherapy (ie, lynestrenol[y]), the lipid profile was significantly more unfavorable compared to those who received progestin/testosterone combination therapy. Testosterone (with or without androgenic progestins) was also associated with significant increases in hemoglobin (from 13.5 to 15.0 g/dl) and hematocrit (from 39.4% to 44.5%). No HDL or hemoglobin/hematocrit changes were associated with GAHT in n = 44 transfeminine individuals in Jarin (2017).[136] *TGNB patients vs cisgender peers: GnRH analogs were associated with improvements in metabolic and CV risk factors that were similar to or more favorable than that of cisgender peers in 1 primary study.* • Pretreatment obesity prevalence was 9.9% among n = 81 trans girls 6.6% in and n = 121 trans boys, compared to 2.2% and 3.0% in cis girls and boys, respectively. GnRH analog therapy started at a mean age of 15 years was associated with changes in BMI, SBP/DPB, glucose, HOMA-IR, and lipid values that were similar to or more favorable than that of cisgender peers by age 22 in Klaver (2020).[139]
Ludvigsson (2023)[49] **Primary studies:** Cardiovascular and metabolic changes were assessed in 7 primary studies out of 24 included by review	**Metabolic measures** *Authors concluded from 2 primary studies that GnRH analogs were associated with no changes in serum lipids or blood pressure, insulin level is increased in MTF patients, and there was decreased insulin sensitivity* • GnRH analogs for 0.5-5.8 years were assessed for changes/differences in insulin, glucose, HbA1c, HOMA-IR, body fat, % lean mass among N=17 TGNB adolescents (mean age 12 years at start of treatment) in Nokoff (2020). [z][131] • GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.5 years were assessed for changes/differences in BMI, SDP, DBP, glucose, insulin, HOMA-IR, cholesterol, and triglycerides by age 22 years among N=192 TGNB adolescents (mean age 14.9 years at start of treatment) in Klaver (2020).[139] *Other included primary studies that examined lipids, blood pressure, insulin levels, and/or insulin sensitivity associated with GnRH analogs*

[u] *Lynestrenol is an androgenic progesterone not available in the US.*

[v] *Cyproterone is an antiandrogen not available in the US.*

[w] *Lynestrenol is an androgenic progesterone not available in the US.*

[x] *D'hoore looked for but did not find studies addressing cancer risk in TGNB adolescents.*

[y] *Lynestrenol is an androgenic progesterone not available in the US.*

[z] *Publication year is erroneously listed as 2021 in Ludvigsson tables, but actual publication year is 2020.*

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.E.7. Systematic reviews addressing cardiovascular/metabolic risk factors (eg, thrombotic/thromboembolic, insulin sensitivity, blood pressure, cholesterol, liver, and kidney outcomes) in TGNB adolescents who receive GnRH analogs for puberty suppression

First author (Year) **Primary studies**	**Findings**
authors. Review authors based their conclusions about psychosocial outcomes on only 3 primary studies, omitting any results from 4. **Author conclusions** GnRH analogs were associated with no change in lipids or blood pressure, increased insulin levels in MTF patients, and decreased insulin sensitivity. They are also associated with a change in blood pressure (direction unspecified).	• GnRH analogs for 3 months-3 years followed by CSHT for 5 months-3 years were assessed for changes/differences in height, BP, BMD, Z-score (FN, LS) among N=64 transgender males (mean age 16 years at start of treatment) in Stoffers (2019).[149] • GnRH analogs for 2-4 months followed by CSHT for 2-6 months were assessed for changes/differences in BMI and BP among N=48 TGNB adolescents (mean age 14 years at start of treatment) in Perl (2020).[144] • GnRH analogs followed by CSHT were assessed for changes/differences in BMI, BP, hematocrit, Hb, and cholesterol among N=116 TGNB adolescents (ages 10+ years at start of treatment) after an average follow-up for 2 years in Jarin (2017).[136] **Blood pressure** *Authors concluded from 1 primary study that GnRH analogs were associated with changes in BP.* • GnRH analogs for 2-4 months followed by CSHT for 2-6 months were assessed for changes/differences in BP among N=48 TGNB adolescents (mean age 14 years at start of treatment) in Perl (2020).[144] *Other included primary studies that also examined changes in BP associated with GnRH analogs* • GnRH analogs for 3 months-3 years followed by CSHT for 5 months-3 years were assessed for changes/differences in height, BP, BMD, Z-score (FN, LS) among N=64 transgender males (mean age 16 years at start of treatment) in Stoffers (2019).[149] • GnRH analogs for a mean of 1.5 years followed by CSHT for a mean of 2.5 years were assessed for changes/differences in BMI, SDP, DBP, glucose, insulin, HOMA-IR, cholesterol, and triglycerides by age 22 years among N=192 TGNB adolescents (mean age 14.9 years at start of treatment) in Klaver (2020).[139] • GnRH analogs followed by CSHT were assessed for changes/differences in BMI, BP, hematocrit, Hb, and cholesterol among N=116 TGNB adolescents (ages 10+ years at start of treatment) after an average follow-up for 2 years in Jarin (2017).[136]
Mahfouda (2019)[50] **Primary studies**: CV risk factors and metabolic outcomes were examined in 5 out of 12 primary studies that addressed TGNB adolescents.	**Hematocrit** *TGNB patients, pre-post:* • Unspecified GAHT was associated with significant changes in hematocrit in N=14 transgender males but not in N=6 transgender females; no other metabolic factors were affected in Trotman (2014).[449] **Metabolic parameters** *TGNB patients, pre-post:* • Puberty suppression with lynestrenol[aa] followed by testosterone CSHT was associated with no major changes in unspecified liver enzymes among N=70 transgender males (mean age 15.8 years) in Tack (2016).[446] • CSHT was associated with safe short-term metabolic parameter levels in N=116 TGNB adolescents (mean age 16 years for transgender males and 18 years for transgender females) in Jarin (2017).[136] • Puberty suppression with cyproterone[bb] followed by estradiol CSHT was associated with transient increases in ALT and AST that did not require treatment discontinuation among N=27 transgender females (mean age 16.5 years at start of therapy) in Tack (2017).[150] • GAHT (including GnRH analogs and subsequent CSHT) for 2 years was associated with no clinically significant changes in "laboratory parameters" among N=101 TGNB adolescents (mean age at start of treatment 18 years) in Olson-Kennedy (2018).[143] **Cardiovascular parameters** • CSHT was associated with safe short-term CV parameter levels in N=116 TGNB adolescents (mean age 16 years for transgender males and 18 years for transgender females) in Jarin (2017).[136]
Ramos (2021)[51] **Primary studies**: Metabolic changes	**Metabolic changes:** *TGNB patients, pre-post: One primary study showed no changes in key markers of metabolism and renal function.*

[aa] *Lynestrenol is an androgenic progesterone not available in the US.*

[bb] *Cyproterone is an antiandrogen not available in the US.*

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.E.7. Systematic reviews addressing cardiovascular/metabolic risk factors (eg, thrombotic/thromboembolic, insulin sensitivity, blood pressure, cholesterol, liver, and kidney outcomes) in TGNB adolescents who receive GnRH analogs for puberty suppression

First author (Year) **Primary studies**	**Findings**
were examined in 1 primary study out of 3 reviewed studies/4 reviewed publications that addressed adolescent TGNB patients.	• GnRH analog puberty suppression for 3 months to 3 years was associated with no changes in AST, ALT, FA, GT, or creatinine among TGNB patients in Schagen (2016).[148]
Rew (2021)[52] **Primary studies:** Metabolic changes were examined in 2 primary studies out of 9 that addressed TGNB adolescents.	**"Fasting labs"** *Case findings:* • Triptorelin puberty suppression at age 13.7 years followed by CSHT with testosterone at age 18.6 was associated with fasting labs "within normal limits" in N=1 AFAB patient in Cohen-Kettenis (2011).[168] • Creatinine *TGNB patients, pre-post:* • Triptorelin was associated with no sustained creatinine abnormalities among N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148] **Liver function** *TGNB patients, pre-post:* • Triptorelin was associated with no sustained LFT abnormalities among N=116 TGNB patients (age range 11.1-18.6 years) in Schagen (2016).[148]

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

APPENDIX I.F: BIBLIOGRAPHY OF ALL INCLUDED STUDIES

Guidelines

American College of Obstetricians, Gynecologists' Committee on Clinical Consensus-Gynecology. General Approaches to Medical Management of Menstrual Suppression: ACOG Clinical Consensus No. 3. *Obstet Gynecol*. 2022;140(3):528-541. doi:10.1097/AOG.0000000000004899 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36356248

Abstract: The purpose of this document is to review currently available management options, general principles, and counseling approaches for reproductive-aged patients requesting menstrual suppression. It includes considerations for unique populations, including adolescents, patients with physical or cognitive disabilities or both, and those with limited access to health care. Gynecologists should be familiar with the use of hormonal therapy for menstrual suppression (including combined oral contraceptive pills, combined hormonal patches, vaginal rings, progestin-only pills, depot medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine device, and the etonogestrel implant). Approaches to counseling should be individualized based on patient preferences and goals, average treatment effectiveness, and contraindications or risk factors for adverse events. Counseling regarding the choice of hormonal medication for menstrual suppression should be approached with the utmost respect for patient autonomy and be free of coercion. Complete amenorrhea may be difficult to achieve; thus, obstetrician-gynecologists and other clinicians should counsel patients and caregivers, if applicable, about realistic expectations.

Annotation: Guidelines for managing menstrual suppression, including in TGNB patients

Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health*. 2022;23(Suppl 1):S1-S259. doi:10.1080/26895269.2022.2100644 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36238954

Abstract: Background: Transgender healthcare is a rapidly evolving interdisciplinary field. In the last decade, there has been an unprecedented increase in the number and visibility of transgender and gender diverse (TGD) people seeking support and gender-affirming medical treatment in parallel with a significant rise in the scientific literature in this area. The World Professional Association for Transgender Health (WPATH) is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. One of the main functions of WPATH is to promote the highest standards of health care for TGD people through the Standards of Care (SOC). The SOC was initially developed in 1979 and the last version (SOC-7) was published in 2012. In view of the increasing scientific evidence, WPATH commissioned a new version of the Standards of Care, the SOC-8. Aim: The overall goal of SOC-8 is to provide health care professionals (HCPs) with clinical guidance to assist TGD people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment. Methods: The SOC-8 is based on the best available science and expert professional consensus in transgender health. International professionals and stakeholders were selected to serve on the SOC-8 committee. Recommendation statements were developed based on data derived from

independent systematic literature reviews, where available, background reviews and expert opinions. Grading of recommendations was based on the available evidence supporting interventions, a discussion of risks and harms, as well as the feasibility and acceptability within different contexts and country settings. Results: A total of 18 chapters were developed as part of the SOC-8. They contain recommendations for health care professionals who provide care and treatment for TGD people. Each of the recommendations is followed by explanatory text with relevant references. General areas related to transgender health are covered in the chapters Terminology, Global Applicability, Population Estimates, and Education. The chapters developed for the diverse population of TGD people include Assessment of Adults, Adolescents, Children, Nonbinary, Eunuchs, and Intersex Individuals, and people living in Institutional Environments. Finally, the chapters related to gender-affirming treatment are Hormone Therapy, Surgery and Postoperative Care, Voice and Communication, Primary Care, Reproductive Health, Sexual Health, and Mental Health. Conclusions: The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and guidance for the treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria set forth in this document for gender-affirming medical interventions are clinical guidelines; individual health care professionals and programs may modify these in consultation with the TGD person.

Annotation: WPATH's best practices for treating TGNB patients

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658 Accessed May 18, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945902

Abstract: OBJECTIVE: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009. PARTICIPANTS: The participants include an Endocrine Society-appointed task force of nine experts, a methodologist, and a medical writer. EVIDENCE: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies. CONSENSUS PROCESS: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines. CONCLUSION: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments-appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health professional for adults (recommended)-should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the

endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment.

Annotation: A guideline for treating gender dysphoria

T'Sjoen G, Arcelus J, De Vries ALC, et al. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction". *J Sex Med*. 2020;17(4):570-584. doi:10.1016/j.jsxm.2020.01.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32111534

Abstract: BACKGROUND: There is a general lack of recommendations for and basic information tailored at sexologists and other health-care professionals for when they encounter trans people in their practice. AIM: We present to clinicians an up-to-date overview of clinical consensus statements on trans health care with attention for sexual function and satisfaction. METHODS: The task force consisted of 7 clinicians experienced in trans health care, selected among European Society for Sexual Medicine (ESSM) scientific committee. The consensus was guided by clinical experience and a review of the available literature and by interactive discussions on trans health, with attention for sexual function and satisfaction where available. OUTCOMES: The foci of the study are assessment and hormonal aspects of trans health care. RESULTS: As the available literature for direct recommendations was limited, most of the literature was used as background or indirect evidence. Clinical consensus statements were developed based on clinical experiences and the available literature. With the multiple barriers to care that many trans people experience, basic care principles still need to be stressed. We recommend that health-care professionals (HCPs) working with trans people recognize the diversity of genders,

including male, female, and nonbinary individuals. In addition, HCPs assessing gender diverse children and adolescents should take a developmental approach that acknowledges the difference between prepubescent gender diverse children and pubescent gender diverse adolescents and trans adults. Furthermore, trans people seeking gender-affirming medical interventions should be assessed by HCPs with expertise in trans health care and gender-affirming psychological practice. If masculinization is desired, testosterone therapy with monitoring of serum sex steroid levels and signs of virilization is recommended. Similarly, if feminization is desired, we recommend estrogens and/or antiandrogen therapy with monitoring of serum sex steroid levels and signs of feminization. HCPs should be aware of the influence of hormonal therapy on sexual functioning and satisfaction. We recommend HCPs be aware of potential sexual problems during all surgical phases of treatment. CLINICAL IMPLICATIONS: This is an up-to-date ESSM position statement. STRENGTHS & LIMITATIONS: These statements are based on the data that are currently available; however, it is vital to recognize that this is a rapidly changing field and that the literature, particularly in the field of sexual functioning and satisfaction, is limited. CONCLUSION: This ESSM position statement provides relevant information and references to existing clinical guidelines with the aim of informing relevant HCPs on best practices when working with transgender people. T'Sjoen G, Arcelus J, De Vries ALC, et al. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction". J Sex Med 2020;17:570-584.

Annotation: Clinical guidelines for working with transgender patients

Systematic Reviews

Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. *J Endocr Soc*. 2021;5(4):bvab011. doi:10.1210/jendso/bvab011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644622

Abstract: We sought to systematically review the effect of gender-affirming hormone therapy on psychological outcomes among transgender people. We searched PubMed, Embase, and PsycINFO through June 10, 2020 for studies evaluating quality of life (QOL), depression, anxiety, and death by suicide in the context of gender-affirming hormone therapy among transgender people of any age. We excluded case studies and studies reporting on less than 3 months of follow-up. We included 20 studies reported in 22 publications. Fifteen were trials or prospective cohorts, one was a retrospective cohort, and 4 were cross-sectional. Seven assessed QOL, 12 assessed depression, 8 assessed anxiety, and 1 assessed death by suicide. Three studies included trans-feminine people only; 7 included trans-masculine people only, and 10 included both. Three studies focused on adolescents. Hormone therapy was associated with increased QOL, decreased depression, and decreased anxiety. Associations were similar across gender identity and age. Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions. We could not draw any conclusions about death by suicide. Future studies should investigate the psychological benefits of hormone therapy among larger and more diverse groups of transgender people using study designs that more effectively isolate the effects of hormone treatment.

Annotation: A systematic review examining mental health outcomes in TGNB children, adolescents, and adults.

Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. *Pediatrics*. 2018;141(4)doi:10.1542/peds.2017-3742 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29514975

Abstract: CONTEXT: Hormonal interventions are being increasingly used to treat young people with gender dysphoria, but their effects in this population have not been systematically reviewed before. OBJECTIVE: To review evidence for the physical, psychosocial, and cognitive effects of gonadotropin-releasing hormone analogs (GnRHa), gender-affirming hormones, antiandrogens, and progestins on transgender adolescents. DATA SOURCES: We searched Medline, Embase, and PubMed databases from January 1, 1946, to June 10, 2017. STUDY SELECTION: We selected primary studies in which researchers examined the hormonal treatment of transgender adolescents and assessed their psychosocial, cognitive, and/or physical effects. DATA EXTRACTION: Two authors independently screened studies for inclusion and extracted data from eligible articles using a standardized recording form. RESULTS: Thirteen studies met our inclusion criteria, in which researchers examined GnRHas (n = 9), estrogen (n = 3), testosterone (n = 5), antiandrogen (cyproterone acetate) (n = 1), and progestin (lynestrenol) (n = 1). Most treatments successfully achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones and estrogen or testosterone causing feminization or masculinization of secondary sex characteristics. GnRHa treatment was associated with improvement across multiple measures of psychological functioning but not gender dysphoria itself, whereas the psychosocial effects of gender-affirming hormones in transgender youth have not yet been adequately assessed. LIMITATIONS: There are few studies in this field and they have all been observational. CONCLUSIONS: Low-quality evidence suggests that hormonal treatments for transgender adolescents can achieve their intended physical effects, but evidence regarding their psychosocial and cognitive impact are generally lacking. Future research to address these knowledge gaps and improve understanding of the long-term effects of these treatments is required.

Annotation: A systematic review examining the impact of GnRH analogues, with or without cross-sex hormones, antiandrogens, and progestins, on body changes (eg, endogenous hormone levels, height, growth velocity, lean and fat body mass), gender and body dysphoria, BMD, safety, and cognitive (eg, executive functioning, mental rotation), psychosocial (eg, global functioning, anger, behavioral and emotional problems), and mental health (eg, anxiety, depression) outcomes in TGNB adolescents and young adults.

D'hoore L, T'Sjoen G. Gender-affirming hormone therapy: An updated literature review with an eye on the future. *J Intern Med*. 2022;291(5):574-592. doi:10.1111/joim.13441 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34982475

Abstract: In line with increasing numbers of transgender (trans) and gender nonbinary people requesting hormone treatment, the body of available research is expanding. More clinical research groups are presenting data, and the numbers of participants in these studies are rising. Many previous review papers have focused on all available data, as these were scarce, but a more recent literature review is timely. Hormonal regimens have changed over time, and older data may be less relevant for today's practice. In recent literature, we have found that even though mental health problems are more prevalent in trans people compared to cisgender people, less psychological difficulties occur, and life satisfaction increases with gender-affirming hormone treatment (GAHT) for those who feel this is a necessity. With GAHT, body composition and contours change towards the affirmed sex. Studies in bone health are reassuring, but

special attention is needed for adolescent and adult trans women, aiming at adequate dosage of hormonal supplementation and stimulating therapy compliance. Existing epidemiological data suggest that the use of (certain) estrogens in trans women induces an increased risk of myocardial infarction and stroke, the reason that lifestyle management can be an integral part of trans health care. The observed cancer risk in trans people does not exceed the known cancer-risk differences between men and women. Now it is time to integrate the mostly reassuring data, to leave the overly cautious approach behind, to not copy the same research questions repeatedly, and to focus on longer follow-up data with larger cohorts.

Annotation: A systematic review examining recent information from larger cohorts of adult and adolescent TGNB patients taking modern GAHT regimens. Outcomes include cognitive (eg, executive functioning, mental rotation), psychosocial (eg, global functioning, anger, behavioral and emotional problems), mental health (anxiety, depression), and gender and body dysphoria outcomes.

Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*. 2023, 10.1111/apa.16791:ePub ahead of print. doi:10.1111/apa.16791 Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/apa.16791?download=true

Abstract: Aim: The aim of this systematic review was to assess the effects on psychosocial and mental health, cognition, body composition, and metabolic markers of hormone treatment in children with gender dysphoria. Methods: Systematic review essentially follows PRISMA. We searched PubMed, EMBASE and thirteen other databases until 9 November 2021 for English-language studies of hormone therapy in children with gender dysphoria. Of 9934 potential studies identified with abstracts reviewed, 195 were assessed in full text, and 24 were relevant. Results: In 21 studies, adolescents were given gonadotropin-releasing hormone analogues (GnRHa) treatment. In three studies, cross-sex hormone treatment (CSHT) was given without previous GnRHa treatment. No randomised controlled trials were identified. The few longitudinal observational studies were hampered by small numbers and high attrition rates. Hence, the long-term effects of hormone therapy on psychosocial health could not be evaluated. Concerning bone health, GnRHa treatment delays bone maturation and bone mineral density gain, which, however, was found to partially recover during CSHT when studied at age 22 years. Conclusion: Evidence to assess the effects of hormone treatment on the above fields in children with gender dysphoria is insufficient. To improve future research, we present the GENDHOR checklist, a checklist for studies in gender dysphoria.

Annotation: A systematic review of GAHT for TGNB adolescents

Mahfouda S, Moore JK, Siafarikas A, et al. Gender-affirming hormones and surgery in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2019;7(6):484-498. doi:10.1016/S2213-8587(18)30305-X Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30528161

Abstract: The Endocrine Society Clinical Practice Guidelines on the treatment of gender incongruent people recommend the use of gender-affirming cross-sex hormone (CSH) interventions in transgender children and adolescents who request this treatment, who have undergone psychiatric assessment, and have maintained a persistent transgender identity. The

intervention can help to affirm gender identity by inducing masculine or feminine physical characteristics that are congruent with an individual's gender expression, while aiming to improve mental health and quality-of-life outcomes. Some transgender individuals might also wish to access gender-affirming surgeries during adolescence; however, research to inform best clinical practice for surgeons and other medical professionals is scarce. This Review explores the available published evidence on gender-affirming CSH and surgical interventions in transgender children and adolescents, amalgamating findings on mental health outcomes, cognitive and physical effects, side-effects, and safety variables. The small amount of available data suggest that when clearly indicated in accordance with international guidelines, gender-affirming CSHs and chest wall masculinisation in transgender males are associated with improvements in mental health and quality of life. Evidence regarding surgical vaginoplasty in transgender females younger than age 18 years remains extremely scarce and conclusions cannot yet be drawn regarding its risks and benefits in this age group. Further research on an international scale is urgently warranted to clarify long-term outcomes on psychological functioning and safety.

Annotation: A systematic review examining psychological benefits of cross-sex hormone therapy in TGNB adolescents.

Ramos GGF, Mengai ACS, Daltro CAT, Cutrim PT, Zlotnik E, Beck APA. Systematic Review: Puberty suppression with GnRH analogues in adolescents with gender incongruity. *J Endocrinol Invest*. 2021;44(6):1151-1158. doi:10.1007/s40618-020-01449-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33111215

Abstract: CONTEXT: Gender incongruence is defined as disharmony between assigned gender and gender identity. Several interventions are liable in this case including genital affirming surgery among other surgical interventions such as harmonization, and also the use of gonadotropin-releasing hormone agonists (GnRHa) for gonadal shielding. This aids in preventing the development of secondary sexual characteristics related to the genetic sex. OBJECTIVE: Systematically review the treatment of gender incongruity with GnRHa analogues. DATA SOURCES: The data source of this research is from Pubmed-Medline and Embase. STUDY SELECTION: Articles published between 2009 and 2019 which studied transgender adolescents treated with GnRHa were carefully selected. DATA EXTRACTION: Were extracted: design, sample size, study context, targeted subjects of intervention, outcome measures, and results. RESULTS: Eleven studies were included. The use of GnRHa seems to be well tolerated by the studied population. When started in pubertal transition, it was associated with a more distinct resemblance to body shape than to the affirmed sex. In addition to preventing the irreversible phenotypic changes that occur in cross-hormonal therapy, the use of GnRHa can equally contribute to the mental health of these adolescents. LIMITATION: There are few consistent studies on the use of GnRHa for gender incongruence. CONCLUSION: As the population of transgender children and adolescents grows, they acquire knowledge and greater access to the various forms and stages of treatment for sex reassignment. The medical community needs to be adequately prepared to better serve this population and offer the safest resources available.

Annotation: A systematic review examining mental health, psychosocial function, body changes, and liver and kidney function outcomes in TGNB adolescents who receive GnRH analogues.

Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child Adolesc Ment Health*. 2021;26(1):3-14.

doi:10.1111/camh.12437 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33320999

Abstract: BACKGROUND: Increasingly, early adolescents who are transgender or gender diverse (TGD) are seeking gender-affirming healthcare services. Pediatric healthcare providers supported by professional guidelines are treating many of these children with gonadotropin-releasing hormone agonists (GnRHa), which reversibly block pubertal development, giving the child and their family more time in which to explore the possibility of medical transition. METHODS: We conducted a critical review of the literature to answer a series of questions about criteria for using puberty-blocking medications, the specific drugs used, the risks and adverse consequences and/or the positive outcomes associated with their use. We searched four databases: LGBT Life, PsycINFO, PubMed, and Web of Science. From an initial sample of 211 articles, we systematically reviewed 9 research studies that met inclusion/exclusion criteria. RESULTS: Studies reviewed had samples ranging from 1 to 192 (N = 543). The majority (71%) of participants in these studies required a diagnosis of gender dysphoria to qualify for puberty suppression and were administered medication during Tanner stages 2 through 4. Positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage. One study met all quality criteria and was judged 'excellent', five studies met the majority of quality criteria resulting in 'good' ratings, whereas three studies were judged fair and had serious risks of bias. CONCLUSION: Given the potentially life-saving benefits of these medications for TGD youth, it is critical that rigorous longitudinal and mixed methods research be conducted that includes stakeholders and members of the gender diverse community with representative samples.

Annotation: A systematic review examining physical and psychologial outcomes associated with puberty blockers in TGNB children.

Experimental Studies

Beking T, Burke SM, Geuze RH, et al. Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. *Psychoneuroendocrinology*. 2020;111:104461. doi:10.1016/j.psyneuen.2019.104461 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31630051

Abstract: The influence of testosterone on the development of human brain lateralization has been subject of debate for a long time, partly because studies investigating this are necessarily mostly correlational. In the present study we used a quasi-experimental approach by assessing functional brain lateralization in trans boys (female sex assigned at birth, diagnosed with Gender Dysphoria, n = 21) before and after testosterone treatment, and compared these results to the functional lateralization of age-matched control groups of cisgender boys (n = 20) and girls (n = 21) around 16 years of age. The lateralization index of the amygdala was determined with functional magnetic resonance imaging (fMRI) during an emotional face matching task with angry and fearful faces, as the literature indicates that boys show more activation in the right amygdala than girls during the perception of emotional faces. As expected, the lateralization index in trans boys shifted towards the right amygdala after testosterone treatment, and the cumulative dose of testosterone treatment correlated significantly with amygdala lateralization after treatment. However, we did not find any significant group differences in lateralization and

endogenous testosterone concentrations predicted rightward amygdala lateralization only in the cis boys, but not in cis girls or trans boys. These inconsistencies may be due to sex differences in sensitivity to testosterone or its metabolites, which would be a worthwhile course for future studies.

Annotation: A quasi-experimental study examining the effects of testosterone on amygdala lateralization between transgender boys and cis boys/girls.

Observational Studies

Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol*. 2020;2020(1):8. doi:10.1186/s13633-020-00078-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32368216

Abstract: BACKGROUND/AIMS: Transgender youths experience high rates of depression and suicidal ideation compared to cisgender peers. Previous studies indicate that endocrine and/or surgical interventions are associated with improvements to mental health in adult transgender individuals. We examined the associations of endocrine intervention (puberty suppression and/or cross sex hormone therapy) with depression and quality of life scores over time in transgender youths. METHODS: At approximately 6-month intervals, participants completed depression and quality of life questionnaires while participating in endocrine intervention. Multiple linear regression and residualized change scores were used to compare outcomes. RESULTS: Between 2013 and 2018, 50 participants (mean age 16.2 + 2.2 yr) who were naive to endocrine intervention completed 3 waves of questionnaires. Mean depression scores and suicidal ideation decreased over time while mean quality of life scores improved over time. When controlling for psychiatric medications and engagement in counseling, regression analysis suggested improvement with endocrine intervention. This reached significance in male-to-female participants. CONCLUSION: Endocrine intervention may improve mental health in transgender youths in the US. This effect was observed in both male-to-female and female-to-male youths, but appears stronger in the former.

Annotation: A US-based observational study examining the effect of hormonal treatments on mental health outcomes in TGNB adolescents.

Alvares LAM, Santos MR, Souza FR, et al. Cardiopulmonary capacity and muscle strength in transgender women on long-term gender-affirming hormone therapy: a cross-sectional study. *Br J Sports Med*. 2022;56(22):1292-1298. doi:10.1136/bjsports-2021-105400 Accessed September 15, 2023. Available at https://bjsm.bmj.com/content/bjsports/56/22/1292.full.pdf

Abstract: OBJECTIVE: For transgender women (TW) on oestrogen therapy, the effects of prior exposure to testosterone during puberty on their performance, mainly cardiopulmonary capacity (CPC), while exerting physical effort are unknown. Our objective was to evaluate CPC and muscle strength in TW undergoing long-term gender-affirming hormone therapy. METHODS: A cross-sectional study was carried out with 15 TW (34.2±5.2 years old), 13 cisgender men (CM) and 14 cisgender women (CW). The TW received hormone therapy for 14.4±3.5 years. Bioimpedance, the hand grip test and cardiopulmonary exercise testing on a treadmill with an incremental effort were performed. RESULTS: The mean VO2peak (L/min) was 2606±416.9 in TW, 2167±408.8 in CW and 3358±436.3 in CM (TW vs CW, $p<0.05$; TW vs CM, $p<0.0001$; CW vs

CM, p<0.0001). The O2 pulse in TW was between that in CW and CM (TW vs CW, p<0.05, TW vs CM, p<0.0001). There was a high correlation between VO2peak and fat-free mass/height2 among TW (r=0.7388; p<0.01), which was not observed in the other groups. The mean strength (kg) was 35.3±5.4 in TW, 29.7±3.6 in CW and 48.4±6.7 in CM (TW vs CW, p<0.05; TW vs CM, p<0.0001). CONCLUSION: CPC in non-athlete TW showed an intermediate pattern between that in CW and CM. The mean strength and VO2 peak in non-athlete TW while performing physical exertion were higher than those in non-athlete CW and lower than those in CM.

Annotation: A cross-sectional study comparing cardiopulmonary capacity and muscle strength (ie, determinants of physical performance) in Brazilian transgender women versus cisgender men and women, none of whom were athletes

Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry*. 2022;27(4):1069-1076. doi:10.1177/13591045221091652 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35638479

Abstract: BACKGROUND: Concerns exist regarding effects of puberty suppression on neurodevelopment. Intelligence is strongly correlated with educational achievement in the general population. This study aimed to examine the association between pre-treatment intelligence and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents to contribute to the emerging understanding of the effect that gender-affirming treatment including puberty suppression may have on cognitive development. METHODS: IQ was measured in 72 adolescents (45 trans boys, 27 trans girls) at clinical entry (mean age 12.78 years), educational achievement was evaluated after gender-affirming treatment (mean age 20.40 years). RESULTS: IQ pre-treatment and educational achievement post-treatment were positively associated (Nagelkerke R = 0.71). DISCUSSION: The association between IQ pre-treatment and educational achievement post-treatment in transgender adolescents who received gender-affirming medical treatment including puberty suppression appears to be similar to the general population. This may reflect that gender-affirming medical treatment including puberty suppression does not negatively affect the association between IQ and educational achievement.

Annotation: Examines changes in IQ and educational achievement after puberty suppression with GnRH agonists and GAHT in TGNB adolescents from a gender specialty clinic

Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? *Eur Child Adolesc Psychiatry*. 2020;29(6):803-811. doi:10.1007/s00787-019-01394-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305255/pdf/787_2019_Article_1394.pdf

Abstract: The background of this article is to examine whether consecutively transgender clinic-referred adolescents between 2000 and 2016 differ over time in demographic, psychological, diagnostic, and treatment characteristics. The sample under study consisted of 1072 adolescents (404 assigned males, 668 assigned females, mean age 14.6 years, and range 10.1–18.1 years). The data regarding the demographic, diagnostic, and treatment characteristics were collected from the adolescents' files. Psychological functioning was measured by the Child

Behaviour Check List and the Youth Self-Report, intensity of gender dysphoria by the Utrecht Gender Dysphoria Scale. Time trend analyses were performed with 2016 as reference year. Apart from a shift in sex ratio in favour of assigned females, no time trends were observed in demographics and intensity of dysphoria. It was found, however, that the psychological functioning improved somewhat over time (CBCL β − 0.396, p < 0.001, 95% CI − 0.553 to − 0.240, YSR β − 0.278, p < 0.001, 95% CI − 0.434 to − 0.122). The percentage of referrals diagnosed with gender dysphoria (mean 84.6%, range 75–97.4%) remained the same. The percentage of diagnosed adolescents that started with affirmative medical treatment (puberty suppression and/or gender-affirming hormones) did not change over time (mean 77.7%; range 53.8–94.9%). These findings suggest that the recently observed exponential increase in referrals might reflect that seeking help for gender dysphoria has become more common rather than that adolescents are referred to gender identity services with lower intensities of gender dysphoria or more psychological difficulties.

Annotation: A cohort study examining the association between birth-assigned sex and psychosocial functioning in TGNB adolescents, including 404 AFAB and 668 AMAB youths.

Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. *J Adolesc Health*. 2019;65(6):815-817. doi:10.1016/j.jadohealth.2019.06.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31500946

Abstract: PURPOSE: Body dissatisfaction in transgender youth (TY) may increase the risk for eating disorders. This is the first study using the Eating Disorders Examination Questionnaire (EDE-Q) to assess for eating disorder psychopathology in TY. METHODS: Youth aged 13-22 years (n = 106) presenting to a gender clinic from January 2018 to January 2019 completed the EDE-Q and answered questions on weight manipulation for gender-affirming purposes. RESULTS: Respondents identified as transmasculine (61%), transfeminine (28%), or nonbinary (11%). Mean age was 16.5 years (standard deviation = 2.0), mean weight was 119.9% median body mass index (standard deviation = 32.9), and 32% were on hormonal therapy. Of the participants, 15% had elevated EDE-Q scores. Most (63%) disclosed weight manipulation for gender-affirming purposes, with 11% of assigned females doing so for menstrual suppression. These behaviors had poor concordance with elevated EDE-Q scores (kappa = .137 and .148). CONCLUSIONS: Disordered eating behaviors are relatively common among TY. Further studies are needed to validate the EDE-Q in TY and establish meaningful cutoff score values.

Annotation: Cross-sectional study comparing eating disorder outcome scores (EDE-Q; see Appendix H) between treated and untreated TGNB subjects

Bauer GR, Pacaud D, Couch R, et al. Transgender Youth Referred to Clinics for Gender-Affirming Medical Care in Canada. *Pediatrics*. 2021;148(5)doi:10.1542/peds.2020-047266 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34620727

Abstract: BACKGROUND AND OBJECTIVES: Referrals of transgender and gender-diverse (trans) youth to medical clinics for gender-affirming care have increased. We described characteristics of trans youth in Canada at first referral visit. METHODS: Baseline clinical and survey data (2017-2019) were collected for Trans Youth CAN!, a 10-clinic prospective cohort of n = 174 pubertal and postpubertal youth <16 years with gender dysphoria, referred for hormonal suppression or hormone therapy, and 160 linked parent-participants. Measures assessed health, demographics, and visit outcome. RESULTS: Of youth, 137 were transmasculine (assigned female) and 37

transfeminine (assigned male); 69.0% were aged 14 to 15, 18.8% Indigenous, 6.6% visible minorities, 25.7% from immigrant families, and 27.1% low income. Most (66.0%) were gender-aware before age 12. Only 58.1% of transfeminine youth lived in their gender full-time versus 90.1% of transmasculine (P < .001). Although transmasculine youth were more likely than transfeminine youth to report depressive symptoms (21.2% vs 10.8%; P = .03) and anxiety (66.1% vs 33.3%; P < .001), suicidality was similarly high overall (past-year ideation: 34.5%, attempts: 16.8%). All were in school; 62.0% reported strong parental gender support, with parents the most common support persons (91.9%). Two-thirds of families reported external gender-related stressors. Youth had met with a range of providers (68.5% with a family physician). At clinic visit, 62.4% were prescribed hormonal suppression or hormone therapy, most commonly depot leuprolide acetate. CONCLUSIONS: Trans youth in Canada attending clinics for hormonal suppression or gender-affirming hormones were generally healthy but with depression, anxiety, and support needs.

Annotation: A Canadian study comparing characteristics and mental health needs between TGNB groups.

Becker I, Auer M, Barkmann C, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. *Arch Sex Behav*. 2018;47(8):2335-2347. doi:10.1007/s10508-018-1278-4 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30088234

Abstract: Persistent feelings of gender dysphoria (GD) are accompanied by distress and body dissatisfaction in most clinically referred adolescents and adults. Transition-related medical interventions (e.g., puberty suppression, hormones, or surgery) may alleviate body dissatisfaction. The aim of the present cross-sectional study was to compare multidimensional body image across clinically referred adolescents and adults undergoing different transition-related medical interventions. Two clinical samples of adolescents (n = 82) and adults (n = 120) referred to specialized departments of four different transgender health services in Germany participated in the study. In total, 202 individuals from the female-to-male (FtM individuals) and male-to-female (MtF individuals) spectrum aged 14-74 years were included at different stages of their transition. Four scales assessing multidimensional aspects of body image (measured by the Body Image Assessment Questionnaire, FBeK) were compared across three groups: sample, gender, and medical interventions (while controlling for age and treatment duration). The results indicated less favorable body image scores compared with the norm in both adolescents and adults with GD. Individuals who had undergone transition-related medical interventions presented a significantly better body image on two of the four scales. Differences according to gender and age were also present. These findings suggest that medical interventions, especially gender-affirming hormones and surgery, are generally beneficial to the body image in individuals with GD. However, not all of the less favorable outcomes in multidimensional body image were positively influenced by the treatment conditions and may thus benefit from additional integrative counseling before and during transition.

Annotation: A cross-sectional study examining the effect of hormones and GnRH analogues on body image outcomes in TNGB adolescents

Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity

Service. *Eur Child Adolesc Psychiatry*. 2021;30(11):1755-1767. doi:10.1007/s00787-020-01640-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32990772

Abstract: Empirical evidence concerning the psychosocial health outcomes after puberty suppression and gender-affirming (GA) medical interventions of adolescents with gender dysphoria (GD) is scarce. The aim of the present study was to describe how dimensions of psychosocial health were distributed among different intervention groups of adolescents with a GD diagnosis from the Hamburg Gender Identity Service before and after treatment. Participants included n = 75 adolescents and young adults from a clinical cohort sample, measured at their initial intake and on average 2 years later (M treatment duration = 21.4 months). All cases were divided into four different intervention groups, three of which received medical interventions. At baseline, both psychological functioning and quality of life scores were significantly below the norm mean for all intervention groups. At follow-up, adolescents in the gender-affirming hormone (GAH) and surgery (GAS) group reported emotional and behavioral problems and physical quality of life scores similar to the German norm mean. However, some of the psychosocial health outcome scores were still significantly different from the norm. Because this study did not test for statistically significant differences between the four intervention groups or before and after treatment, the findings cannot be generalized to other samples of transgender adolescents. However, GA interventions may help to improve psychosocial health outcomes in this sample of German adolescents. Long-term treatment decisions during adolescence warrant careful evaluation and informed, participatory decision-making by a multidisciplinary team and should include both medical interventions and psychosocial support. The present study highlights the urgent need for further ongoing longitudinal research.

Annotation: A cohort study examining the effect of unspecified GnRH analogues and cross-sex hormone therapy on psychosocial functioning in treated versus untreated TGNB youth. Also contains within-group longitudinal comparisons vs baseline (pre-post descriptive study).

Boogers LS, Wiepjes CM, Klink DT, et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. *J Clin Endocrinol Metab*. 2022;107(9):e3805-e3815. doi:10.1210/clinem/dgac349 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35666195

Abstract: CONTEXT: Transgender adolescents can receive gonadotropin-releasing hormone analogues (GnRH) and gender-affirming hormone therapy (GAHT), but little is known about effects on growth and adult height. This is of interest since height differs between sexes and some transgender girls wish to limit their growth. OBJECTIVE: This work aims to investigate the effects of GnRHa and GAHT on growth, and the efficacy of growth-reductive treatment. METHODS: This retrospective cohort study took place at a specialized tertiary gender clinic. A total of 161 transgender girls were treated with GnRHa and estradiol at a regular dose (2 mg) or high growth-reductive doses of estradiol (6 mg) or ethinyl estradiol (EE, 100-200 microg). Main outcome measures included growth, adult height, and the difference from predicted adult height (PAH) and target height. RESULTS: Growth velocity and bone maturation decreased during GnRHa, but increased during GAHT. Adult height after regular-dose treatment was 180.4 +/- 5.6 cm, which was 1.5 cm below PAH at the start GnRHa (95% CI, 0.2 cm to 2.7 cm), and close to target height (-1.1 cm; 95% CI, -2.5 cm to 0.3 cm). Compared to regular-dose treatment, high-dose estradiol and EE reduced adult height by 0.9 cm (95% CI, -0.9 cm to 2.8 cm) and 3.0 cm (95% CI, 0.2 cm to 5.8 cm), respectively. CONCLUSION: Growth decelerated during GnRHa

and accelerated during GAHT. After regular-dose treatment, adult height was slightly lower than predicted at start of GnRHa, likely due to systematic overestimation of PAH as described in boys from the general population, but not significantly different from target height. High-dose EE resulted in greater reduction of adult height than high-dose estradiol, but this needs to be weighed against possible adverse effects.

Annotation: A cohort study comparing dosages, growth, bone age, IGF-1 levels, and more outcomes among transgender females with different hormone treatments and dosages from a gender specialty clinic

Burke SM, Bakker J. The Role of Pubertal Hormones in the Development of Gender Identity: fMRI Studies. In: Bourguignon J-P, Carel J-C, Christen Y, eds. *Research and Perspectives in Endocrine Interactions*. Springer Cham; 2015:29-43:chap 3. Accessed May 17, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L601349832&from=export

Burke SM, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Klink DT, Bakker J. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. *J Psychiatry Neurosci*. 2016;41(6):395-404. doi:10.1503/jpn.150147 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27070350

Abstract: BACKGROUND: Sex differences in performance and regional brain activity during mental rotation have been reported repeatedly and reflect organizational and activational effects of sex hormones. We investigated whether adolescent girls with gender dysphoria (GD), before and after 10 months of testosterone treatment, showed male-typical brain activity during a mental rotation task (MRT). METHODS: Girls with GD underwent fMRI while performing the MRT twice: when receiving medication to suppress their endogenous sex hormones before onset of testosterone treatment, and 10 months later during testosterone treatment. Two age-matched control groups participated twice as well. RESULTS: We included 21 girls with GD, 20 male controls and 21 female controls in our study. In the absence of any group differences in performance, control girls showed significantly increased activation in frontal brain areas compared with control boys (p(FWE) = 0.012). Girls with GD before testosterone treatment differed significantly in frontal brain activation from the control girls (p(FWE) = 0.034), suggesting a masculinization of brain structures associated with visuospatial cognitive functions. After 10 months of testosterone treatment, girls with GD, similar to the control boys, showed increases in brain activation in areas implicated in mental rotation. LIMITATIONS: Since all girls with GD identified as gynephilic, their resemblance in spatial cognition with the control boys, who were also gynephilic, may have been related to their shared sexual orientation rather than their shared gender identity. We did not account for menstrual cycle phase or contraceptive use in our analyses. CONCLUSION: Our findings suggest atypical sexual differentiation of the brain in natal girls with GD and provide new evidence for organizational and activational effects of testosterone on visuospatial cognitive functioning.

Annotation: A cohort study examining effects of testosterone on fMRI outcomes in TGNB adolescents vs age- and sex-matched controls

Chen D, Abrams M, Clark L, et al. Psychosocial Characteristics of Transgender Youth Seeking Gender-Affirming Medical Treatment: Baseline Findings From the Trans Youth Care Study. *J Adolesc Health*. 2021;68(6):1104-1111. doi:10.1016/j.jadohealth.2020.07.033 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32839079

Abstract: PURPOSE: This study aimed to characterize two developmental cohorts of transgender and nonbinary youth enrolled in the Trans Youth Care Network Study and describe their gender identity-related milestones and baseline mental health and psychosocial functioning. METHODS: Trans Youth Care participants were recruited from four pediatric academic medical centers in the U.S. before initiating medical treatment for gender dysphoria either with gonadotropin-releasing hormone agonists (GnRHa) or gender-affirming hormones (GAH). GnRHa cohort data were collected from youth and a parent; GAH cohort data were collected from youth only. RESULTS: A total of 95 youth were enrolled in the GnRHa cohort. Mean age was 11.22 years (standard deviation = 1.46), and the majority were white (52.6%) and designated male at birth (51.6%). Elevated depression symptoms were endorsed by 28.6% of GnRHa cohort youth, and 22.1% endorsed clinically significant anxiety. Approximately one fourth (23.6%) endorsed lifetime suicidal ideation, with 7.9% reporting a past suicide attempt. A total of 316 youth were enrolled in the GAH cohort. The mean age was 16.0 years (standard deviation = 1.88), and the majority were white (62%) and designated female at birth (64.9%). Elevated depression symptoms were endorsed by 51.3% of the GAH cohort, and 57.3% endorsed clinically significant anxiety. Two-thirds (66.6%) endorsed lifetime suicidal ideation, with 24.6% reporting a past suicide attempt. Life satisfaction was lower among both cohorts compared with population-based norms. CONCLUSIONS: GnRHa cohort youth appear to be functioning better from a psychosocial standpoint than GAH cohort youth, pointing to possible benefits of accessing gender-affirming treatment earlier in life.

Annotation: Cross-sectional study examining psychosocial outcomes in TGNB youth initiating treatment with GnRH agonists or CSHT.

Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of Adolescents Referred to a Gender Clinic: Are Youth Seen Now Different from Those in Initial Reports? *Horm Res Paediatr*. 2018;89(6):434-441. doi:10.1159/000489608 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29920505

Abstract: BACKGROUND/AIMS: To examine characteristics, including mental health comorbidities, among adolescents presenting to a transgender clinic and to compare these data to previous reports. METHODS: Retrospective chart review among youth seen at The Hospital for Sick Children between January 2014 and June 2016. Demographic data, clinical characteristics, and mental health comorbidities were assessed. Baseline and repeat blood work were also examined. RESULTS: Charts from 203 adolescents aged 12-18 years were reviewed (156 assigned female at birth [AFAB] (77%) aged 16.3 +/- 1.63 years, 47 assigned male at birth [AMAB] aged 16.1 +/- 1.70 years). There was no statistically significant difference between gender groups except for Tanner stage (AFAB, mean 4.42 +/- 0.8 and AMAB, mean 4.03 +/- 1.1, p = 0.040). Individuals from racial/ethnic minority populations were under-represented compared to the background population. Self-report and baseline psychological questionnaires showed high levels of gender dysphoria, mood disorders, and suicidal ideation, with higher levels of anxiety detected on questionnaires among AFAB (p = 0.03). Laboratory abnormalities identified on baseline and repeat testing were minor; on cross-sex hormones, hemoglobin levels increased slightly in AFAB (p = 0.002, highest = 166 g/L) and decreased among AMAB (p = 0.02, lowest = 132 g/L). CONCLUSION: Our study supports an evolving demographic trend with more AFAB than AMAB youth now presenting to gender clinics. The data also corroborate studies indicating that extensive laboratory testing may not be a necessary part of caring for these youths. Why more AFAB are now presenting to clinic and racial/ethnic minorities are

underrepresented is not clear, but these trends have important implications for clinical care and warrant further study.

Annotation: A Toronto-based study examining mental health in TGNB youth

Conn BM, Chen D, Olson-Kennedy J, et al. High Internalized Transphobia and Low Gender Identity Pride Are Associated With Depression Symptoms Among Transgender and Gender-Diverse Youth. *J Adolesc Health*. 2023;72(6):877-884. doi:10.1016/j.jadohealth.2023.02.036 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00146-5/pdf

Abstract: Purpose: Prior studies have identified a significant relationship between internalized transphobia and poor mental health among transgender and gender-diverse (TGD) adults; however, this relationship has not been extensively examined among youth. Further, little research has sought to explore protective factors, such as identity pride, and their influence on this relationship. We examined the association between internalized transphobia and depression and anxiety symptoms among TGD youth and explored the moderating role of gender identity pride on these associations. Methods: Participants were 315 TGD youth ages 12–20 years (mean = 16; standard deviation = 1.89) seeking gender-affirming hormone treatment at one of four major pediatric hospitals across the United States. At the time of enrollment, participants were naïve to gender-affirming hormone treatment. Participants self-reported mental health, internalized transphobia, and identity pride. Multiple regression models were used with depression and anxiety symptoms as outcomes and age, designated sex at birth, and perceived parental support included as covariates. Results: Greater internalized transphobia was associated with greater depressive symptoms, and gender identity pride moderated this relationship, such that greater gender identity pride was associated with fewer depressive symptoms. Greater internalized transphobia was significantly associated with greater anxiety symptoms; no moderation effect was observed for this relationship. Discussion: Gender identity pride influenced mental health symptoms for youth experiencing internalized transphobia and represents a potential key protective factor. These results support efforts to further develop, test, and implement clinical inventions to bolster identity pride for TGD youth.

Annotation: A pair of case reports, including one transfeminine and one transmasculine adolescent

Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *J Sex Med*. 2015;12(11):2206-2214. doi:10.1111/jsm.13034 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26556015

Abstract: INTRODUCTION: Puberty suppression by gonadotropin-releasing hormone analogs (GnRHa) is prescribed to relieve the distress associated with pubertal development in adolescents with gender dysphoria (GD) and thereby to provide space for further exploration. However, there are limited longitudinal studies on puberty suppression outcome in GD. Also, studies on the effects of psychological support on its own on GD adolescents' well-being have not been reported. AIM: This study aimed to assess GD adolescents' global functioning after psychological support and puberty suppression. METHODS: Two hundred one GD adolescents were included in this study. In a longitudinal design we evaluated adolescents' global functioning every 6 months from the first visit. MAIN OUTCOME MEASURES: All adolescents completed the Utrecht Gender Dysphoria Scale (UGDS), a self-report measure of GD-related

discomfort. We used the Children's Global Assessment Scale (CGAS) to assess the psychosocial functioning of adolescents. RESULTS: At baseline, GD adolescents showed poor functioning with a CGAS mean score of 57.7 +/- 12.3. GD adolescents' global functioning improved significantly after 6 months of psychological support (CGAS mean score: 60.7 +/- 12.5; P < 0.001). Moreover, GD adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa (67.4 +/- 13.9) compared with when they had received only psychological support (60.9 +/- 12.2, P = 0.001). CONCLUSION: Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescents. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescents.

Annotation: A London-based cohort study examining mental health changes in TGNB adolescents, including a comparison between transgender males vs transgender females treated with unspecified GnRH agonists according to the WPATH guideline. Only natal sexes were reported: 76 AMAB and 125 AFAB adolescents. They also looked at changes over time within groups.

de Graaf NM, Steensma TD, Carmichael P, et al. Suicidality in clinic-referred transgender adolescents. *Eur Child Adolesc Psychiatry*. 2022;31(1):67-83. doi:10.1007/s00787-020-01663-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33165650

Abstract: Gender and sexually diverse adolescents have been reported to be at an elevated risk for suicidal thoughts and behaviors. For transgender adolescents, there has been variation in source of ascertainment and how suicidality was measured, including the time-frame (e.g., past 6 months, lifetime). In studies of clinic-referred samples of transgender adolescents, none utilized any type of comparison or control group. The present study examined suicidality in transgender adolescents (M age, 15.99 years) seen at specialty clinics in Toronto, Canada, Amsterdam, the Netherlands, and London, UK (total N = 2771). Suicidality was measured using two items from the Child Behavior Checklist (CBCL) and the Youth Self-Report (YSR). The CBCL/YSR referred and non-referred standardization samples from both the U.S. and the Netherlands were used for comparative purposes. Multiple linear regression analyses showed that there was significant between-clinic variation in suicidality on both the CBCL and the YSR; in addition, suicidality was consistently higher among birth-assigned females and strongly associated with degree of general behavioral and emotional problems. Compared to the U.S. and Dutch CBCL/YSR standardization samples, the relative risk of suicidality was somewhat higher than referred adolescents but substantially higher than non-referred adolescents. The results were discussed in relation to both gender identity specific and more general risk factors for suicidality.

Annotation: A cross-sectional study examining mental health characteristics of TGNB patients who were referred (ie, for GnRH analogue treatment) versus non-referred across 3 clinics. Only natal sexes were reported: 937 AMAB and 1834 AFAB.

de Vries AL, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011;52(11):1195-1202. doi:10.1111/j.1469-7610.2011.02426.x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21671938

Abstract: BACKGROUND: This study examined psychiatric comorbidity in adolescents with a gender identity disorder (GID). We focused on its relation to gender, type of GID diagnosis and eligibility for medical interventions (puberty suppression and cross-sex hormones). METHODS: To ascertain DSM-IV diagnoses, the Diagnostic Interview Schedule for Children (DISC) was administered to parents of 105 gender dysphoric adolescents. RESULTS: 67.6% had no concurrent psychiatric disorder. Anxiety disorders occurred in 21%, mood disorders in 12.4% and disruptive disorders in 11.4% of the adolescents. Compared with natal females (n = 52), natal males (n = 53) suffered more often from two or more comorbid diagnoses (22.6% vs. 7.7%, p = .03), mood disorders (20.8% vs. 3.8%, p = .008) and social anxiety disorder (15.1% vs. 3.8%, p = .049). Adolescents with GID considered to be 'delayed eligible' for medical treatment were older [15.6 years (SD = 1.6) vs. 14.1 years (SD = 2.2), p = .001], their intelligence was lower [91.6 (SD = 12.4) vs. 99.1 (SD = 12.8), p = .011] and a lower percentage was living with both parents (23% vs. 64%, p < .001). Although the two groups did not differ in the prevalence of psychiatric comorbidity, the respective odds ratios ('delayed eligible' adolescents vs. 'immediately eligible' adolescents) were >1.0 for all psychiatric diagnoses except specific phobia. CONCLUSIONS: Despite the suffering resulting from the incongruence between experienced and assigned gender at the start of puberty, the majority of gender dysphoric adolescents do not have co-occurring psychiatric problems. Delayed eligibility for medical interventions is associated with psychiatric comorbidity although other factors are of importance as well.

Annotation: A cross-sectional study examining mental health diagnoses among AFAB vs AMAB TGNB adolescents, and between treated vs untreated TGNB patients

de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25201798

Abstract: BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach. METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated. RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being. CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults.

Annotation: A cohort study examining psychosocial functioning after GnRHas, cross-sex hormones, and surgery among TGNB adolescents.

de Vries AL, Steensma TD, Cohen-Kettenis PT, VanderLaan DP, Zucker KJ. Poor peer relations predict parent- and self-reported behavioral and emotional problems of adolescents with gender dysphoria: a cross-national, cross-clinic comparative analysis. *Eur Child Adolesc Psychiatry*. 2016;25(6):579-588. doi:10.1007/s00787-015-0764-7 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26373289

Abstract: This study is the third in a series to examine behavioral and emotional problems in children and adolescents with gender dysphoria in a comparative analysis between two clinics in Toronto, Ontario, Canada and Amsterdam, the Netherlands. In the present study, we report Child Behavior Checklist (CBCL) and Youth Self-Report (YSR) data on adolescents assessed in the Toronto clinic (n = 177) and the Amsterdam clinic (n = 139). On the CBCL and the YSR, we found that the percentage of adolescents with clinical range behavioral and emotional problems was higher when compared to the non-referred standardization samples but similar to the referred adolescents. On both the CBCL and the YSR, the Toronto adolescents had a significantly higher Total Problem score than the Amsterdam adolescents. Like our earlier studies of CBCL data of children and Teacher's Report Form data of children and adolescents, a measure of poor peer relations was the strongest predictor of CBCL and YSR behavioral and emotional problems in gender dysphoric adolescents.

Annotation: A cross-sectional study examining mental health characteristics of TGNB patients who were referred (ie, for GnRH analogue treatment) versus non-referred across 2 clinics. Only natal sexes were reported: 173 AMAB and 143 AFAB

Durwood L, McLaughlin KA, Olson KR. Mental Health and Self-Worth in Socially Transitioned Transgender Youth. *J Am Acad Child Adolesc Psychiatry*. 2017;56(2):116-123 e112. doi:10.1016/j.jaac.2016.10.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28117057

Abstract: OBJECTIVE: Social transitions are increasingly common for transgender children. A social transition involves a child presenting to other people as a member of the "opposite" gender in all contexts (e.g., wearing clothes and using pronouns of that gender). Little is known about the well-being of socially transitioned transgender children. This study examined self-reported depression, anxiety, and self-worth in socially transitioned transgender children compared with 2 control groups: age- and gender-matched controls and siblings of transgender children. METHOD: As part of a longitudinal study (TransYouth Project), children (9-14 years old) and their parents completed measurements of depression and anxiety (n = 63 transgender children, n = 63 controls, n = 38 siblings). Children (6-14 years old; n = 116 transgender children, n = 122 controls, n = 72 siblings) also reported on their self-worth. Mental health and self-worth were compared across groups. RESULTS: Transgender children reported depression and self-worth that did not differ from their matched-control or sibling peers (p = .311), and they reported marginally higher anxiety (p = .076). Compared with national averages, transgender children showed typical rates of depression (p = .290) and marginally higher rates of anxiety (p = .096). Parents similarly reported that their transgender children experienced more anxiety than children in the control groups (p = .002) and rated their transgender children as having equivalent levels of depression (p = .728). CONCLUSION: These findings are in striking contrast to previous work with gender-nonconforming children who had not socially transitioned, which

found very high rates of depression and anxiety. These findings lessen concerns from previous work that parents of socially transitioned children could be systematically underreporting mental health problems.

Annotation: A cross-sectional study comparing mental health and self-worth outcomes between TGNB treatment groups and between TGNB adolescents versus controls

Eitel KB, Hodax JK, DiVall S, Kidd KM, Salehi P, Sequeira GM. Leuprolide Acetate for Puberty Suppression in Transgender and Gender Diverse Youth: A Comparison of Subcutaneous Eligard Versus Intramuscular Lupron. *J Adolesc Health*. 2023;72(2):307-311. doi:10.1016/j.jadohealth.2022.09.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36404242

Abstract: PURPOSE: To compare the efficacy of intramuscular Lupron and subcutaneous Eligard, two formulations of leuprolide, for puberty suppression in transgender and gender diverse (TGD) youth. METHODS: A retrospective chart review of TGD youth receiving Lupron or Eligard 22.5 mg every 3 months was conducted to determine hormone levels obtained 1 hour after an injection (1hrPost) and patient-reported clinical puberty suppression. RESULTS: Forty eight patients were analyzed: 33% assigned female at birth of which 25% were premenarchal, mean age at first injection 13.7 years, and 50% received concurrent gender affirming hormones. Of these, 13% received Lupron, 52% Eligard, and 35% initially received Lupron then transitioned to Eligard due to drug shortages. There were 55 incidents of 1hrPost levels, 42 after Eligard and 13 after Lupron. Clinical puberty suppression occurred in all patients; however, biochemical suppression occurred in 90% of Eligard and 69% of Lupron ($p = .06$). DISCUSSION: Eligard and Lupron were both effective in suppressing clinical puberty progression in our population of TGD youth, of which 50% were receiving concurrent gender affirming hormones.

Annotation: A cohort study comparing hormone levels and puberty suppression outcomes between transgender youths receiving Lupron vs Eligard.

Grannis C, Leibowitz SF, Gahn S, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology*. 2021;132:105358. doi:10.1016/j.psyneuen.2021.105358 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34333318

Abstract: OBJECTIVE: Many transgender adolescents experience clinically elevated anxiety and depression. Testosterone (T), used as a gender affirming treatment, may reduce symptoms of anxiety and depression. We assessed the effect of gender affirming T treatment on internalizing symptoms, body image dissatisfaction, and activation patterns within the amygdala-prefrontal cortex circuit in transgender adolescent boys. METHOD: Symptoms of generalized anxiety, social anxiety, depression, suicidality and body image dissatisfaction were measured by self-report and brain activation was measured during a face processing task with functional MRI in a group of 19 adolescent transgender boys receiving T treatment and 23 not receiving gonadal hormone treatment (UT). RESULTS: Severity of anxiety and depression was significantly lower in the T treated group relative to the UT group, along with a trend of lower suicidality. The T group also reported less distress with body features and exhibited stronger connectivity within the amygdala-prefrontal cortex circuit compared to the UT group. Finally, group differences on depression and suicidality were directly associated with body image dissatisfaction, and anxiety symptoms were moderated by amygdala-prefrontal cortex connectivity differences between

groups. CONCLUSION: T treatment is associated with lower levels of internalizing symptoms among transgender adolescent boys. T is also associated with greater body satisfaction and greater connectivity in a neural circuit associated with anxiety and depression. Satisfaction with body image was found to overlap with the association between T and both depression and suicidality, and amygdala-prefrontal co-activation moderated the role of T on anxiety.

Annotation: A cohort study comparing depression and anxiety severity between treated and untreated transgender boys.

Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolesc Health*. 2022;70(4):643-649. doi:10.1016/j.jadohealth.2021.10.036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34920935

Abstract: PURPOSE: There are no large-scale studies examining mental health among transgender and nonbinary youth who receive gender-affirming hormone therapy (GAHT). The purpose of this study is to examine associations among access to GAHT with depression, thoughts of suicide, and attempted suicide among a large sample of transgender and nonbinary youth. METHODS: Data were collected as part of a 2020 survey of 34,759 lesbian, gay, bisexual, transgender, queer, and questioning youth aged 13-24, including 11,914 transgender or nonbinary youth. Adjusted logistic regression assessed whether receipt of GAHT was associated with lower levels of depression, thoughts of suicide, and attempted suicide among those who wanted to receive GAHT. RESULTS: Half of transgender and nonbinary youth said they were not using GAHT but would like to, 36% were not interested in receiving GAHT, and 14% were receiving GAHT. Parent support for their child's gender identity had a strong relationship with receipt of GAHT, with nearly 80% of those who received GAHT reporting they had at least one parent who supported their gender identity. Use of GAHT was associated with lower odds of recent depression (adjusted odds ratio [aOR] = .73, $p < .001$) and seriously considering suicide (aOR = .74, $p < .001$) compared to those who wanted GAHT but did not receive it. For youth under age 18, GAHT was associated with lower odds of recent depression (aOR = .61, $p < .01$) and of a past-year suicide attempt (aOR = .62, $p < .05$). CONCLUSIONS: Findings support a relationship between access to GAHT and lower rates of depression and suicidality among transgender and nonbinary youth.

Annotation: A US-based cross-sectional study comparing demographic and mental health characteristics between TGNB patients who self-reported receiving GAHT versus not.

Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. *J Pediatr Adolesc Gynecol*. 2021;34(5):706-716. doi:10.1016/j.jpag.2021.04.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33910088

Abstract: STUDY OBJECTIVE: Amenorrhea is a goal of many transgender and gender diverse adolescent and young adult (TGD AYA) patients on testosterone gender-affirming hormone therapy (T-GAHT). Breakthrough bleeding can contribute to worsening gender dysphoria. Our objective was to evaluate breakthrough bleeding in TGD AYA on T-GAHT. DESIGN: Institutional review board-approved retrospective cohort. SETTING: Tertiary-care children's hospital. PARTICIPANTS: TGD AYA on T-GAHT >1 year. INTERVENTIONS: None; observational. MAIN OUTCOME MEASURES: Presence of, and risk factors for, breakthrough bleeding. RESULTS: Of the

232 patients who met inclusion criteria, one-fourth (n = 58) had 1 or more episodes of breakthrough bleeding, defined as bleeding after more than 1 year on T-GAHT. In comparing patients with breakthrough bleeding to those without, there were no significant differences between age of initiation, body mass index (BMI), race/ethnicity, testosterone type used, use of additional menstrual suppression, serum testosterone, or estradiol levels. Patients with breakthrough bleeding patients were on T-GAHT longer (37.3 +/- 17.0 vs 28.5 +/- 14.6 months, P < .001) and were more likely to have endometriosis (P = .049). Breakthrough bleeding began at a mean of 24.3 +/- 17.2 months after T-GAHT initiation. Of those with breakthrough bleeding, 46 (79.3%) had no known cause, 10 (17.2%) bled only with missed T-GAHT doses, and 2 (3.4%) bled only when withdrawing from concomitant menstrual suppression. No breakthrough bleeding management method was found to be superior. CONCLUSION: Breakthrough bleeding is relatively common (25%) on T-GAHT despite early amenorrhea. Most cases do not have an identifiable cause. Our data did not show superiority of any 1 method for managing breakthrough bleeding on T-GAHT.

Annotation: A cohort study comparing menstrual suppression outcomes in transgender boys in different GnRHa and hormone treatment groups.

Karakilic Ozturan E, Ozturk AP, Bas F, et al. Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey. *J Clin Res Pediatr Endocrinol*. 2023, 10.4274/jcrpe.galenos.2023.2023-1-13doi:10.4274/jcrpe.galenos.2023.2023-1-13 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36987788

Abstract: OBJECTIVE: A significant rise in the number of trans adolescents seeking medical interventions has been reported in recent years. In this study, we aimed to report the clinical features, treatment, and follow-up of adolescents with gender dysphoria (GD) with our increased experience. METHODS: Twenty-six male-to-female (MTF) and twenty-seven female-to-male (FTM) adolescents who were referred to our GD-outpatient clinic between the years 2016 and 2022 were reviewed. The clinical and laboratory findings of thirty transgender adolescents (15FTM /15 MTF) who received medical intervention were evaluated retrospectively. RESULTS: The vast majority of individuals (60.4%) were admitted between 2020 and 2022, and the remaining (39.6%) were admitted between 2016 and 2019. At the referral time, median age was 16.3 years (IQR,1.53; range, 13.2-19.4) in 26 MTF, and 16.4 years (IQR,1.74; range, 11.7-21.6) in 27 FTM adolescents. The median age of the pubertal blockage with gonadotropin-releasing hormone analog (GnRHa) and androgen receptor blocker was 16.4 years (IQR,1.4; range, 11.7-17.8) in 22 adolescents (9 MTF,13 FTM), and 17.4 years (IQR,1.4; range, 15.5-19.4) in 6 MTF individuals, respectively. The cross-sex hormone therapy (CSH) was commenced in 21 adolescents (12 MTF, 9 FTM) at the median age of 17.7 years (IQR,0.61; range,16-19.5). Fifteen individuals (8 MTF, 7 FTM) have been transferred to the adult endocrinology department in transition clinics. CONCLUSION: All treatments were well tolerated and effective including bicalutamide, no side effects were observed. Besides, transition clinics play an important role in the better management of gender reassignment processes.

Annotation: Examines body changes and endogenous hormone levels in TGNB adolescents

Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Pediatr*. 2014;164(4):906-911. doi:10.1016/j.jpeds.2013.10.068 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24315505

Abstract: OBJECTIVE: To describe patient characteristics at presentation, treatment, and response to treatment in youth with gender dysphoria. STUDY DESIGN: A retrospective chart review of 84 youth with a diagnosis of gender dysphoria seen at BC Children's Hospital from 1998-2011. RESULTS: Of the 84 patients, 45 (54%) identified as female-to-male (FtM), 37 (44%) as male-to-female (MtF), and 2 (2%) as natal males who were undecided. Median age of presentation was 16.9 years (range 11.4-19.8 years) and 16.6 years (range 12.3-22.5 years) for FtM and MtF youth, respectively. Gonadotropin-releasing hormone analog treatment was prescribed in 27 (32%) patients. One FtM patient developed sterile abscesses with leuprolide acetate; he was switched to triptorelin and tolerated this well. Cross-sex hormones were prescribed in 63 of 84 patients (39 FtM vs 24 MtF, P < .02). Median age at initiation of testosterone injections in FtM patients was 17.3 years (range 13.7-19.8 years); median age at initiation of estrogen therapy in MtF patients was 17.9 years (range 13.3-22.3 years). Three patients stopped cross-sex hormones temporarily due to psychiatric comorbidities (2 FtM) and distress over androgenic alopecia (1 FtM). No severe complications were noted in patients treated with testosterone or estrogen. CONCLUSION: Treatment with gonadotropin-releasing hormone analog and/or cross-sex hormones, in collaboration with transgender-competent mental health professionals, is an intervention that appears to be appropriate in carefully selected youth with gender dysphoria. Long-term follow-up studies are needed to determine the safety of these treatments in this age group.

Annotation: A cohort study comparing demographic characteristics, adverse effects, GnRH agonist/cross-sex hormone initiation, Tanner stages, and psychiatric comorbidites between MTF and FTM transgender youth.

Lee JY, Finlayson C, Olson-Kennedy J, et al. Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study. *J Endocr Soc*. 2020;4(9):bvaa065. doi:10.1210/jendso/bvaa065 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32832823

Abstract: CONTEXT: Transgender youth may initiate GnRH agonists (GnRHa) to suppress puberty, a critical period for bone-mass accrual. Low bone mineral density (BMD) has been reported in late-pubertal transgender girls before gender-affirming therapy, but little is known about BMD in early-pubertal transgender youth. OBJECTIVE: To describe BMD in early-pubertal transgender youth. DESIGN: Cross-sectional analysis of the prospective, observational, longitudinal Trans Youth Care Study cohort. SETTING: Four multidisciplinary academic pediatric gender centers in the United States. PARTICIPANTS: Early-pubertal transgender youth initiating GnRHa. MAIN OUTCOME MEASURES: Areal and volumetric BMD Z-scores. RESULTS: Designated males at birth (DMAB) had below-average BMD Z-scores when compared with male reference standards, and designated females at birth (DFAB) had below-average BMD Z-scores when compared with female reference standards except at hip sites. At least 1 BMD Z-score was < -2 in 30% of DMAB and 13% of DFAB. Youth with low BMD scored lower on the Physical Activity Questionnaire for Older Children than youth with normal BMD, 2.32 +/- 0.71 vs. 2.76 +/- 0.61 (P = 0.01). There were no significant deficiencies in vitamin D, but dietary calcium intake was suboptimal in all youth. CONCLUSIONS: In early-pubertal transgender youth, BMD was lower than reference standards for sex designated at birth. This lower BMD may be explained, in part, by suboptimal calcium intake and decreased physical activity-potential targets for intervention. Our results suggest a potential need for assessment of BMD in prepubertal gender-diverse youth and continued monitoring of BMD throughout the pubertal period of gender-affirming therapy.

Annotation: A US-based cohort study examining changes in bone between TGNB patients treated with GnRHa.

Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. *Hypertens Res*. 2023;46(1):219-225. doi:10.1038/s41440-022-01067-z Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36229533

Abstract: In order to assess the risk of hypertension development, we performed a retrospective analysis of the clinical records of consecutive transgender patients who began gender-affirming hormonal therapy in our Outpatient Gender Identity Clinic with <30 years of age and had a follow-up >5 years. 149 transgender women treated with estradiol and 153 transgender men treated with testosterone were included; 129 of the transgender women received also androgen blockers (54 spironolactone, 49 cyproterone acetate and 26 LHRH agonists). The annual incidence of hypertension in young transgender men (1.18%) seemed comparable to that of the general population. In young transgender women, it seemed higher (2.14%); we found that the choice of androgen blocker had a remarkable effect, with a highly significant increase in patients treated with cyproterone acetate (4.90%) vs. the rest (0.80%); the adjusted hazard-ratio was 0.227 ($p = 0.001$). Correlation, logistic regression and mediation analyses were performed for the associations of the available clinical variables with the increase in systolic blood pressure and the onset of hypertension, but besides the use of cyproterone acetate, only the ponderal gain was found significant (Spearman's r: 0.361, $p < 0.001$); with a 36.7% mediation effect (31.2-42.3%). Cyproterone acetate has additional known risks, such as meningioma; although we cannot conclusively prove that it has a role in the development of hypertension, we conclude that the use of cyproterone acetate for this indication should be reconsidered.

Annotation: A cohort study comparing blood pressure outcomes in young transgender patients receiving different hormone therapies.

Maru J, Millington K, Carswell J. Greater Than Expected Prevalence of Type 1 Diabetes Mellitus Found in an Urban Gender Program. *Transgend Health*. 2021;6(1):57-60. doi:10.1089/trgh.2020.0027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644323

Abstract: The prevalence of type 1 diabetes mellitus among transgender and gender diverse (TGD) youth is nearly five times higher than in the general pediatric population (9.9 per 1000 people vs. 1.93 per 1000 people). We hypothesize that minority stress experienced by TGD youth may lead to a higher prevalence of diabetes.

Annotation: A Boston-based cross-sectional study examining treatment exposures in TGNB youth with type I DM versus those without.

Marwa A, Misra M, Lopez X. Determinants of Bone Mineral Density in Transgender Youth. *Transgend Health*. 2022;7(3):213-218. doi:10.1089/trgh.2020.0111 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36643057

Abstract: PURPOSE: We aimed to study determinants of bone health in transgender youth in anticipation of or shortly after initiating puberty suppression and/or gender-affirming hormone therapy. METHODS: This was a retrospective review of records of transgender adolescents in our institution between June 2014 and June 2019. Dual energy X-ray absorptiometry was used

to assess bone mineral density (BMD). Baseline characteristics were collected and included in a multilinear regression model to assess determinants of lumbar spine (LS) BMD Z-scores adjusted for age and height and accounting for race. Welch's t-test was used to compare characteristics across genders. RESULTS: One hundred nineteen patient records were analyzed. Forty-six patients (38.7%) were assigned male at birth (AMAB) and 73 patients (61.3%) were assigned female at birth (AFAB). Mean (+/-standard deviation [SD]) age (years) was 14.7+/-2.6 for AMAB and 15.0+/-2.2 for AFAB. The adjusted LS BMD Z-score was lower in the AMAB population with a mean (+SD) of -0.605+/-1.42 compared with 0.043+/-1.09 in AFAB (p=0.010). In a multivariate model, AMAB gender, vitamin D deficiency, and lower body mass index (BMI) z-scores were determinants of lower LS BMD Z-scores (R (2)=0.206). Age, race, ethnicity, insurance status, and Tanner stage were not determinants of BMD. However, post hoc analysis did show that pubertal status modified the results. CONCLUSION: AMAB transgender adolescents have lower BMD compared with AFAB patients, before or shortly after starting puberty suppression and/or gender-affirming hormone therapy. Lower BMI and vitamin D deficiency were determinants of lower BMD. Further studies are needed to explore etiology for bone health discrepancy in this population.

Annotation: A US-based cohort study examining differences in bone density between TGNB patients based on natal sex.

Millington K, Liu E, Chan YM. The Utility of Potassium Monitoring in Gender-Diverse Adolescents Taking Spironolactone. *J Endocr Soc*. 2019;3(5):1031-1038. doi:10.1210/js.2019-00030 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31065620

Abstract: CONTEXT: Current guidelines recommend close monitoring of electrolytes in transgender patients using spironolactone given the risk of hyperkalemia from mineralocorticoid antagonism. In patients taking spironolactone for other conditions, the rate of hyperkalemia is low, and the utility of frequent monitoring has been questioned. OBJECTIVE: We hypothesized that the rate of hyperkalemia in gender-diverse adolescents taking spironolactone is low and, when present, clinically insignificant. DESIGN AND OUTCOMES: A retrospective chart review of adolescents seen in a specialty gender clinic at a tertiary care pediatric hospital over 10 years identified patients prescribed spironolactone for gender transition. Study outcomes were the incidence of hyperkalemia, defined as serum potassium concentration >5.0 mmol/L, and the relationship between potassium levels and spironolactone dose and duration. RESULTS: Records were reviewed for 85 subjects with a mean +/- SD age of 16.6 +/- 1.7 years. There were a total of 269 potassium measurements (80 prior to spironolactone initiation and 189 during spironolactone treatment). Six potassium measurements in five subjects were >5.0 mmol/L, indicating a rate of hyperkalemia of 2.2%. None of the subjects had symptoms of hyperkalemia, and all elevated measurements were normal when repeated. Only one subject discontinued spironolactone after an elevated potassium measurement. There was no relationship between hyperkalemia and spironolactone dose. Potassium measurements decreased with increasing treatment duration. CONCLUSIONS: Hyperkalemia in patients taking spironolactone for gender transition is rare and when present is transient and asymptomatic. In the absence of other medical comorbidities, routine electrolyte monitoring in this population may be unnecessary.

Annotation: Cohort study examining the risk of hyperkalemia associated with spironolactone in transfeminine or nonbinary adolescents in a pediatric gender specialty clinic

Mirabella M, Piras I, Fortunato A, et al. Gender Identity and Non-Binary Presentations in Adolescents Attending Two Specialized Services in Italy. *J Sex Med*. 2022;19(6):1035-1048. doi:10.1016/j.jsxm.2022.03.215 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/19/6/1035/6961405?redirectedFrom=fulltext

Abstract: Background: Recently, the variability and heterogeneity of gender presentations in transgender youths have gained significant attention worldwide. Alongside this, specialized gender services have reported an increase in referrals of youths reporting non-binary identities. In Italy, studies investigating gender identity and expression in gender non-conforming youths are lacking, as are data regarding the non-binary population. Aim: The present study aimed at dimensionally exploring how transgender and non-binary Italian adolescents identify and express their gender. Outcomes: Gender expression in trans binary youths and non-binary youths. Methods: The Gender Diversity Questionnaire (GDQ; Twist & de Graaf, 2019) was used to investigate gender identity, gender fluidity, and gender expression in a sample of 125 adolescent patients from the Gender Identity Development Service (SAIFIP) in Rome and the Gender Incongruence Unit of the Careggi Hospital in Florence, between April 2019–June 2021. Results: The majority of participants (74.4%) identified as trans* binary and the remaining (25.6%) participants identified as non-binary. Trans binary participants reported a stable gender identity, whereas non-binary participants reported a more fluid gender identity across time and contexts. Almost all participants rated external appearance as important to their gender expression, yet trans binary participants attributed more importance to the body in this respect. Body discomfort and pubertal stage emerged as the most influential factors in participants' experiences of gender. Participants who were assigned male at birth expressed significantly more desire for puberty blockers, whereas those who were assigned female at birth had a stronger desire to engage in breast/chest surgery. Non-binary participants sought different medical interventions relative to trans binary participants. Clinical Implications: These results may be useful for clinicians working with transgender youths as they provide awareness regarding the features of young people who identify within and outside of binary constructions of gender. Strengths & Limitations: This study provides useful data in gaining insight into understanding the variety of experiences and challenges of gender non-conforming youths. However as the sample was recruited from specialized services, it may not represent the entire gender non-conforming population in Italy. Conclusion: The results describe the range of gender identities and expressions among gender non-conforming youths attending gender specialized services in Italy, thereby improving our understanding of the variety of identities experienced and the specific medical needs of both trans binary and non-binary adolescents. Mirabella M, Piras I, Fortunato A, et al. Gender Identity and Non-Binary Presentations in Adolescents Attending Two Specialized Services in Italy. J Sex Med 2022;19:1035–1048.

Annotation: A study examining gender identity changes between AMAB vs AFAB TGNB subjects, and between trans binary vs nonbinary TGNB subjects. Only natal sexes reported: 40 AMAB and 85 AFAB.

Morningstar M, Thomas P, Anderson AM, et al. Exogenous testosterone administration is associated with differential neural response to unfamiliar peer's and own caregiver's voice in transgender adolescents. *Dev Cogn Neurosci*. 2023;59:101194. doi:10.1016/j.dcn.2022.101194 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36634500

Abstract: Changes in gonadal hormones during puberty are thought to potentiate adolescents' social re-orientation away from caregivers and towards peers. This study investigated the effect

of testosterone on neural processing of emotional (vocal) stimuli by unfamiliar peers vs. parents, in transgender boys receiving exogenous testosterone as a gender-affirming hormone (GAH+) or not (GAH-). During fMRI, youth heard angry and happy vocal expressions spoken by their caregiver and an unfamiliar teenager. Youth also self-reported on closeness with friends and parents. Whole-brain analyses (controlling for age) revealed that GAH+ youth showed blunted neural response to caregivers' angry voices-and heightened response to unfamiliar teenage angry voices-in the anterior cingulate cortex. This pattern was reversed in GAH- youth, who also showed greater response to happy unfamiliar teenager vs. happy caregiver voices in this region. Blunted ACC response to angry caregiver voices-a pattern characteristic of GAH+ youth-was associated with greater relative closeness with friends over parents, which could index more "advanced" social re-orientation. Consistent with models of adolescent neurodevelopment, increases in testosterone during adolescence may shift the valuation of caregiver vs. peer emotional cues in a brain region associated with processing affective information.

Annotation: A cross-sectional study comparing neural responses to peer and caregiver voices between TGNB groups.

Mullins ES, Geer R, Metcalf M, et al. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. *Pediatrics*. 2021;147(4)doi:10.1542/peds.2020-023549 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33753543

Abstract: BACKGROUND AND OBJECTIVES: Many transgender youth experience gender dysphoria, a risk factor for suicide. Gender-affirming hormone therapy (GAHT) ameliorates this risk but may increase the risk for thrombosis, as seen from studies in adults. The aim with this study was to examine thrombosis and thrombosis risk factors among an exclusively adolescent and young adult transgender population. METHODS: This retrospective chart review was conducted at a pediatric hospital-associated transgender health clinic. The primary outcome was incidence of arterial or venous thrombosis during GAHT. Secondary measures included the prevalence of thrombosis risk factors. RESULTS: Among 611 participants, 28.8% were transgender women and 68.1% were transgender men. Median age was 17 years at GAHT initiation. Median follow-up time was 554 and 577 days for estrogen and testosterone users, respectively. Individuals starting GAHT had estradiol and testosterone levels titrated to physiologic normal. Multiple thrombotic risk factors were noted among the cohort, including obesity, tobacco use, and personal and family history of thrombosis. Seventeen youth with risk factors for thrombosis were referred for hematologic evaluation. Five individuals were treated with anticoagulation during GAHT: 2 with a previous thrombosis and 3 for thromboprophylaxis. No participant developed thrombosis while on GAHT. CONCLUSIONS: In this study, we examined thrombosis and thrombosis risk factors in an exclusively adolescent and young adult population of transgender people receiving GAHT. These data suggest that GAHT in youth, titrated within physiologic range, does not carry a significant risk of thrombosis in the short-term, even with the presence of preexisting thrombosis risk factors.

Annotation: A cohort study examining thrombosis risk factors and outcomes in TGNB adolescents initiating GAHT

Nahata L, Quinn GP, Caltabellotta NM, Tishelman AC. Mental Health Concerns and Insurance Denials Among Transgender Adolescents. *LGBT health*. 2017;4(3):188-193. doi:10.1089/lgbt.2016.0151 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L621194440&from=export

Abstract: RESULTS: Seventy-nine records (51 transgender males, 28 transgender females) met inclusion criteria (median age: 15 years, range: 9-18). Seventy-three subjects (92.4%) were diagnosed with one or more of the following conditions: depression, anxiety, post-traumatic stress disorder, eating disorders, autism spectrum disorder, and bipolar disorder. Fifty-nine (74.7%) reported suicidal ideation, 44 (55.7%) exhibited self-harm, and 24 (30.4%) had one or more suicide attempts. Forty-six (58.2%) subjects reported school victimization. Of the 27 patients prescribed gonadotropin-releasing hormone analogues, only 8 (29.6%) received insurance coverage.CONCLUSION: Transgender youth face significant barriers in accessing appropriate hormone therapy. Given the high rates of mental health concerns, self-injurious behavior, and school victimization among this vulnerable population, healthcare professionals must work alongside policy makers toward insurance coverage reform.PURPOSE: Transgender youth are at high risk for mental health morbidities. Based on treatment guidelines, puberty blockers and gender-affirming hormone therapy should be considered to alleviate distress due to discordance between an individual's assigned sex and gender identity. The goals of this study were to examine the: (1) prevalence of mental health diagnoses, self-injurious behaviors, and school victimization and (2) rates of insurance coverage for hormone therapy, among a cohort of transgender adolescents at a large pediatric gender program, to understand access to recommended therapy.METHODS: An IRB-approved retrospective medical record review (2014-2016) was conducted of patients with ICD 9/10 codes for gender dysphoria referred to pediatric endocrinology within a large multidisciplinary gender program. Researchers extracted the following details: demographics, age, assigned sex, identified gender, insurance provider/coverage, mental health diagnoses, self-injurious behavior, and school victimization.

Annotation: A cross-sectional study examining mental health and psychosocial outcomes between transgender males and transgender females

Navabi B, Tang K, Khatchadourian K, Lawson ML. Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2020-039339 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34497118

Abstract: BACKGROUND AND OBJECTIVES: Puberty onset and development contribute substantially to adolescents' bone mass and body composition. Our objective with this study was to examine the effects of gonadotropin-releasing hormone agonists (GnRHa) on these puberty-induced changes among youth with gender dysphoria (GD). METHODS: Medical records of the endocrine diversity clinic in an academic children's hospital were reviewed for youth with GD seen from January 2006 to April 2017 with at least 1 baseline dual-energy radiograph absorptiometry measurement. RESULTS: At baseline, transgender females had lower lumbar spine (LS) and left total hip (LTH) areal bone mineral density (aBMD) and LS bone mineral apparent density (BMAD) z scores. Only 44.7% of transgender youth were vitamin D sufficient. Baseline vitamin D status was associated with LS, LTH aBMD, and LS BMAD z scores. Post-GnRHa assessments revealed a significant drop in LS and LTH aBMD z scores (transgender males and transgender females) without fractures and LS BMAD (transgender males), an increase in gynoid (fat percentage), and android (fat percentage) (transgender males and transgender females), and no changes in BMI z score. CONCLUSIONS: GnRHa monotherapy negatively affected bone mineral density of youth with GD without evidence of fractures or changes in BMI z score. Transgender youth body fat redistribution (android versus gynoid) were in keeping with their affirmed gender. The majority of transgender youth had vitamin D insufficiency or deficiency with baseline status associated with bone mineral density. Vitamin D supplementation should be considered for all youth with GD.

Annotation: A cohort study examining baseline and follow-up changes in bone mass, body composition, vitamin D, and pubertal suppression outcomes between transgender males vs transgender females who received GnRH agonists. Note that this was also a descriptive study that looked at changes from baseline in each group.

Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. *J Clin Endocrinol Metab*. 2020;105(3):e704-714. doi:10.1210/clinem/dgz029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31544944

Abstract: CONTEXT: As many as 1.8% of adolescents identify as transgender and many more seek care, yet the impact of gender-affirming hormone therapy (GAHT) on cardiometabolic health is unknown. OBJECTIVE: To determine insulin sensitivity and body composition among transgender females (TF) and males (TM) on estradiol or testosterone, compared with cisgender females (CF) and males (CM). DESIGN: Pilot, cross-sectional study conducted from 2016-2018. SETTING: Academic regional transgender referral center. PARTICIPANTS: Transgender adolescents on either testosterone or estradiol for at least 3 months were recruited. Nineteen TM were matched to 19 CM and 42 CF on pubertal stage and body mass index (BMI). Eleven TF were matched to 23 CF and 13 TF to 24 CM on age and BMI. MAIN OUTCOME MEASURES: 1/[fasting insulin] and body composition (dual-energy x-ray absorptiometry). RESULTS: Total body fat was lower in TM than CF mean +/- SD: (29% +/- 7% vs 33% +/- 7%; P = 0.002) and higher than in CM (28% +/- 7% vs 24% +/- 9%; P = 0.047). TM had higher lean mass than CF (68% +/- 7% vs 64% +/- 7%, P = 0.002) and lower than CM (69% +/- 7% vs 73% +/- 8%; P = 0.029). Insulin sensitivity was not different between the groups.TF had lower body fat than CF (31% +/- 7% vs 35% +/- 8%; P = 0.033) and higher than CM (28% +/- 6% vs 20% +/- 10%; P = 0.001). TF had higher lean mass than CF (66% +/- 6% vs 62% +/- 7%; P = 0.032) and lower than CM (69% +/- 5% vs 77% +/- 9%; P = 0.001). TF were more insulin resistant than CM (0.078 +/- 0.025 vs 0.142 +/- 0.064 mL/muU; P = 0.011). CONCLUSIONS: Transgender adolescents on GAHT have significant differences in body composition compared with cisgender controls, with a body composition intermediate between BMI-matched CMs and CFs. These changes in body composition may have consequences for the cardiometabolic health of transgender adolescents. CLINICALTRIALS.GOV: NCT02550431.

Annotation: A cohort study comparing insulin and DEXA outcomes between TGNB patients versus cisgender peers.

Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists. *Transgend Health*. 2021;6(2):111-119. doi:10.1089/trgh.2020.0029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33937527

Abstract: Purpose: Up to 1.8% of youth identify as transgender; many will be treated with a gonadotropin-releasing hormone agonist (GnRHa). The impact of GnRHa on insulin sensitivity and body composition in transgender youth is understudied. We aimed to evaluate differences in insulin sensitivity and body composition in transgender youth on GnRHa therapy compared with cisgender youth. Methods: Transgender participants were matched to cisgender participants on age, body mass index, and sex assigned at birth. Transgender males (n=9, ages 10.1-16.0 years) on GnRHa (mean+/-standard deviation duration of exposure: 20.9+/-19.8 months) were compared with cisgender females (n=14, ages 10.6-16.2). Transgender females

(n=8, ages 12.6-16.1) on GnRHa (11.3+/-7 months) were compared with cisgender males (n=17, ages 12.5-15.5). Differences in insulin sensitivity (1/[fasting insulin], homeostatic model of insulin resistance [HOMA-IR]), glycemia (hemoglobin A1C [HbA1c], fasting glucose), and body composition (dual-energy X-ray absorptiometry) were evaluated using a mixed linear regression model. Results: Transgender males had lower 1/fasting insulin and higher HOMA-IR (p=0.031, p=0.01, respectively), fasting glucose (89+/-4 vs. 79+/-13 mg/dL, p=0.012), HbA1c (5.4+/-0.2 vs. 5.2+/-0.2%, p=0.039), and percent body fat (36+/-7 vs. 32+/-5%, p=0.042) than matched cisgender females. Transgender females had lower 1/fasting insulin and higher HOMA-IR (p=0.028, p=0.035), HbA1c (5.4+/-0.1% vs. 5.1+/-0.2%, p=0.007), percent body fat (31+/-9 vs. 24+/-10%, p=0.002), and lower percent lean mass (66+/-8 vs. 74+/-10%, p<0.001) than matched cisgender males. Conclusion: Transgender youth on a GnRHa have lower estimated insulin sensitivity and higher glycemic markers and body fat than cisgender controls with similar characteristics. Longitudinal studies are needed to understand the significance of these changes. Clinical Trial.gov ID: NCT02550431.

Annotation: A cohort study comparing insulin sensitivity and glycemic control outcomes between transgender males versus cisgender females

Olsavsky AL, Grannis C, Bricker J, et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. *J Adolesc Health*. 2023;72(6):860-868. doi:10.1016/j.jadohealth.2023.01.031 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00097-6/pdf

Abstract: Purpose: We aimed to examine the concurrent associations of gender-affirming hormonal interventions (i.e., puberty blockers, testosterone, estrogen), as well as family and friend social support, on transgender and nonbinary (TNB) adolescents' reports of anxiety symptoms, depressive symptoms, nonsuicidal self-injury (NSSI), and suicidality. We hypothesized that gender-affirming hormonal interventions and greater social support would be associated with lower levels of mental health concerns. Methods: Participants (n = 75; aged 11–18; Mage = 16.39 years) were recruited for this cross-sectional study from a gender-affirming multidisciplinary clinic. Fifty-two percent were receiving gender-affirming hormonal interventions. Surveys assessed anxiety and depressive symptoms, NSSI and suicidality in the past year, and social support from family, friends, and significant others. Hierarchical linear regression models examined associations between gender-affirming hormonal interventions and social support (i.e., family, friend) with mental health while accounting for nonbinary gender identity. Results: Regression models explained 15%–23% of variance in TNB adolescents' mental health outcomes. Gender-affirming hormonal interventions were associated with fewer anxiety symptoms ($\beta = -0.23$; $p < .05$). Family support was associated with fewer depressive symptoms ($\beta = -0.33$; $p = .003$) and less NSSI ($\beta = -0.27$; $p = .02$). Friend support was associated with fewer anxiety symptoms ($\beta = -0.32$; $p = .007$) and less suicidality ($\beta = -0.25$; $p = .03$). Discussion: TNB adolescents had better mental health outcomes in the context of receiving gender-affirming hormonal interventions and having greater support from family and friends. Findings highlight the important role of quality family and friend support for TNB mental health. Providers should aim to address both medical and social factors to optimize TNB mental health outcomes.

Annotation: A cross-sectional study examining associations between treatments and mental health outcomes among TGNB adolescents

Olson-Kennedy J, Streeter LH, Garofalo R, Chan YM, Rosenthal SM. Histrelin Implants for Suppression of Puberty in Youth with Gender Dysphoria: A Comparison of 50 mcg/Day (Vantas) and 65 mcg/Day (SupprelinLA). *Transgend Health*. 2021;6(1):36-42. doi:10.1089/trgh.2020.0055 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644320

Abstract: Purpose: Development of incongruent secondary sex characteristics in transgender youth can intensify or trigger the onset of gender dysphoria. Guidelines from professional organizations recommend gonadotropin-releasing hormone agonists, including histrelin implants (Vantas and SupprelinLA) to suppress endogenous puberty. Although Vantas does not have a pediatric indication, it is anecdotally being used in pediatric gender centers throughout the United States because of its substantially lower cost. This retrospective study aimed to determine if both implants were effective in suppressing the hypothalamic-pituitary-gonadal axis in early-to-mid pubertal youth with gender dysphoria. Methods: Youth with gender dysphoria receiving care at the Center for Transyouth Health and Development at Children's Hospital Los Angeles (CHLA) or participants from an ongoing observational trial with a histrelin implant placed for pubertal suppression at Tanner stage 2 or 3 were included. Sex steroid (testosterone or estradiol) and gonadotropin measurements at baseline (T0) and then 2 to 12 months following implant placement (T1) were abstracted from medical records. Results: Of the 66 eligible participants, 52% were designated female at birth. Most participants were white (60.6%). Twenty participants (30.3%) had a Vantas implant and 46 (69.7%) had a SupprelinLA implant. Mean age of insertion was 11.3 years. Gonadotropin and sex steroid levels were significantly decreased at T1 (2-12 months after insertion of implant), with no differences between implants. Conclusion: These results indicate that both implants are effective in suppressing puberty in early-to-mid pubertal youth with gender dysphoria. These data may inform decisions about insurance coverage of Supprelin and/or Vantas for youth with gender dysphoria.

Annotation: A cohort study comparing puberty suppression outcomes in TGNB subjects receiving two forms of histrelin (Vantas vs SupprelinLA).

Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *J Clin Endocrinol Metab*. 2020;105(12):e4252-4263. doi:10.1210/clinem/dgaa604 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32909025

Abstract: CONTEXT: Hormonal interventions in adolescents with gender dysphoria may have adverse effects, such as reduced bone mineral accrual. OBJECTIVE: To describe bone mass development in adolescents with gender dysphoria treated with gonadotropin-releasing hormone analogues (GnRHa), subsequently combined with gender-affirming hormones. DESIGN: Observational prospective study. SUBJECTS: 51 transgirls and 70 transboys receiving GnRHa and 36 transgirls and 42 transboys receiving GnRHa and gender-affirming hormones, subdivided into early- and late-pubertal groups. MAIN OUTCOME MEASURES: Bone mineral apparent density (BMAD), age- and sex-specific BMAD z-scores, and serum bone markers. RESULTS: At the start of GnRHa treatment, mean areal bone mineral density (aBMD) and BMAD values were within the normal range in all groups. In transgirls, the mean z-scores were well below the population mean. During 2 years of GnRHa treatment, BMAD stabilized or showed a small decrease, whereas z-scores decreased in all groups. During 3 years of combined administration of GnRHa and gender-affirming hormones, a significant increase of BMAD was found. Z-scores normalized in transboys but remained below zero in transgirls. In transgirls and early pubertal transboys, all

bone markers decreased during GnRHa treatment. CONCLUSIONS: BMAD z-scores decreased during GnRHa treatment and increased during gender-affirming hormone treatment. Transboys had normal z-scores at baseline and at the end of the study. However, transgirls had relatively low z-scores, both at baseline and after 3 years of estrogen treatment. It is currently unclear whether this results in adverse outcomes, such as increased fracture risk, in transgirls as they grow older.

Annotation: A cohort study comparing bone changes over time for TGNB subjects at different pubertal stages. This was also a pre-post descriptive study examining changes over time in treated patients.

Schulmeister C, Millington K, Kaufman M, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. *J Adolesc Health*. 2022;70(1):108-113. doi:10.1016/j.jadohealth.2021.06.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34315674

Abstract: PURPOSE: Transgender/gender-diverse (TGD) youth are treated with gonadotropin-releasing hormone agonists (GnRHas) to halt endogenous puberty and prevent the development of secondary sex characteristics discordant with their gender identity. This treatment may have significant impact on growth and height velocity (HV). METHODS: Participants were recruited prior to GnRHa initiation from four gender specialty clinics in the U.S. Anthropometric, laboratory, and Tanner-stage data were abstracted from medical records. RESULTS: Fifty-five TGD youth (47% designated male at birth) with a mean +/- standard deviation age of 11.5 +/- 1.2 years were included in the analysis. HV in the first year of GnRHa use was median (interquartile range) 5.1 (3.7-5.6) cm/year. Later Tanner stage at GnRHa initiation was associated with lower HV: 5.3 (4.4-5.6) cm/year for Tanner stage II, 4.4 (3.3-6.0) cm/year for Tanner stage III, and 1.6 (1.5-2.9) cm/year for Tanner stage IV ($p = .001$). When controlled for age, there was not a significant difference in mean HV between TGD youth and prepubertal youth; however, when stratified by Tanner stage individuals starting GnRHa at Tanner stage IV had an HV below that of prepubertal youth, 1.6 (1.5-2.9) versus 6.1 (4.3-6.5) cm/year, $p = .006$. CONCLUSIONS: Overall, TGD youth treated with GnRHa have HV similar to that of prepubertal children, but TGD youth who start GnRHa later in puberty have an HV below the prepubertal range. Ongoing follow-up of this cohort will determine the impact of GnRHa treatment on adult height.

Annotation: A cohort study comparing height velocity (ie, growth) in TGNB patients who initiated GnRHa puberty suppression at the various Tanner stages.

Segev-Becker A, Israeli G, Elkon-Tamir E, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. *Endocr Pract*. 2020;26(4):423-428. doi:10.4158/EP-2019-0418 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32045294

Abstract: Objective: To describe patient characteristics at presentation, management, and fertility preservation rates among a cohort of Israeli children and adolescents with gender dysphoria (GD). Methods: We performed a retrospective chart review of 106 consecutive children and adolescents with GD (<18 years) referred to and followed at the multidisciplinary Israeli Pediatric Gender Dysphoria Clinic from March 2013 through December 2018. Results: Of the 106 patients, 10 were prepubertal (9 prepubertal transgender females), and 96 were pubertal (38 pubertal transgender females). The GD population increased 11-fold since the

establishment of our clinic in 2013. The subject's median age at referral was 15.5 years (range, 4.6 to 18 years). At the time of referral, 91 (95%) of the pubertal group had completed sexual maturation in their assigned gender at birth. Thirteen (13.5%) patients had attempted suicide, and 11 (11.5%) reported having had suicidal thoughts. Fourteen (45%) pubertal transgender females and 3 (6.5%) pubertal transgender males completed fertility preservation. Gonadotropin-releasing hormone analog treatment was prescribed in 77 (80%) patients at a mean age of 15.9 +/- 1.6 years. Gender-affirming hormones were prescribed in 61 (64%) patients at a mean age of 16.5 +/- 1.3 years. No severe side effects were recorded. Two (2%) of the pubertal group expressed regret about medical treatment. Conclusion: Children and adolescents with GD are presenting for medical attention at increasing rates. Israeli adolescents with GD have high fertility preservation rates, perhaps attributable to cultural perspectives. Taking advantage of the option to preserve fertility can be achieved when proper counseling is both available and promoted by medical personnel. Abbreviations: GAH = gender-affirming hormone; GD = gender dysphoria; GnRHa = gonadotropin-releasing hormone analog; MHP = mental health professional.

Annotation: Examines mental health and behavioral outcomes in transgender boys vs girls

Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental Health and Timing of Gender-Affirming Care. *Pediatrics*. 2020;146(4)doi:10.1542/peds.2019-3600 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_20193600.pdf

Abstract: BACKGROUND: Gender-incongruent (GI) youth have high rates of mental health problems. Although gender-affirming medical care (GAMC) provides psychological benefit, some GI youth present to care at older ages. Whether a relationship exists between age of presentation to GAMC and mental health difficulties warrants study., METHODS: A cross-sectional chart review of patients presenting to GAMC. Subjects were classified a priori as younger presenting youth (YPY) (<15 years of age at presentation) or older presenting youth (OPY) (>=15 years of age). Self-reported rates of mental health problems and medication use were compared between groups. Binary logistic regression analysis was used to identify determinants of mental health problems. Covariates included pubertal stage at presentation, social transition status, and assigned sex., RESULTS: Of 300 youth, there were 116 YPY and 184 OPY. After presentation, more OPY than YPY reported a diagnosis of depression (46% vs 30%), had self-harmed (40% vs 28%), had considered suicide (52% vs 40%), had attempted suicide (17% vs 9%), and required psychoactive medications (36% vs 23%), with all P < .05. After controlling for covariates, late puberty (Tanner stage 4 or 5) was associated with depressive disorders (odds ratio 5.49; 95% confidence interval [CI]: 1.14-26.32) and anxiety disorders (odds ratio 4.18 [95% CI: 1.22-14.49]), whereas older age remained associated only with psychoactive medication use (odd ratio 1.31 [95% CI: 1.05-1.63])., CONCLUSIONS: Late pubertal stage and older age are associated with worse mental health among GI youth presenting to GAMC, suggesting that this group may be particularly vulnerable and in need of appropriate care.

Annotation: A Toronto-based cross-sectional study examining mental health problems in older- versus younger-presenting TGNB adolescents

Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;56:190-199.

doi:10.1016/j.psyneuen.2015.03.007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25837854

Abstract: Adolescents with gender dysphoria (GD) may be treated with gonadotropin releasing hormone analogs (GnRHa) to suppress puberty and, thus, the development of (unwanted) secondary sex characteristics. Since adolescence marks an important period for the development of executive functioning (EF), we determined whether the performance on the Tower of London task (ToL), a commonly used EF task, was altered in adolescents with GD when treated with GnRHa. Furthermore, since GD has been proposed to result from an atypical sexual differentiation of the brain, we determined whether untreated adolescents with GD showed sex-atypical brain activations during ToL performance. We found no significant effect of GnRHa on ToL performance scores (reaction times and accuracy) when comparing GnRHa treated male-to-females (suppressed MFs, n=8) with untreated MFs (n=10) or when comparing GnRHa treated female-to-males (suppressed FMs, n=12) with untreated FMs (n=10). However, the suppressed MFs had significantly lower accuracy scores than the control groups and the untreated FMs. Region-of-interest (ROI) analyses showed significantly greater activation in control boys (n=21) than control girls (n=24) during high task load ToL items in the bilateral precuneus and a trend ($p<0.1$) for greater activation in the right DLPFC. In contrast, untreated adolescents with GD did not show significant sex differences in task load-related activation and had intermediate activation levels compared to the two control groups. GnRHa treated adolescents with GD showed sex differences in neural activation similar to their natal sex control groups. Furthermore, activation in the other ROIs (left DLPFC and bilateral RLPFC) was also significantly greater in GnRHa treated MFs compared to GnRHa treated FMs. These findings suggest that (1) GnRHa treatment had no effect on ToL performance in adolescents with GD, and (2) pubertal hormones may induce sex-atypical brain activations during EF in adolescents with GD.

Annotation: A cohort or cross-sectional analysis of the impact of GAH hormones on executive function.

Tollit MA, May T, Maloof T, et al. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. *International journal of transgender health*. 2023;24(1):59-69. doi:10.1080/26895269.2021.1939221 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9879187/pdf/WIJT_24_1939221.pdf

Abstract: Objectives: To better understand the clinical profile of patients attending a large Australian pediatric gender service. Retrospective clinical audit of patients seen at the Royal Children's Hospital Gender Service (RCHGS) over 10 years (2007-16). Setting: The RCHGS: Australia's largest pediatric gender service. Participants: Patients were eligible for inclusion if they had an appointment with the RCHGS between January 2007 - December 2016, and had either a self-reported gender which differed from what was presumed for them at birth or sought guidance regarding gender identity/expression. Main outcome measures: Demographic/developmental history, clinical presentation including information about gender identity/dysphoria, comorbidities, self-harm, suicidal ideation, gender-affirming treatment, psychosocial functioning. Results: 359 patients were first seen during the study period. Assigned females (54%) slightly outnumbered assigned males (46%), and presented at an older age (14.8 vs 12.4 years. Patients predominantly identified as transgender (87.2%) or non-binary (7.2%). Across the cohort, gender diversity was evident from a young age (median age 3), and symptoms of gender dysphoria were noted earlier in assigned males (median age 4) than

assigned females (median age 11). Although 81% of patients met eligibility for GD, rates of hormonal treatment were much lower, with 29% of young people >=10 years of age receiving puberty blocking treatment and 38% of adolescents >= 16 years of age receiving gender-affirming hormones (i.e. testosterone or estrogen). Many patients had mental health difficulties and/or neurodevelopment disorders, including major depressive disorder/low mood (51%), self-harm (25%), suicidal ideation (30%) and autism spectrum disorder (16%). Conclusion: This audit illustrates the complex profile and needs of transgender and gender diverse children and adolescents presenting to specialist gender services. Supplemental data for this article is available online at https://doi.org/10.1080/26895269.2021.1939221 . Copyright © 2021 Taylor & Francis Group, LLC.

Annotation: An cross-sectional study examining characteristics of AFAB vs AMAB TGNB adolescents, including mental health and psychosocial parameters. Natal genders were reported: 166 AMAB and 193 AFAB.

Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. *JAMA Netw Open*. 2022;5(2):e220978. doi:10.1001/jamanetworkopen.2022.0978 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35212746

Abstract: IMPORTANCE: Transgender and nonbinary (TNB) youths are disproportionately burdened by poor mental health outcomes owing to decreased social support and increased stigma and discrimination. Although gender-affirming care is associated with decreased long-term adverse mental health outcomes among these youths, less is known about its association with mental health immediately after initiation of care. OBJECTIVE: To investigate changes in mental health over the first year of receiving gender-affirming care and whether initiation of puberty blockers (PBs) and gender-affirming hormones (GAHs) was associated with changes in depression, anxiety, and suicidality. DESIGN, SETTING, AND PARTICIPANTS: This prospective observational cohort study was conducted at an urban multidisciplinary gender clinic among TNB adolescents and young adults seeking gender-affirming care from August 2017 to June 2018. Data were analyzed from August 2020 through November 2021. EXPOSURES: Time since enrollment and receipt of PBs or GAHs. MAIN OUTCOMES AND MEASURES: Mental health outcomes of interest were assessed via the Patient Health Questionnaire 9-item (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) scales, which were dichotomized into measures of moderate or severe depression and anxiety (ie, scores >/=10), respectively. Any self-report of self-harm or suicidal thoughts over the previous 2 weeks was assessed using PHQ-9 question 9. Generalized estimating equations were used to assess change from baseline in each outcome at 3, 6, and 12 months of follow-up. Bivariate and multivariable logistic models were estimated to examine temporal trends and investigate associations between receipt of PBs or GAHs and each outcome. RESULTS: Among 104 youths aged 13 to 20 years (mean [SD] age, 15.8 [1.6] years) who participated in the study, there were 63 transmasculine individuals (60.6%), 27 transfeminine individuals (26.0%), 10 nonbinary or gender fluid individuals (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question (3.8%). At baseline, 59 individuals (56.7%) had moderate to severe depression, 52 individuals (50.0%) had moderate to severe anxiety, and 45 individuals (43.3%) reported self-harm or suicidal thoughts. By the end of the study, 69 youths (66.3%) had received PBs, GAHs, or both interventions, while 35 youths had not received either intervention (33.7%). After adjustment for temporal trends and potential confounders, we observed 60% lower odds of depression (adjusted odds ratio [aOR], 0.40; 95% CI, 0.17-0.95) and 73% lower odds of suicidality (aOR, 0.27; 95% CI, 0.11-0.65)

among youths who had initiated PBs or GAHs compared with youths who had not. There was no association between PBs or GAHs and anxiety (aOR, 1.01; 95% CI, 0.41, 2.51). CONCLUSIONS AND RELEVANCE: This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months. These data add to existing evidence suggesting that gender-affirming care may be associated with improved well-being among TNB youths over a short period, which is important given mental health disparities experienced by this population, particularly the high levels of self-harm and suicide.

Annotation: A cohort study examining mental health outcomes (depression/anxiety) in TGNB adolescents and young adults receiving puberty blockers, cross-sex hormones, or both.

Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1725 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974216

Abstract: BACKGROUND AND OBJECTIVES: Gonadotropin-releasing hormone analogues are commonly prescribed to suppress endogenous puberty for transgender adolescents. There are limited data regarding the mental health benefits of this treatment. Our objective for this study was to examine associations between access to pubertal suppression during adolescence and adult mental health outcomes. METHODS: Using a cross-sectional survey of 20 619 transgender adults aged 18 to 36 years, we examined self-reported history of pubertal suppression during adolescence. Using multivariable logistic regression, we examined associations between access to pubertal suppression and adult mental health outcomes, including multiple measures of suicidality. RESULTS: Of the sample, 16.9% reported that they ever wanted pubertal suppression as part of their gender-related care. Their mean age was 23.4 years, and 45.2% were assigned male sex at birth. Of them, 2.5% received pubertal suppression. After adjustment for demographic variables and level of family support for gender identity, those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2-0.6). CONCLUSIONS: This is the first study in which associations between access to pubertal suppression and suicidality are examined. There is a significant inverse association between treatment with pubertal suppression during adolescence and lifetime suicidal ideation among transgender adults who ever wanted this treatment. These results align with past literature, suggesting that pubertal suppression for transgender adolescents who want this treatment is associated with favorable mental health outcomes.

Annotation: A cross-sectional survey study including cisgender and transgender adolescent respondents from 2017 and 2019, including an examination of the association between self-reported GnRH agonist use and suicide ideation in TGNB adolescents

Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLoS One*. 2022;17(1):e0261039. doi:10.1371/journal.pone.0261039 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35020719

Abstract: OBJECTIVE: To examine associations between recalled access to gender-affirming hormones (GAH) during adolescence and mental health outcomes among transgender adults in the U.S. METHODS: We conducted a secondary analysis of the 2015 U.S. Transgender Survey, a cross-sectional non-probability sample of 27,715 transgender adults in the U.S. Using

multivariable logistic regression adjusting for potential confounders, we examined associations between access to GAH during early adolescence (age 14-15), late adolescence (age 16-17), or adulthood (age >/=18) and adult mental health outcomes, with participants who desired but never accessed GAH as the reference group. RESULTS: 21,598 participants (77.9%) reported ever desiring GAH. Of these, 8,860 (41.0%) never accessed GAH, 119 (0.6%) accessed GAH in early adolescence, 362 (1.7%) accessed GAH in late adolescence, and 12,257 (56.8%) accessed GAH in adulthood. After adjusting for potential confounders, accessing GAH during early adolescence (aOR = 0.4, 95% CI = 0.2-0.6, p < .0001), late adolescence (aOR = 0.5, 95% CI = 0.4-0.7, p < .0001), or adulthood (aOR = 0.8, 95% CI = 0.7-0.8, p < .0001) was associated with lower odds of past-year suicidal ideation when compared to desiring but never accessing GAH. In post hoc analyses, access to GAH during adolescence (ages 14-17) was associated with lower odds of past-year suicidal ideation (aOR = 0.7, 95% CI = 0.6-0.9, p = .0007) when compared to accessing GAH during adulthood. CONCLUSION: Access to GAH during adolescence and adulthood is associated with favorable mental health outcomes compared to desiring but not accessing GAH.

Annotation: A cross-sectional study examining the association between self-reported GnRHa use and suicide ideation in TGNB adolescents.

Valentine A, Davis S, Furniss A, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. *J Clin Endocrinol Metab*. 2022;107(10):e4004-e4014. doi:10.1210/clinem/dgac469 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35945152

Abstract: CONTEXT: Studies on cardiometabolic health in transgender and gender-diverse youth (TGDY) are limited to small cohorts. OBJECTIVE: This work aimed to determine the odds of cardiometabolic-related diagnoses in TGDY compared to matched controls in a cross-sectional analysis, using a large, multisite database (PEDSnet). METHODS: Electronic health record data (2009-2019) were used to determine odds of cardiometabolic-related outcomes based on diagnosis, anthropometric, and laboratory data using logistic regression among TGDY youth vs controls. The association of gender-affirming hormone therapy (GAHT) with these outcomes was examined separately among TGDY. TGDY (n = 4172) were extracted from 6 PEDSnet sites and propensity-score matched on 8 variables to controls (n = 16 648). Main outcomes measures included odds of having cardiometabolic-related diagnoses among TGDY compared to matched controls, and among TGDY prescribed GAHT compared to those not prescribed GAHT. RESULTS: In adjusted analyses, TGDY had higher odds of overweight/obesity (1.2; 95% CI, 1.1-1.3) than controls. TGDY with a testosterone prescription alone or in combination with a gonadotropin-releasing hormone agonist (GnRHa) had higher odds of dyslipidemia (1.7; 95% CI, 1.3-2.3 and 3.7; 95% CI, 2.1-6.7, respectively) and liver dysfunction (1.5; 95% CI, 1.1-1.9 and 2.5; 95% CI, 1.4-4.3) than TGDY not prescribed GAHT. TGDY with a testosterone prescription alone had higher odds of overweight/obesity (1.8; 95% CI, 1.5-2.1) and hypertension (1.6 95% CI, 1.2-2.2) than those not prescribed testosterone. Estradiol and GnRHa alone were not associated with greater odds of cardiometabolic-related diagnoses. CONCLUSION: TGDY have increased odds of overweight/obesity compared to matched controls. Screening and tailored weight management, sensitive to the needs of TGDY, are needed.

Annotation: A cohort study comparing cardiometabolic parameters between testosterone-treated transgender males and cisgender females. This study also compares testosterone-treated vs untreated TGNB youth.

Valentine A, Nokoff N, Bonny A, et al. Cardiometabolic Parameters Among Transgender Adolescent Males on Testosterone Therapy and Body Mass Index-Matched Cisgender Females. *Transgend Health*. 2021;6(6):369-373. doi:10.1089/trgh.2020.0052 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993308

Abstract: Limited data are available on changes in metabolic parameters in transgender youth on testosterone therapy in comparison with cisgender females. Data from 42 transgender males on testosterone therapy were retrospectively analyzed. Body mass index (BMI) and lipid profile changes were compared with BMI-matched females. There was a significant increase in BMI over time in the transgender males as compared with the cisgender females, and a decrease in high-density lipoprotein in the transgender males after starting testosterone therapy. Longitudinal prospective studies with cisgender controls are needed to better define effects of testosterone therapy in adolescents.

Annotation: A cohort study examining cardiometabolic parameters in TGNB adolescents receiving testosterone versus not. Note thte study also compares TGNB versus cis-gender peers.

van de Grift TC, van Gelder ZJ, Mullender MG, Steensma TD, de Vries ALC, Bouman MB. Timing of Puberty Suppression and Surgical Options for Transgender Youth. *Pediatrics*. 2020;146(5)doi:10.1542/peds.2019-3653 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106340

Abstract: OBJECTIVES: Puberty suppression (PS) is a cornerstone of treatment in youth experiencing gender dysphoria. In this study, we aim to inform prescribing professionals on the long-term effects of PS treatment on the development of sex characteristics and surgical implications. METHODS: Participants received PS according to the Endocrine Society guideline at Tanner 2 or higher. Data were collected from adolescents who received PS between 2006 and 2013 and from untreated transgender controls. Data collection pre- and post-PS and before surgery included physical examination and surgical information. RESULTS: In total, 300 individuals (184 transgender men and 116 transgender women) were included. Of these, 43 individuals started PS treatment at Tanner 2/3, 157 at Tanner 4/5, and 100 used no PS (controls). Breast development was significantly less in transgender men who started PS at Tanner 2/3 compared with those who started at Tanner 4/5 and controls. Mastectomy was more frequently omitted or less invasive after PS. In transgender women, the mean penile length was significantly shorter in the PS groups compared with controls (by 4.8 cm [Tanner 2/3] and 2.1 cm [Tanner 4/5]). As a result, the likelihood of undergoing intestinal vaginoplasty was increased (odds ratio = 84 [Tanner 2/3]; odds ratio = 9.8 [Tanner 4/5]). CONCLUSIONS: PS reduces the development of sex characteristics in transgender adolescents. As a result, transgender men may not need to undergo mastectomy, whereas transgender women may require an alternative to penile inversion vaginoplasty. These surgical implications should inform decision-making when initiating PS.

Annotation: Compares surgical outcomes between TGNB youths who received early versus late puberty suppression.

van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *J Bone*

Miner Res. 2021;36(5):931-941. doi:10.1002/jbmr.4262 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33507568

Abstract: Bone geometry can be described in terms of periosteal and endocortical growth and is partly determined by sex steroids. Periosteal and endocortical apposition are thought to be regulated by testosterone and estrogen, respectively. Gender-affirming hormone (GAH) treatment with sex steroids in transgender people might affect bone geometry. However, in adult transgender people, no change in bone geometry during GAH was observed. In this study, we investigated changes in bone geometry among transgender adolescents using a gonadotropin-releasing hormone agonist (GnRHa) and GAH before achieving peak bone mass. Transgender adolescents treated with GnRHa and subsequent GAH before the age of 18 years were eligible for inclusion. Participants were grouped based on their Tanner stage at the start of GnRHa treatment and divided into early, mid, and late puberty groups. Hip structure analysis software calculating subperiosteal width (SPW) and endocortical diameter (ED) was applied to dual-energy X-ray absorptiometry scans performed at the start of GnRHa and GAH treatments, and after >/=2 years of GAH treatment. Mixed-model analyses were performed to study differences over time. Data were visually compared with reference values of the general population. A total of 322 participants were included, of whom 106 were trans women and 216 trans men. In both trans women and trans men, participants resembled the reference curve for SPW and ED of the experienced gender but only when GnRHa was started during early puberty. Those who started during mid and late puberty remained within the reference curve of the gender assigned at birth. A possible explanation might be sought in the phenomenon of programming, which conceptualizes that stimuli during critical windows of development can have major consequences throughout one's life span. Therefore, this study adds insights into sex-specific bone geometry development during puberty of transgender adolescents treated with GnRHa, as well as the general population. (c) 2021 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

Annotation: Reports on bone changes over time in TGNB adolescents seen in a gender specialty clinic. Reports the size of the ACOG as 8210 patients in 2018, up from 6793 patients in 2015.

Van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *J Adolesc Health*. 2020;66(6):699-704. doi:10.1016/j.jadohealth.2019.12.018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32273193

Abstract: PURPOSE: Transgender adolescents are at risk for internalizing and externalizing problems, along with high suicidality rates, and poor peer relations. The present study compared transgender adolescents before and after gender-affirmative care with a sample of nonclinical age-equivalent cisgender adolescents from the general population on psychological well-being and aimed to investigate the possible effect of transgender care involving puberty suppression. METHODS: In this cross-sectional study, emotional and behavioral problems were assessed by the Youth Self-Report in a sample of 272 adolescents referred to a specialized gender identity clinic who did not yet receive any affirmative medical treatment and compared with 178 transgender adolescents receiving affirmative care consisting of puberty suppression and compared with 651 Dutch high school cisgender adolescents from the general population. RESULTS: Before medical treatment, clinic-referred adolescents showed more internalizing problems and reported increased self-harm/suicidality and poorer peer relations compared with

their age-equivalent peers. Transgender adolescents receiving puberty suppression had fewer emotional and behavioral problems than the group that had just been referred to transgender care and had similar or fewer problems than their same-age cisgender peers on the Youth Self-Report domains. CONCLUSIONS: Transgender adolescents show poorer psychological well-being before treatment but show similar or better psychological functioning compared with cisgender peers from the general population after the start of specialized transgender care involving puberty suppression.

Annotation: A study comparing mental health outcomes in treated versus untreated TGNB adolescents; also compares mental health outcomes between TGNB adolescents and cisgender peers

Vehmas N, Holopainen E, Suomalainen L, Savolainen-Peltonen H. Somatic Health and Psychosocial Background Among Finnish Adolescents with Gender Dysphoria Seeking Hormonal Interventions. *Transgend Health*. 2022;7(6):505-513. doi:10.1089/trgh.2021.0084 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644116

Abstract: PURPOSE: Although the number of young adults suffering from gender dysphoria (GD) is increasing, reports focusing on their somatic health remain scarce. We studied the somatic health, pubertal development, psychosocial background, and interest regarding gender-affirming surgical treatment of Finnish adolescents seeking gender-affirming hormonal treatment (GAHT). METHODS: In this retrospective register study at an adolescent gynecology clinic in Helsinki University Hospital, Finland we included 124 adolescents diagnosed with GD and referred to GAHT between January 1, 2011 and December 31, 2018. This cohort covered two thirds of all Finnish adolescents referred to GAHT during the follow-up. Data on the general adolescent population were obtained from the Finnish School Health Promotion (SHP) study of year 2017. RESULTS: Most adolescents were assigned female at birth. Sex ratio increased from 1.2 in 2012 to 5.2 in 2017. One-third of the patients were overweight or obese (body mass index [BMI] >25 kg/m(2)). Other somatic comorbidities were rare. Interest toward reconstructive genital surgery was more common among male-to-female than female-to-male patients (80% vs. 22%, respectively, $p<0.001$). Depression (29%) and anxiety (19%) were common psychiatric comorbidities. Parental divorce rate (57%) was higher than in the general adolescent population in Finland (23%, $p<0.001$). CONCLUSION: Finnish adolescents diagnosed with GD-seeking GAHT have good somatic health, but a higher proportion of overweight, depression, and anxiety than the general adolescent population. Prospective follow-up of this cohort will provide an opportunity to evaluate the somatic and psychosocial outcomes and quality of life during GAHT.

Annotation: A cross-sectional study examining characteristics of TGNB patients presenting for treatment.

Vrouenraets LJJJ, de Vries ALC, de Vries MC, van der Miesen AIR, Hein IM. Assessing Medical Decision-Making Competence in Transgender Youth. *Pediatrics*. 2021;148(6)doi:10.1542/peds.2020-049643 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_2020049643.pdf

Abstract: BACKGROUND: According to international transgender care guidelines, an important prerequisite for puberty suppression (PS) is transgender adolescents' competence to give informed consent (IC). In society, there is doubt whether transgender adolescents are capable of this, which in some countries has even led to limited access to this intervention. Therefore, this

study examined transgender adolescents' medical decision-making competence (MDC) to give IC for starting PS in a structured, replicable way. Additionally, potential associated variables on MDC, such as age, intelligence, sex, psychological functioning, were investigated. METHODS: A cross-sectional semistructured interview study with 74 transgender adolescents (aged 10-18 years; 16 birth-assigned boys, 58 birth-assigned girls) within two Dutch specialized gender-identity clinics was performed. To assess MDC, judgements based on the reference standard (clinical assessment) and the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), a validated semistructured interview, were used. RESULTS: Of the transgender adolescents, 93.2% (reference standard judgements; 69 of 74) and 89.2% (MacCAT-T judgements; 66 of 74) were assessed competent to consent. Intermethod agreement was 87.8% (65 of 74). Interrater agreements of the reference standard and MacCAT-T-based judgements were 89.2% (198 of 222) and 86.5% (192 of 222), respectively. IQ and sex were both significantly related to MacCAT-T total score, whereas age, level of emotional and behavioral challenges, and diagnostic trajectories duration were not. CONCLUSIONS: By using the MacCAT-T and clinicians' assessments, 93.2% and 89.2%, respectively, of the transgender adolescents in this study were assessed competent to consent for starting PS.

Annotation: A cross-sectional study examining medical competence and related outcomes in TGNB adolescents. Natal sexes reported only: 16 AMAB and 58 AFAB.

Zucker KJ, Bradley SJ, Owen-Anderson A, Singh D, Blanchard R, Bain J. Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study. *Journal of Gay & Lesbian Mental Health*. 2010;15(1):58-82. doi:10.1080/19359705.2011.530574 Accessed June 12, 2023. Available at https://www.tandfonline.com/doi/abs/10.1080/19359705.2011.530574

Abstract: The use of puberty-delaying or blocking hormonal treatment of adolescents with gender identity disorder (GID) has become increasingly common. In the present study, we examined demographic, behavior problem, and psychosexual measures to see if any of them correlated with the clinical decision to recommend, or not recommend, puberty-blocking hormonal therapy in a consecutive series of 109 adolescents (55 females, 54 males) with GID evaluated between 2000 and 2009. Of the 109 adolescents, 66 (60.6%) were recommended for puberty-blocking hormonal therapy and 43 (39.4%) were not. A combination of five (of 15) demographic, behavior problem, and psychosexual measures were identified in a logistic regression analysis to significantly predict this clinical recommendation. The quantitative data were complemented by clinical case descriptions and some follow-up information. We discuss our data in relation to the Dutch model of early biomedical treatment for youth with GID and consider areas that require further clinical and empirical examination.

Annotation: A cross-sectional study examining correlates of puberty suppressive treatment in treated vs untreated TGNB patients. Only natal sexes were reported: 54 AMAB and 55 AFAB.

Longitudinal Pre-Post Descriptive Studies

Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. *Clinical Practice in Pediatric Psychology*. 2019;7(3):302-311. doi:10.1037/cpp0000288 Accessed September 15, 2023. Available at https://psycnet.apa.org/record/2019-52280-009

Abstract: Objective: This study is a longitudinal evaluation of the effectiveness of gender-affirming hormones for improving psychological well-being and decreasing suicidality among transgender youth referred to a transgender health specialty clinic at a large Midwest children's hospital. Method: Forty-seven youth (13.73–19.04 years; M = 16.59, SD = 1.19) who received gender-affirming hormones were assessed at least 2 times: before the start of treatment and at least 3 months after treatment. Results: After gender-affirming hormones, a significant increase in levels of general well-being and a significant decrease in levels of suicidality were observed. Conclusion: These findings suggest that gender-affirming hormones are a valuable medical intervention with promising psychosocial outcomes for transgender youth. (PsycInfo Database Record (c) 2022 APA, all rights reserved)

Annotation: Examines mental health and suicidality outcomes among TGNB adolescents who received GnRH agonists followed by CSHT vs CSHT only

Arnoldussen M, van der Miesen AIR, Elzinga WS, et al. Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT health*. 2022;9(4):238-246. doi:10.1089/lgbt.2020.0494 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/pdf/10.1089/lgbt.2020.0494?download=true

Abstract: Purpose: Early medical treatment for transgender adolescents should contribute to healthy psychological development, including the development of positive self-perception. However, at present, there are no longitudinal studies that have examined whether current treatment approaches meet this expectation. Therefore, the aim of this single-arm retrospective study was to examine transgender adolescents' self-perception changes over the course of irreversible medical gender-affirming treatment. Methods: The total study sample consisted of 70 adolescents (49 trans men and 21 trans women). Self-perception was assessed before the start of gender-affirming hormone treatment (mean age = 14.65, standard deviation (SD) = 2.08) and at least 6 months after gender-affirming surgeries (mean age = 20.70, SD = 1.49) by Self-Perception Profile for Adolescents (SPPA). The SPPA is a self-report measure that examines self-perception on seven different domains: Scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, close friendship, and global self-worth. Multilevel modeling (random intercepts model) was conducted to determine the effect of time for all domains of self-perception. Results: It was found that the domains of physical appearance and global self-worth improved significantly over the course of treatment. No domain worsened significantly over the course of treatment. The domains of scholastic competence, social acceptance, athletic competence, and close friendship remained stable over time. Conclusion: This study provides the first suggestive evidence that irreversible gender-affirming treatment for adolescents could contribute to the development of a more positive self-perception.

Annotation: Examines changes in psychosocial outcomes in TGNB adolescents before (while on hormonal treatments only) vs after gender-affirming surgery.

Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. *Transgend Health*. 2020;5(3):196-200. doi:10.1089/trgh.2019.0077 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644311

Abstract: Monitoring acute distress in transgender youth initiating gender-affirming care is important given their increased risk for significant mental health symptoms. The current study

examined changes in anxiety, depression, and suicidality from initial appointment to first follow-up in 80 youth, ages 11-18. Average time between visits was approximately 4 months but varied across participants. Results revealed no change in acute distress from intake to follow-up. Neither distance from medical center nor initiation of hormone therapy was associated with symptom changes. While research shows decreased distress with initiation of hormones, study findings suggest changes may actually take longer to occur.

Annotation: Examines changes in anxiety and depression in treated and untreated TGNB youths

Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS One*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33529227

Abstract: BACKGROUND: In adolescents with severe and persistent gender dysphoria (GD), gonadotropin releasing hormone analogues (GnRHa) are used from early/middle puberty with the aim of delaying irreversible and unwanted pubertal body changes. Evidence of outcomes of pubertal suppression in GD is limited. METHODS: We undertook an uncontrolled prospective observational study of GnRHa as monotherapy in 44 12-15 year olds with persistent and severe GD. Prespecified analyses were limited to key outcomes: bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour CheckList (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices; at 12, 24 and 36 months. Semistructured interviews were conducted on GnRHa. RESULTS: 44 patients had data at 12 months follow-up, 24 at 24 months and 14 at 36 months. All had normal karyotype and endocrinology consistent with birth-registered sex. All achieved suppression of gonadotropins by 6 months. At the end of the study one ceased GnRHa and 43 (98%) elected to start cross-sex hormones. There was no change from baseline in spine BMD at 12 months nor in hip BMD at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline (BMC +6.0 (95% CI: 4.0, 7.9); BMD +0.05 (0.03, 0.07)). There were no changes from baseline to 12 or 24 months in CBCL or YSR total t-scores or for CBCL or YSR self-harm indices, nor for CBCL total t-score or self-harm index at 36 months. Most participants reported positive or a mixture of positive and negative life changes on GnRHa. Anticipated adverse events were common. CONCLUSIONS: Overall patient experience of changes on GnRHa treatment was positive. We identified no changes in psychological function. Changes in BMD were consistent with suppression of growth. Larger and longer-term prospective studies using a range of designs are needed to more fully quantify the benefits and harms of pubertal suppression in GD.

Annotation: A London-based pre-post descriptive study examining short-term (ie, 1-3 years) bone and psychosocial outcomes in TGNB youths ages 12-15 years who received GnRH analogue monotherapy. Only natal sexes were reported: 25 AMAB and 19 AFAB

Chen D, Berona J, Chan YM, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *N Engl J Med*. 2023;388(3):240-250. doi:10.1056/NEJMoa2206297 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36652355

Abstract: BACKGROUND: Limited prospective outcome data exist regarding transgender and nonbinary youth receiving gender-affirming hormones (GAH; testosterone or estradiol). METHODS: We characterized the longitudinal course of psychosocial functioning during the 2 years after GAH initiation in a prospective cohort of transgender and nonbinary youth in the

United States. Participants were enrolled in a four-site prospective, observational study of physical and psychosocial outcomes. Participants completed the Transgender Congruence Scale, the Beck Depression Inventory-II, the Revised Children's Manifest Anxiety Scale (Second Edition), and the Positive Affect and Life Satisfaction measures from the NIH (National Institutes of Health) Toolbox Emotion Battery at baseline and at 6, 12, 18, and 24 months after GAH initiation. We used latent growth curve modeling to examine individual trajectories of appearance congruence, depression, anxiety, positive affect, and life satisfaction over a period of 2 years. We also examined how initial levels of and rates of change in appearance congruence correlated with those of each psychosocial outcome. RESULTS: A total of 315 transgender and nonbinary participants 12 to 20 years of age (mean [+/-SD], 16+/-1.9) were enrolled in the study. A total of 190 participants (60.3%) were transmasculine (i.e., persons designated female at birth who identify along the masculine spectrum), 185 (58.7%) were non-Latinx or non-Latine White, and 25 (7.9%) had received previous pubertal suppression treatment. During the study period, appearance congruence, positive affect, and life satisfaction increased, and depression and anxiety symptoms decreased. Increases in appearance congruence were associated with concurrent increases in positive affect and life satisfaction and decreases in depression and anxiety symptoms. The most common adverse event was suicidal ideation (in 11 participants [3.5%]); death by suicide occurred in 2 participants. CONCLUSIONS: In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.).

Annotation: Examines mental health and psychosocial outcomes in TGNB adolescents after 2 years of CSHT. Also compares mental health outcomes between early- and late-treated adolescents.

de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;8(8):2276-2283. doi:10.1111/j.1743-6109.2010.01943.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20646177

Abstract: INTRODUCTION: Puberty suppression by means of gonadotropin-releasing hormone analogues (GnRHa) is used for young transsexuals between 12 and 16 years of age. The purpose of this intervention is to relieve the suffering caused by the development of secondary sex characteristics and to provide time to make a balanced decision regarding actual gender reassignment. AIM: To compare psychological functioning and gender dysphoria before and after puberty suppression in gender dysphoric adolescents. METHODS: Of the first 70 eligible candidates who received puberty suppression between 2000 and 2008, psychological functioning and gender dysphoria were assessed twice: at T0, when attending the gender identity clinic, before the start of GnRHa; and at T1, shortly before the start of cross-sex hormone treatment. MAIN OUTCOME MEASURES: Behavioral and emotional problems (Child Behavior Checklist and the Youth-Self Report), depressive symptoms (Beck Depression Inventory), anxiety and anger (the Spielberger Trait Anxiety and Anger Scales), general functioning (the clinician's rated Children's Global Assessment Scale), gender dysphoria (the Utrecht Gender Dysphoria Scale), and body satisfaction (the Body Image Scale) were assessed. RESULTS: Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved significantly during puberty suppression. Feelings of anxiety and anger did not change between T0 and T1. While changes over time were equal for both sexes, compared with natal males, natal females were older when they started puberty suppression

and showed more problem behavior at both T0 and T1. Gender dysphoria and body satisfaction did not change between T0 and T1. No adolescent withdrew from puberty suppression, and all started cross-sex hormone treatment, the first step of actual gender reassignment. CONCLUSION: Puberty suppression may be considered a valuable contribution in the clinical management of gender dysphoria in adolescents.

Annotation: Examines mental health outcomes in TGNB patients treated with GnRH agonists. Only natal sex reported: 33 AMAB and 37 AFAB

de Vries ALC. Puberty Suppression Followed by Cross-sex Hormones and Gender Reassignment Surgery: A Prospective Follow-up of Gender Dysphoric Adolescents into Adulthood. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:91-106:chap 7. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. *J Pediatr Endocrinol Metab*. 2020;33(1):107-112. doi:10.1515/jpem-2019-0045 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31834861

Abstract: Background Sex hormones initiate profound physical and physiological changes during the pubertal process, but to what extent are they responsible for continuing the body composition changes of late adolescence and what happens to body composition on sudden sex hormone withdrawal? Methods Thirty-six healthy, phenotypically and chromosomally normal late and post-pubertal individuals aged 15-17 years with gender dysphoria (transgirls - birth-registered males identifying as female n = 11; and transboys - birth-registered females identifying as male n = 25) underwent Tanita body composition analysis at 0, 6 and 12 months during reproductive hormone suppression with Triptorelin as part of the standard therapeutic protocol. Results and conclusions In the transgirl cohort, paired t-test analysis demonstrated a significant decrease in height and lean mass standard deviation scores over the 12-month period, going against an expected trajectory over that time. In contrast, oestrogen suppression appeared not to affect the body composition of transboys; their measurements were not significantly different at baseline and after 12 months of treatment. The withdrawal of sex hormone secretion does not appear to have a significant impact on female post-pubertal body composition, in contrast to that seen at the menopause. This suggests that other factors may preserve normal body balance in adolescents in the absence of sex steroids.

Annotation: A London-based study examining body composition changes in TGNB adolescents receiving triptorelin for puberty suppression

Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. *J Clin Endocrinol Metab*. 2017;102(7):2356-2363. doi:10.1210/jc.2017-00373 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28419243

Abstract: CONTEXT: Puberty suppression using gonadotropin-releasing hormone agonists, followed by induction of the desired sex characteristics using sex steroids, has been recommended by the current guidelines as the treatment of choice for gender dysphoric adolescents, although little evidence is available. AIM: To evaluate the efficacy and safety of estrogen treatment for pubertal induction in transgirls (female-identifying adolescents assigned

male at birth). METHODS: Twenty-eight adolescents treated with oral estrogen for >/=1 year were included. The Tanner stage, anthropometry, laboratory parameters, bone age, and body composition were evaluated. RESULTS: Breast development started within 3 months in 83% of adolescents, and after 3 years, 86% had Tanner breast stage 4 to 5. The hip circumference increased and the waist/hip ratio decreased. The median serum estradiol was 100 pmol/L (range, 24 to 380) at the standard adult dose of 2 mg of 17beta-estradiol. The adult height standard deviation score was +1.9 (for females). The body mass index standard deviation score, lean body mass percentage, fat percentage, and blood pressure did not change. No abnormalities of creatinine or liver enzymes were detected, and the hematocrit and hemoglobin A1c did not change. One individual developed hyperprolactinemia during high-dose ethinylestradiol treatment to limit growth. CONCLUSIONS: Pubertal induction using estradiol is effective; however, an adult dose of 2 mg does not always result in appropriate serum estradiol levels. Monitoring renal function, liver enzymes, hematocrit, and hemoglobin A1c during pubertal induction with estradiol is not necessary. Further studies are needed to establish effective and safe methods to limit growth.

Annotation: Examines changes in endogenous hormone levels, anthropometric measures, bone, blood pressure measures among transgender girls treated with estradiol seen in a gender specialty clinic

Jarin J, Pine-Twaddell E, Trotman G, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. *Pediatrics*. 2017;139(5)doi:10.1542/peds.2016-3173 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28557738

Abstract: BACKGROUND AND OBJECTIVES: The Endocrine Society states that adolescents with gender dysphoria may start cross-sex hormones. The goal of this study was to identify patterns in metabolic parameters in transgender adolescents receiving cross-sex hormones. METHODS: Data from adolescents aged 14 to 25 years seen in 1 of 4 clinical sites between 2008 and 2014 were retrospectively analyzed. Subjects were divided into affirmed male (female-to-male) patients taking testosterone and affirmed female (male-to-female) patients taking estrogen. Previously recorded measurements of blood pressure, BMI, testosterone, estradiol, prolactin, lipids, electrolytes, liver function tests, hemoglobin/hematocrit, and hemoglobin A1c were reviewed. These values were obtained from before the start of therapy, at 1 to 3 months after initiation, at 4 to 6 months, and at 6 months and beyond. Repeated measures analysis of variance models were used to evaluate changes over time. RESULTS: One hunderd and sixteen adolescents were included (72 female-to-male subjects and 44 male-to-female subjects). Of the 72 subjects taking testosterone, a significant increase in hemoglobin/hematocrit levels and BMI, as well as a decrease in high-density lipoprotein level, was recorded at each visit. No significant changes in any other parameter tested were found. Of the 44 subjects taking estrogen, no statistically significant changes were noted in the measured metabolic parameters. CONCLUSIONS: Testosterone use was associated with increased hemoglobin and hematocrit, increased BMI, and lowered high-density lipoprotein levels; estrogen was associated with lower testosterone and alanine aminotransferase levels. Otherwise, cross-sex hormone administration in adolescents was not associated with significant differences in the selected metabolic parameters over time.

Annotation: Examines cardiovascular and metabolic changes associated with CSHT in adolescents with gender dysphoria

Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab*. 2019;32(10):1077-1081. doi:10.1515/jpem-2019-0046 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31472062

Abstract: Background More young people with gender dysphoria (GD) are undergoing hormonal intervention starting with gonadotropin-releasing hormone analogue (GnRHa) treatment. The impact on bone density is not known, with guidelines mentioning that bone mineral density (BMD) should be monitored without suggesting when. This study aimed to examine a cohort of adolescents from a single centre to investigate whether there were any clinically significant changes in BMD and bone mineral apparent density (BMAD) whilst on GnRHa therapy. Methods A retrospective review of 70 subjects aged 12-14 years, referred to a national centre for the management of GD (2011-2016) who had yearly dual energy X-ray absorptiometry (DXA) scans. BMAD scores were calculated from available data. Two analyses were performed, a complete longitudinal analysis (n=31) where patients had scans over a 2-year treatment period, and a larger cohort over the first treatment year (n=70) to extend the observation of rapid changes in lumbar spine BMD when puberty is blocked. Results At baseline transboys had lower BMD measures than transgirls. Although there was a significant fall in hip and lumbar spine BMD and lumbar spine BMAD Z-scores, there was no significant change in the absolute values of hip or spine BMD or lumbar spine BMAD after 1 year on GnRHa and a lower fall in BMD/BMAD Z-scores in the longitudinal group in the second year. Conclusions We suggest that reference ranges may need to be re-defined for this select patient cohort. Long-term BMD recovery studies on sex hormone treatment are needed.

Annotation: A Britain-based pre-post descriptive study examining bone outcomes in TGNB adolescents treated with GnRHa.

Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nord J Psychiatry*. 2020;74(3):213-219. doi:10.1080/08039488.2019.1691260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31762394

Abstract: Purpose: To assess how adolescent development progresses and psychiatric symptoms develop among transsexual adolescents after starting cross-sex hormone treatment.Materials and methods: Retrospective chart review among 52 adolescents who came into gender identity assessment before age 18, were diagnosed with transsexualism and started hormonal gender reassignment. The subjects were followed over the so-called real-life phase of gender reassignment.Results: Those who did well in terms of psychiatric symptoms and functioning before cross-sex hormones mainly did well during real-life. Those who had psychiatric treatment needs or problems in school, peer relationships and managing everyday matters outside of home continued to have problems during real-life.Conclusion: Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development.

Annotation: A Finnish pre-post study examining psychosocial functioning before and after 1-year of treatment with cross-sex hormones.

Klaver M, de Mutsert R, van der Loos M, et al. Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. *Pediatrics*. 2020;145(3)doi:10.1542/peds.2019-0741 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32102929

Abstract: BACKGROUND AND OBJECTIVES: The effects of endocrinological treatment on cardiovascular risk profile in transgender adolescents are unknown. In this retrospective cohort study, we aim to investigate these effects and assess obesity and dyslipidemia prevalence in transgender adolescents at 22 years compared with peers. METHODS: Changes in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, homeostatic model assessment for insulin resistance (HOMA-IR), and lipid values during treatment, along with the prevalence of obesity and dyslipidemia at 22 years, were recorded in 71 transwomen and 121 transmen who started gonadotropin-releasing hormone agonists in their adolescence (15 years), with a subsequent addition of sex hormones (17 years). RESULTS: In transwomen, changes in BMI (+3.0; 95% confidence interval [CI] 1.6 to 4.4), SBP (-2 mm Hg; 95% CI -7 to 3), DBP (+10 mm Hg; 95% CI 7 to 14), glucose (0.0 mmol/L; 95% CI -0.2 to 0.2), HOMA-IR (+0.6; 95% CI -0.6 to 1.9), and lipid values were similar or more favorable compared with peers. The same was true for transmen regarding changes in BMI (+2.3; 95% CI 1.7 to 2.9), SBP (+7 mm Hg; 95% CI 3 to 10), DBP (+7 mm Hg; 95% CI 5 to 10), glucose (+0.1 mmol/L; 95% CI -0.1 to 0.3), HOMA-IR (-0.2; 95% CI -0.8 to 0.3), and lipid values. At age 22, obesity prevalence was 9.9% in transwomen, 6.6% in transmen, 2.2% in ciswomen, and 3.0% in cismen. CONCLUSIONS: Generally, endocrinological treatment in transgender adolescents is safe regarding cardiovascular risk. Because obesity is more prevalent in transgender adolescents compared with peers, body weight management should be important during the medical trajectory.

Annotation: A cohort study comparing changes in cardiovascular risk factors between TGNB subjects who received surgical vs GnRHa gonadal suppression. Note that this is also (1) a cohort study comparing these outcomes between TGNB subjects vs cisgender peers, and (2) a pre-post descriptive study.

Klaver M, de Mutsert R, Wiepjes CM, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. *J Sex Med*. 2018;15(2):251-260. doi:10.1016/j.jsxm.2017.12.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29425666

Abstract: BACKGROUND: Transgender adolescents aspiring to have the body characteristics of the affirmed sex can receive hormonal treatment. However, it is unknown how body shape and composition develop during treatment and whether transgender persons obtain the desired body phenotype. AIM: To examine the change in body shape and composition from the start of treatment with gonadotropin-releasing hormone agonists (GnRHa) until 22 years of age and to compare these measurements at 22 years with those of age-matched peers. METHODS: 71 transwomen (birth-assigned boys) and 121 transmen (birth-assigned girls) who started treatment from 1998 through 2014 were included in this retrospective study. GnRHa treatment was started and cross-sex hormonal treatment was added at 16 years of age. Anthropometric and whole-body dual-energy x-ray absorptiometry data were retrieved from medical records. Linear mixed model regression was performed to examine changes over time. SD scores (SDS) were calculated to compare body shape and composition with those of age-matched peers. OUTCOMES: Change in waist-hip ratio (WHR), total body fat (TBF), and total lean body mass (LBM) during hormonal treatment. SDS of measures of body shape and composition compared with age-matched peers at 22 years of age. RESULTS: In transwomen, TBF increased (+10%, 95%

CI = 7-11) while total LBM (-10%, 95% CI = -11 to -7) and WHR (-0.04, 95% CI = -0.05 to -0.02) decreased. Compared with ciswomen, SDS at 22 years of age were +0.3 (95% CI = 0.0-0.5) for WHR, and 0.0 (95% CI = -0.2 to 0.3) for TBF. Compared with cismen, SDS were -1.0 (95% CI = -1.3 to -0.7) for WHR, and +2.2 (95% CI = 2.2-2.4) for TBF. In transmen, TBF decreased (-3%, 95% CI = -4 to -1), while LBM (+3%, 95% CI = 1-4) and WHR (+0.03, 95% CI = 0.01-0.04) increased. Compared with ciswomen, SDS at 22 years of age were +0.6 (95% CI = 0.4-0.8) for WHR, and -1.1 (95% CI = -1.4 to -0.9) for TBF. Compared with cismen, SDS were -0.5 (95% CI = -0.8 to -0.3) for WHR, and +1.8 (95% CI = 1.6-1.9) for TBF. CLINICAL IMPLICATIONS: Knowing body shape and composition outcomes at 22 years of age will help care providers in counseling transgender youth on expectations of attaining the desired body phenotype. STRENGTHS AND LIMITATIONS: This study presents the largest group of transgender adults to date who started treatment in their teens. Despite missing data, selection bias was not found. CONCLUSIONS: During treatment, WHR and body composition changed toward the affirmed sex. At 22 years of age, transwomen compared better to age-matched ciswomen than to cismen, whereas transmen were between reference values for ciswomen and cismen. Klaver M, de Mutsert R, Wiepjes CM, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. J Sex Med 2018;15:251-260.

Annotation: An Amsterdam-based cohort study examining body composition outcomes in patients who received unspecified GnRH analogues and cross-sex hormones, including comparisons between TGNB patients and cisgender peers.

Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;100(2):E270-275. doi:10.1210/jc.2014-2439 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25427144

Abstract: CONTEXT: Sex steroids are important for bone mass accrual. Adolescents with gender dysphoria (GD) treated with gonadotropin-releasing hormone analog (GnRHa) therapy are temporarily sex-steroid deprived until the addition of cross-sex hormones (CSH). The effect of this treatment on bone mineral density (BMD) in later life is not known. OBJECTIVE: This study aimed to assess BMD development during GnRHa therapy and at age 22 years in young adults with GD who started sex reassignment (SR) during adolescence. DESIGN AND SETTING: This was a longitudinal observational study at a tertiary referral center. PATIENTS: Young adults diagnosed with gender identity disorder of adolescence (DSM IV-TR) who started SR in puberty and had undergone gonadectomy between June 1998 and August 2012 were included. In 34 subjects BMD development until the age of 22 years was analyzed. INTERVENTION: GnRHa monotherapy (median duration in natal boys with GD [transwomen] and natal girls with GD [transmen] 1.3 and 1.5 y, respectively) followed by CSH (median duration in transwomen and transmen, 5.8 and 5.4 y, respectively) with discontinuation of GnRHa after gonadectomy. MAJOR OUTCOME MEASURES: How BMD develops during SR until the age of 22 years. RESULTS AND CONCLUSION: Between the start of GnRHa and age 22 years the lumbar areal BMD z score (for natal sex) in transwomen decreased significantly from -0.8 to -1.4 and in transmen there was a trend for decrease from 0.2 to -0.3. This suggests that the BMD was below their pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated.

Annotation: Examines patient characteristics and bone outcomes over time in GnRH agonist- and CSHT-treated adolescents in a gender specialty clinic

Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*. 2020;145(4)doi:10.1542/peds.2019-3006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32220906

Abstract: OBJECTIVES: Our first aim was to examine baseline differences in body dissatisfaction, depression, and anxiety symptoms by gender, age, and Tanner (ie, pubertal) stage. Our second aim was to test for changes in youth symptoms over the first year of receiving gender-affirming hormone therapy. Our third aim was to examine potential differences in change over time by demographic and treatment characteristics. Youth experiences of suicidal ideation, suicide attempt, and nonsuicidal self-injury (NSSI) are also reported. METHODS: Participants (n = 148; ages 9-18 years; mean age 14.9 years) were receiving gender-affirming hormone therapy at a multidisciplinary program in Dallas, Texas (n = 25 puberty suppression only; n = 123 feminizing or masculinizing hormone therapy). Participants completed surveys assessing body dissatisfaction (Body Image Scale), depression (Quick Inventory of Depressive Symptoms), and anxiety (Screen for Child Anxiety Related Emotional Disorders) at initial presentation to the clinic and at follow-up. Clinicians completed the Quick Inventory of Depressive Symptoms and collected information on youth experiences of suicidal ideation, suicide attempt, and NSSI. RESULTS: Affirmed males reported greater depression and anxiety at baseline, but these differences were small ($P < .01$). Youth reported large improvements in body dissatisfaction ($P < .001$), small to moderate improvements in self-report of depressive symptoms ($P < .001$), and small improvements in total anxiety symptoms ($P < .01$). No demographic or treatment-related characteristics were associated with change over time. Lifetime and follow-up rates were 81% and 39% for suicidal ideation, 16% and 4% for suicide attempt, and 52% and 18% for NSSI, respectively. CONCLUSIONS: Results provide further evidence of the critical role of gender-affirming hormone therapy in reducing body dissatisfaction. Modest initial improvements in mental health were also evident.

Annotation: A US-based pre-post descriptive study examining changes in body dissatisfaction and mental health (anxiety/depression) among adolescents receiving GAH.

Laurenzano SE, Newfield RS, Lee E, Marinkovic M. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents and Young Adults: A Single Center's 8-Year Experience. *Transgend Health*. 2021;6(6):343-352. doi:10.1089/trgh.2020.0103 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34988290

Abstract: Purpose: To describe our Center's 8-year experience with subcutaneous testosterone (SC-T) as gender-affirming hormone therapy (GAHT) in transmasculine and gender-diverse (TM/GD) youth. Methods: An Institutional Review Board (IRB)-approved retrospective study for 119 TM/GD subjects who started SC-T at age 13-19 and received SC-T for >6 months between 2012 and 2020. Results: SC-T was typically started at 25-50 mg biweekly and dose was escalated at provider's discretion. Over 96% of subjects were on 100-320 mg monthly (divided weekly or biweekly) at last follow-up. There was an overall increase in mean total and free testosterone (T) over the dose range ($p=0.003$), with mean total and free T levels of 460 ng/dL and 92 pg/mL, respectively, at a monthly SC-T dose of 200 mg. For subjects on SC-T without additional menstrual suppression, 54% had cessation of menses at 140 mg monthly and 97% at 200 mg

monthly. On average, menses stopped 4.7 (standard deviation 3.0) months after starting SC-T. There was a decrease in high-density lipoprotein and increase in hematocrit from baseline to follow-up. Body mass index Z-scores did not change significantly with treatment. Mild acne was common; severe acne and significant injection site reactions were uncommon. Sustained hypertension, transaminitis, and dyslipidemia were infrequent. Conclusions: SC-T is well tolerated and effective in reaching recommended T levels and stopping menses in TM/GD youth. Occurrence of serious adverse effects is low and inability to tolerate injections is very uncommon. SC-T is a safe and effective alternative to intramuscular testosterone in initiation and maintenance of GAHT in TM/GD youth.

Annotation: Examines endogenous hormone levels, menstrual outcomes, and body changes in transmasculine and gender-diverse adolescents treated with subcutaneous testosterone

Lavender R, Shaw S, Maninger JK, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. *LGBT Health*. 2023, 10.1089/lgbt.2022.0201doi:10.1089/lgbt.2022.0201 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36989498

Abstract: Purpose: Few studies have assessed the effects of hormonal treatments such as gonadotropin-releasing hormone agonists (GnRHa) and gender-affirming hormones (GAH) on mental health outcomes in clinically referred gender-diverse young people from a younger age. Where this research has been conducted, findings have been mixed. This study investigated a cohort of young people before treatment, 1 year into GnRHa, and 1 year into GAH treatment to understand psychological and behavioral impacts over time. Methods: Thirty-eight young people (28 assigned female and 10 assigned male) referred to endocrinology, younger than 15 years at/beyond Tanner stage two, who received GnRHa followed by GAH treatment, were assessed in a retrospective analysis study. Young people completed the Youth Self Report (YSR), the Body Image Scale, and the Utrecht Gender Dysphoria Scale, while caregivers completed the Child Behavior Checklist (CBCL) and the Social Responsiveness Scale-2 at all time points. Results: Dissatisfaction with primary sexual characteristics ($p = 0.02$), gender dysphoria ($p = 0.01$), and social motivation ($p = 0.04$) improved significantly over time. Self-harm and suicidality also showed a general decrease. Caregivers reported a significant reduction in internalizing ($p = 0.03$) behaviors on the CBCL after GnRHa. Other subcategories of the YSR and CBCL were within normal ranges with no significant difference ($p > 0.05$). Conclusion: These findings demonstrate some improvements in psychological and behavioral outcomes in young people concurrently receiving psychosocial support and hormone treatment. Future research with larger and more diverse samples is warranted to further understand generalizability.

Annotation: A London-based pre-post study examining changes in mental health and suicidality for patients after initiating unspecified GnRH analogues and cross-sex hormones.

Lopez de Lara D, Perez Rodriguez O, Cuellar Flores I, et al. [Psychosocial assessment in transgender adolescents]. *An Pediatr (Engl Ed)*. 2020;93(1):41-48. doi:10.1016/j.anpedi.2020.01.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32144041

Abstract: OBJECTIVES: To evaluate the psychosocial status of the patients who attend a paediatric endocrinology clinic due to gender incongruity (GI), and to establish the impact on this after one-year of cross hormonal therapy (CHT). MATERIAL AND METHODS: An analytical and prospective study conducted on adolescents between 14 and 18 years old with GI, and who

attended the Endocrinology clinic during 2018-2019. The sample included 23 transgender cases (16 male and 7 female cases) and 30 cisgender controls. Study variables were collected at T0 (pre-treatment) and T1 (after one year of CHT) and included sociodemographic data, Utrecht test, SDQ-Cas test, family APGAR test, STAI scale-anxiety Grade, and BDI-II depression assessment test. RESULTS: A significant improvement (P<.05) was found between T0 and T1 in the transgender group in terms of emotional symptoms, behaviour problems, hyperactivity symptoms, pro-social conduct, as well as in the degree of anxiety and depression measured by the SDQ-Cas test, the STAI and the BDI-II scale. There were significant differences in these scales between the transgender group and the controls at T0, however, the scores equalised at T1. The families in this sample of transgender patients provided a very favourable environment according to the scores obtained on the family APGAR scale. CONCLUSIONS: The rates of anxiety, emotional and behaviour distress, depressive symptomatology, as well as the feeling of gender dysphoria of these transgender patients were similar to those of non-transsexual population of the same age after one year of CHT initiated at ages between 14-18 years old.

Annotation: Examines psychosocial outcomes in TGNB patients who attend a pediatric endocrinology clinic before and after one-year of cross hormonal therapy (CHT). In Spanish.

Millington K, Barrera E, Daga A, et al. The effect of gender-affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: implications for estimating GFR. *Pediatr Nephrol*. 2022;37(9):2141-2150. doi:10.1007/s00467-022-05445-0 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35083530

Abstract: BACKGROUND: Equations for estimated glomerular filtration rate (eGFR) based on serum creatinine include terms for sex/gender. For transgender and gender-diverse (TGD) youth, gender-affirming hormone (GAH) treatment may affect serum creatinine and in turn eGFR. METHODS: TGD youth were recruited for this prospective, longitudinal, observational study prior to starting GAH treatment. Data collected as part of routine clinical care were abstracted from the medical record. RESULTS: For participants designated male at birth (DMAB, N = 92), serum creatinine decreased within 6 months of estradiol treatment (mean +/- SD 0.83 +/- 0.12 mg/dL to 0.76 +/- 0.12 mg/dL, p < 0.001); for participants designated female at birth (DFAB, n = 194), serum creatinine increased within 6 months of testosterone treatment (0.68 +/- 0.10 mg/dL to 0.79 +/- 0.11 mg/dL, p < 0.001). Participants DFAB treated with testosterone had serum creatinine similar to that of participants DMAB at baseline, whereas even after estradiol treatment, serum creatinine in participants DMAB remained higher than that of participants DFAB at baseline. Compared to reference groups drawn from the National Health and Nutritional Examination Survey, serum creatinine after 12 months of GAH was more similar when compared by gender identity than by designated sex. CONCLUSION: GAH treatment leads to changes in serum creatinine within 6 months of treatment. Clinicians should consider a patient's hormonal exposure when estimating kidney function via eGFR and use other methods to estimate GFR if eGFR based on serum creatinine is concerning.

Annotation: A cohort study comparing kidney function measures between TGNB adolescents receiving gender-affirming hormone therapy versus a cohort of other adolescents from NHANEs.

Millington K, Finlayson C, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Association of High-Density Lipoprotein Cholesterol With Sex Steroid Treatment in Transgender and Gender-Diverse Youth. *JAMA Pediatr*. 2021;175(5):520-521. doi:10.1001/jamapediatrics.2020.5620 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33587098

Abstract: This cohort study analyzes the association of sex steroids with cholesterol in different sex-chromosome contexts.

Annotation: A research letter examining growth, body composition, and cholesterol changes in TGNB adolescents receiving CSHT. Only natal sex reported (N = 83 AMAB and N = 186 AFAB).

Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an Androgen Blocker With Secondary Effect of Promoting Feminization in Male-to-Female Transgender Adolescents. *J Adolesc Health*. 2019;64(4):544-546. doi:10.1016/j.jadohealth.2018.10.296 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30612811

Abstract: PURPOSE: The purpose of the study was to describe the novel use of bicalutamide in transgender youth. METHODS: This is a retrospective review of patients with gender dysphoria followed in the pediatric endocrine clinic at Riley Hospital for Children. RESULTS: Of 104 patients with gender dysphoria, 23 male-to-female adolescents received bicalutamide 50 mg daily as a second-line puberty blocker after insurance company denial of a gonadotropin-releasing hormone analog. Six patients received estrogen concurrently. Of 13 patients treated exclusively with bicalutamide seen in follow-up, 84.6% had breast development within 6 months, the majority being >/= Tanner stage III. CONCLUSIONS: Bicalutamide may be an alternative to gonadotropin-releasing hormone analogs in transgender male-to-female youth who are also ready to undergo physical transition.

Annotation: Clinical and laboratory characteristics of transfeminine patients treated with the antiandrogen bicalutamide as an androgen blocker after insurance denials of claims for GnRH agonists

Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr*. 2018;172(5):431-436. doi:10.1001/jamapediatrics.2017.5440 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29507933

Abstract: IMPORTANCE: Transmasculine youth, who are assigned female at birth but have a gender identity along the masculine spectrum, often report considerable distress after breast development (chest dysphoria). Professional guidelines lack clarity regarding referring minors (defined as people younger than 18 years) for chest surgery because there are no data documenting the effect of chest surgery on minors. OBJECTIVE: To examine the amount of chest dysphoria in transmasculine youth who had had chest reconstruction surgery compared with those who had not undergone this surgery. DESIGN, SETTING, AND PARTICIPANTS: Using a novel measure of chest dysphoria, this cohort study at a large, urban, hospital-affiliated ambulatory clinic specializing in transgender youth care collected survey data about testosterone use and chest distress among transmasculine youth and young adults. Additional information about regret and adverse effects was collected from those who had undergone surgery. Eligible youth were 13 to 25 years old, had been assigned female at birth, and had an identified gender as something other than female. Recruitment occurred during clinical visits and via telephone between June 2016 and December 2016. Surveys were collected from participants who had undergone chest surgery at the time of survey collection and an equal number of youth who had not undergone surgery. MAIN OUTCOMES AND MEASURES: Outcomes were chest dysphoria composite score (range 0-51, with higher scores indicating greater distress) in all participants; desire for chest surgery in patients who had not had surgery; and regret about surgery and

complications of surgery in patients who were postsurgical. RESULTS: Of 136 completed surveys, 68 (50.0%) were from postsurgical participants, and 68 (50.0%) were from nonsurgical participants. At the time of the survey, the mean (SD) age was 19 (2.5) years for postsurgical participants and 17 (2.5) years for nonsurgical participants. Chest dysphoria composite score mean (SD) was 29.6 (10.0) for participants who had not undergone chest reconstruction, which was significantly higher than mean (SD) scores in those who had undergone this procedure (3.3 [3.8]; P < .001). Among the nonsurgical cohort, 64 (94%) perceived chest surgery as very important, and chest dysphoria increased by 0.33 points each month that passed between a youth initiating testosterone therapy and undergoing surgery. Among the postsurgical cohort, the most common complication of surgery was loss of nipple sensation, whether temporary (59%) or permanent (41%). Serious complications were rare and included postoperative hematoma (10%) and complications of anesthesia (7%). Self-reported regret was near 0. CONCLUSIONS AND RELEVANCE: Chest dysphoria was high among presurgical transmasculine youth, and surgical intervention positively affected both minors and young adults. Given these findings, professional guidelines and clinical practice should consider patients for chest surgery based on individual need rather than chronologic age.

Annotation: Examines the amount of chest dysphoria in transmasculine youth who had had chest reconstruction surgery compared with those who had not undergone this surgery.

Perl L, Elkon-Tamir E, Segev-Becker A, Israeli G, Brener A, Oren A. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab*. 2021;34(6):741-745. doi:10.1515/jpem-2021-0172 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33823098

Abstract: OBJECTIVES: The benefits of gonadotropin-releasing hormone analogues (GnRHa) in the treatment of central precocious puberty are well established, and their use is regarded as both safe and effective. Possible adverse effects on blood pressure (BP) and cardiac outcomes, body composition, bone health and brain development, however, continue to be of some concern. The aim of this study was to analyze BP changes in transgender female adolescents before and after receiving GnRHa and after adding estrogen treatment. METHODS: This was a retrospective pilot study. We analyzed systolic BP (SBP) and diastolic BP (DBP) before and after GnRHa initiation and after adding estrogen. RESULTS: Nineteen transgender female adolescents received GnRHa and 15 continued to estrogen treatment. Their baseline SBP and DBP percentiles did not change significantly after either GnRHa or the addition of estrogen treatment. CONCLUSIONS: Blood pressure is apparently not affected by GnRHa or GnRHa + estrogen treatment in transgender female adolescents. Further larger studies are indicated to confirm these findings.

Annotation: Examines blood pressure, weight, and hormone levels in transfeminine adolescents who received GnRH analogues for puberty suppression, 15 of whom went on to receive CSHT with estradiol

Perl L, Segev-Becker A, Israeli G, Elkon-Tamir E, Oren A. Blood Pressure Dynamics After Pubertal Suppression with Gonadotropin-Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents: A Pilot Study. *LGBT Health*. 2020;7(6):340-344. doi:10.1089/lgbt.2020.0026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32735503

Abstract: Purpose: We analyzed blood pressure (BP) changes in transgender male adolescents treated with gonadotropin-releasing hormone analogs (GnRHa) and after adding testosterone treatment. Methods: This was a retrospective pilot study. Outcome measures included systolic BP (SBP) and diastolic BP (DBP) before and after GnRHa initiation and after adding testosterone. Results: Fifteen transgender male adolescents received GnRHa. DBP percentiles increased significantly after GnRHa treatment (from 55.9% +/- 26.4 to 73.6% +/- 9.4, p = 0.019). BP levels did not meet criteria for hypertension. DBP percentiles were restored after adding testosterone. Conclusion: GnRHa may increase DBP in transgender male adolescents, and testosterone treatment may restore it. Further larger studies are indicated.

Annotation: Examines blood pressure outcomes in transgender males receiving puberty-suppressing GnRH analogues, followed by CSHT for 9 of them

Roy MK, Wilkerson RB, Alexander K, Nokoff NJ, Cree-Green M, D'Alessandro A. Longitudinal metabolic study of red blood cells from patients undergoing gender-affirming testosterone therapy. *Blood Adv*. 2023;7(16):4269-4277. doi:10.1182/bloodadvances.2022008061 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36001490

Annotation: A research letter reporting findings from a Colorado-based, longitudinal, pre-post study of transgender boys receiving testosterone therapy.

Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. *J Sex Med*. 2016;13(7):1125-1132. doi:10.1016/j.jsxm.2016.05.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27318023

Abstract: INTRODUCTION: Puberty suppression using gonadotropin-releasing hormone agonists (GnRHas) is recommended by current guidelines as the treatment of choice for gender dysphoric adolescents. Although GnRHas have long been used to treat precocious puberty, there are few data on the efficacy and safety in gender dysphoric adolescents. Therefore, the Endocrine Society guideline recommends frequent monitoring of gonadotropins, sex steroids, and renal and liver function. AIM: To evaluate the efficacy and safety of GnRHa treatment to suppress puberty in gender dysphoric adolescents. METHODS: Forty-nine male-to-female and 67 female-to-male gender dysphoric adolescents treated with triptorelin were included in the analysis. MAIN OUTCOME MEASURES: Physical examination, including assessment of Tanner stage, took place every 3 months and blood samples were drawn at 0, 3, and 6 months and then every 6 months. Body composition was evaluated using dual energy x-ray absorptiometry. RESULTS: GnRHa treatment caused a decrease in testicular volume in 43 of 49 male-to-female subjects. In one of four female-to-male subjects who presented at Tanner breast stage 2, breast development completely regressed. Gonadotropins and sex steroid levels were suppressed within 3 months. Treatment did not have to be adjusted because of insufficient suppression in any subject. No sustained abnormalities of liver enzymes or creatinine were encountered. Alkaline phosphatase decreased, probably related to a slower growth velocity, because height SD score decreased in boys and girls. Lean body mass percentage significantly decreased during the first year of treatment in girls and boys, whereas fat percentage significantly increased. CONCLUSION: Triptorelin effectively suppresses puberty in gender dysphoric adolescents. These data suggest routine monitoring of gonadotropins, sex steroids, creatinine, and liver function is not necessary during treatment with triptorelin. Further studies should evaluate the extent to

which changes in height SD score and body composition that occur during GnRHa treatment can be reversed during subsequent cross-sex hormone treatment.

Annotation: Examines growth, body composition, and endogenous hormone levels in TGNB adolescents who received GnRH agonists for 1 year in a gender specialty clinic

Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. *J Sex Med*. 2018;15(9):1357-1363. doi:10.1016/j.jsxm.2018.07.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30224022

Abstract: INTRODUCTION: Gender-affirming hormone treatment is known to affect adrenal androgen levels in adult individuals with gender dysphoria (GD). This may be clinically relevant because the adrenal gland plays a critical role in many different metabolic processes. AIM: This study aims to assess the effects of gonadotropin-releasing hormone analogs (GnRHa) treatment and gender-affirming hormone treatment on adrenal androgen levels in adolescents with GD. METHODS: In this prospective study, dehydroepiandrosterone-sulfate (DHEAS) and androstenedione values were measured every 6 months during 2 years of GnRHa treatment only, and 2 years of GnRHa combined with gender-affirming hormone treatment (estradiol or testosterone) in 73 transgirls and 54 transboys. To determine trends in adrenal androgen levels a linear mixed model was used to approximate androgen levels. MAIN OUTCOME MEASURES: DHEAS and androstenedione levels were the main outcome measures. RESULTS: DHEAS levels rose in transboys during GnRHa treatment, which may represent the normal increase during adolescence. In transgirls no change in DHEAS levels during GnRHa treatment was found. Gender-affirming hormone treatment did not affect DHEAS levels in either sex. In transboys androstenedione levels decreased during the first year of GnRHa treatment, which may reflect reduced ovarian androstenedione synthesis, and rose during the first year of gender-affirming hormone treatment, possibly due to conversion of administered testosterone. In transgirls androstenedione levels did not change during either GnRHa or gender-affirming hormone treatment. CLINICAL IMPLICATIONS: No deleterious effects of treatment on adrenal androgen levels were found during approximately 4 years of follow-up. STRENGTHS & LIMITATIONS: This is one of the largest cohort of adolescents with GD, treated using a uniform protocol, with standardized follow-up. The lack of a control group is a limitation. CONCLUSION: The changes in androstenedione levels during GnRHa and gender-affirming hormone treatment in transboys may not be of adrenal origin. The absence of changes in androstenedione levels in transgirls or DHEAS levels in either sex during gender-affirming hormone treatment suggests that gender-affirming hormone treatment does not significantly affect adrenal androgen production. Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, et al. Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. J Sex Med 2018;15:1357-1363.

Annotation: Examines changes in endogenous hormones during puberty suppression and CSHT in adolescents with GD

Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J Sex Med*. 2019;16(9):1459-1468. doi:10.1016/j.jsxm.2019.06.014 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31405768

Abstract: INTRODUCTION: Current treatment guidelines for adolescents with gender dysphoria recommend therapy with gonadotropin-releasing hormone agonists (GnRHa) and testosterone in transgender males. However, most evidence on the safety and efficacy of testosterone is based on studies in adults. AIM: This study aimed to investigate the efficacy and safety of testosterone treatment in transgender adolescents. METHODS: The study included 62 adolescents diagnosed with gender dysphoria who had started GnRHa treatment and had subsequently received testosterone treatment for more than 6 months. MAIN OUTCOME MEASURE: Virilization, anthropometry, laboratory parameters, and bone mineral density (BMD) were analyzed. RESULTS: Adolescents were treated with testosterone for a median duration of 12 months. Voice deepening began within 3 months in 85% of adolescents. Increased hair growth was first reported on the extremities, followed by an increase of facial hair. Acne was most prevalent between 6 and 12 months of testosterone therapy. Most adolescents had already completed linear growth; body mass index and systolic blood pressure increased but diastolic blood pressure did not change. High-density lipoprotein (HDL) cholesterol and sex hormone binding globulin significantly decreased, but hematocrit, hemoglobin, prolactin, androstenedione, and dehydroepiandrosterone sulfate significantly increased, although not all changes were clinically significant. Other lipids and HbA1c did not change. Vitamin D deficiency was seen in 32-54% throughout treatment. BMD z-scores after 12 to 24 months of testosterone treatment remained below z-scores before the start of GnRHa treatment. CLINICAL IMPLICATIONS: Adolescents need to be counseled about side effects with potential longer term implications such as increased hematocrit and decreased HDL cholesterol and decreased BMD z-scores. They should be advised on diet, including adequate calcium and vitamin D intake; physical exercise; and the use of tobacco and alcohol to avoid additional risk factors for cardiovascular disease and osteoporosis. STRENGTHS & LIMITATIONS: Strengths are the standardized treatment regimen and extensive set of safety parameters investigated. Limitations are the limited duration of follow-up and lack of a control group so some of the observed changes may be due to normal maturation rather than to treatment. CONCLUSION: Testosterone effectively induced virilization beginning within 3 months in the majority of adolescents. Acne was a common side effect, but no short-term safety issues were observed. The increased hematocrit, decreased HDL cholesterol, and decreased BMD z-scores are in line with previous studies. Further follow-up studies will need to establish if the observed changes result in adverse outcomes in the long term. Stoffers IE, de Vries MC, Hannema SE. Physical Changes, Laboratory Parameters, and Bone Mineral Density During Testosterone Treatment in Adolescents with Gender Dysphoria. J Sex Med 2019;16:1459-1468.

Annotation: Examines body changes, growth, cardiovascular risk factors, and metabolic outcomes in testosterone-treated adolescents with GD

Tack LJW, Heyse R, Craen M, et al. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. *J Sex Med*. 2017;14(5):747-757. doi:10.1016/j.jsxm.2017.03.251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28499525

Abstract: BACKGROUND: Cyproterone acetate (CA) is an antiandrogenic progestin commonly used in adult transwomen to suppress endogenous androgens, often in combination with estrogens to induce feminization. AIM: To assess the (side) effects and biochemical changes of CA alone and in combination with estrogens in adolescent trans-girls. METHODS: This study was a retrospective analysis of clinical and biochemical data from 27 trans-girls who presented at Tanner stage G4 and were treated with CA monotherapy for at least 6 months (mean = 12

months) and then in combination with incremental doses of estrogens (CA + E; mean = 16 months). Statistical analysis of data included paired or unpaired Student t-test or Wilcoxon signed-ranks or Mann-Whitney U-test as appropriate. OUTCOMES: Anthropometrics, reported beneficial and side effects, safety parameters, and hormone levels. RESULTS: Physical changes included decrease of facial and non-facial hair growth. One third showed breast development under CA (Tanner stages B2-B3), which increased to Tanner stages B3 and B4 in 66.7% and 9.5% respectively, during CA + E. Reported side effects during CA and CA + E were breast tenderness, emotionality, fatigue, and flushes. No relevant weight changes were observed. Main safety parameters showed the following changes. Hemoglobin and hematocrit decreased and liver enzymes transiently and modestly increased during CA. Triglycerides and cholesterol levels slightly decreased during CA but returned to baseline during CA + E; glucose metabolism was unaffected. Relevant hormonal changes included a decrease in gonadotropins during CA + E and in total and free testosterone levels throughout treatment. Prolactin levels increased during CA and were restored during CA + E. CLINICAL IMPLICATIONS: CA produced modest feminizing effects in trans-girls and therefore might be a valuable alternative in situations in which gonadotropin-releasing hormone analogues are not the treatment of choice and/or are not reimbursed. STRENGTHS AND LIMITATIONS: This is the first study to report on the effects of CA in the treatment of trans-girls and one of the few to report on the use of estrogens in this population. Limitations are the modest sample size and the retrospective nature of this study. CONCLUSION: Treatment with CA in late-pubertal trans-girls overall was safe and well tolerated and induced mild clinical and biochemical feminizing changes. Rapid further feminization was observed with incremental doses of E. Tack LJW, Heyse R, Craen M, et al. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. J Sex Med 2017;14:747-757.

Annotation: A Belgian pre-post, descriptive study examining growth, cardiovascular risk factors, and metabolic changes in transgender female adolescents taking estrogen with an antiandrogen not available in the US (cyproterone)

Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*. 2017;95:11-19. doi:10.1016/j.bone.2016.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27845262

Abstract: Puberty is highly important for the accumulation of bone mass. Bone turnover and bone mineral density (BMD) can be affected in transgender adolescents when puberty is suppressed by gonadotropin-releasing hormone analogues (GnRHa), followed by treatment with cross-sex hormone therapy (CSHT). We aimed to investigate the effect of GnRHa and CSHT on bone turnover markers (BTMs) and bone mineral apparent density (BMAD) in transgender adolescents. Gender dysphoria was diagnosed based on diagnostic criteria according to the DSM-IV (TR). Thirty four female-to-male persons (transmen) and 22 male-to-female persons (transwomen)were included. Patients were allocated to a young (bone age of <15years in transwomen or <14 in transmen) or old group (bone age of >/=15years in transwomen or >/=14years in transmen). All were treated with GnRHa triptorelin and CSHT was added in incremental doses from the age of 16years. Transmen received testosterone esters (Sustanon, MSD) and transwomen received 17-beta estradiol. P1NP, osteocalcin, ICTP and BMD of lumbar spine (LS) and femoral neck (FN) were measured at three time points. In addition, BMAD and Z-scores were calculated. We found a decrease of P1NP and 1CTP during GnRHa treatment,

indicating decreased bone turnover (young transmen 95% CI -74 to -50%, p=0.02, young transwomen 95% CI -73 to -43, p=0.008). The decrease in bone turnover upon GnRHa treatment was accompanied by an unchanged BMAD of FN and LS, whereas BMAD Z-scores of predominantly the LS decreased especially in the young transwomen. Twenty-four months after CSHT the BTMs P1NP and ICTP were even more decreased in all groups except for the old transmen. During CSHT BMAD increased and Z-scores returned towards normal, especially of the LS (young transwomen CI 95% 0.1 to 0.6, p=0.01, old transwomen 95% CI 0.3 to 0.8, p=0.04). To conclude, suppressing puberty by GnRHa leads to a decrease of BTMs in both transwomen and transmen transgender adolescents. The increase of BMAD and BMAD Z-scores predominantly in the LS as a result of treatment with CSHT is accompanied by decreasing BTM concentrations after 24months of CSHT. Therefore, the added value of evaluating BTMs seems to be limited and DXA-scans remain important in follow-up of bone health of transgender adolescents.

Annotation: Examines bone changes over time with puberty suppression and CSHT in TGNB adolescents in a gender specialty clinic

Willemsen LA, Boogers LS, Wiepjes CM, et al. Just as Tall on Testosterone; a Neutral to Positive Effect on Adult Height of GnRHa and Testosterone in Trans Boys. *The Journal of clinical endocrinology and metabolism*. 2023;108(2):414-421. doi:10.1210/clinem/dgac571 Accessed September 15, 2023. Available at https://watermark.silverchair.com/dgac571.pdf

Abstract: CONTEXT: Growth is an important topic for many transgender boys. However, few studies have investigated the impact of puberty suppression (PS) and gender-affirming hormone treatment (GAHT) on growth and adult height. OBJECTIVE: To evaluate the effect of PS and GAHT on growth and adult height. DESIGN: Retrospective cohort study. SETTING: Specialized gender identity clinic. PARTICIPANTS: A total of 146 transgender boys treated with GnRH analogues and testosterone who reached adult height. MAIN OUTCOME MEASURES: Growth, bone age (BA), adult height, and difference between adult height and predicted adult height (PAH) and midparental height. RESULTS: In those with BA ≤14 years at start (n = 61), a decrease in growth velocity and bone maturation during PS was followed by an increase during GAHT. Adult height was 172.0 ± 6.9 cm; height SD score was similar to baseline (0.1; 95% CI, -0.2 to 0.4). Adult height was 3.9 ± 6.0 cm above midparental height and 3.0 ± 3.6 cm above PAH at start of PS. A younger BA at start PS was associated with an adult height significantly further above PAH. CONCLUSION: During PS, growth decelerated followed by an acceleration during GAHT. Although adult height SD score was similar to baseline, adult height was taller than predicted based on BA at baseline, especially in those who started treatment at a younger BA. It is reassuring that PS and GAHT do not have a negative impact on adult height in transgender boys and might even lead to a slightly taller adult height, especially in those who start at a younger age.

Annotation: A longitudinal, pre-post descriptive study examining height and weight outcomes in TGNB adolescent boys who initiated GnRH agonists before age 16 years.

Eligible Studies Lacking High-priority Comparisons: Case Studies (Bibliography Only)

Adeleye AJ, Stark BA, Jalalian L, Mok-Lin E, Smith JF. Evidence of Spermatogenesis in the Presence of Hypothalamic Suppression and Low Testosterone in an Adolescent Transgender Female: A Case Report. *Transgender Health*. 2023;8(1):104-107. doi:10.1089/trgh.2021.0034 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0034

Abstract: Objective: To report a novel case of semen cryopreservation after testicular sperm extraction in an adolescent transgender female without cessation of gonadotropin-releasing hormone (GnRH) agonist therapy and feminizing hormone therapy. Methods: This is a case report of a 16-year-old transgender female using leuprolide acetate for 4 years and estradiol for 3 years requesting semen cryopreservation at the time of gender-affirming orchiectomy. She desired to proceed without cessation of gender affirming hormone therapy. The patient's consent was obtained for written publication. Results: The patient underwent testicular sperm extraction followed by orchiectomy. The sample was processed and cryopreserved in a 1:1 Test Yolk Buffer. Multiple early and late spermatids were identified as well as spermatagonium in the TESE specimen. Conclusion(s): Advanced spermatogenesis may occur in the presence of a GnRH agonist. Cessation of GnRH agonist therapy may not be essential for semen cryopreservation in adolescent transgender females.

Annotation: Examines treatment course and outcomes in a transgender female adolescent with spermatogenesis during hypothalamic suppression and low testosterone

Akgül S, Tuzun Z, Pehlivanturk Kizilkan M, Ozon ZA. Menstrual Suppression in Gender Minority Youth. *J Clin Res Pediatr Endocrinol*. 2022;14(4):463-468. doi:10.4274/jcrpe.galenos.2021.2020.0283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34044500

Abstract: The purpose of this case series was to evaluate menstrual suppression in sex assigned at birth female adolescents identifying as male or gender non-conforming. A retrospective chart review of four gender minority youth (GMY), age 14-17, was performed for gender identity history, type and success of menstrual suppression, method satisfaction, side effects and improvement in menstrual distress. Menstrual suppression was successful in three patients, one patient discontinued use due to side effects that caused an increase in gender dysphoria. Menstrual distress and bleeding pattern improved in the majority of GMY in this series but side effects, as well as contraindications, may limit their use. In conclusion, menstrual dysphoria can be life-threatening for GMY and it is important that clinicians consider menstrual suppression in GMY with menstrual dysphoria. This series emphasizes the importance of individualized treatment plans.

Annotation: A case series reporting on use of GnRHa for menstrual suppression in 4 Turkish gender minority youth.

Barnard EP, Dhar CP, Rothenberg SS, et al. Fertility Preservation Outcomes in Adolescent and Young Adult Feminizing Transgender Patients. *Pediatrics*. 2019;144(3)doi:10.1542/peds.2018-3943 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31383814

Abstract: BACKGROUND: Fertility preservation enables patients undergoing gonadotoxic therapies to retain the potential for biological children and now has broader implications in the

care of transgender individuals. Multiple medical societies recommend counseling on fertility preservation before initiating therapy for gender dysphoria; however, outcome data pre- and posttreatment are limited in feminizing transgender adolescents and young adults. METHODS: The University of Pittsburgh Institutional Research Board approved this study. Data were collected retrospectively on transgender patients seeking fertility preservation between 2015 and 2018, including age at initial consultation and semen analysis parameters. RESULTS: Eleven feminizing transgender patients accepted a referral for fertility preservation during this time; consultation occurred at median age 19 (range 16-24 years). Ten patients attempted and completed at least 1 semen collection. Eight patients cryopreserved semen before initiating treatment. Of those patients, all exhibited low morphology with otherwise normal median semen analysis parameters. In 1 patient who discontinued leuprolide acetate to attempt fertility preservation, transient azoospermia of 5 months' duration was demonstrated with subsequent recovery of spermatogenesis. In a patient who had previously been treated with spironolactone and estradiol, semen analysis revealed persistent azoospermia for the 4 months leading up to orchiectomy after discontinuation of both medications. CONCLUSIONS: Semen cryopreservation is a viable method of fertility preservation in adolescent and young adult transgender individuals and can be considered in patients who have already initiated therapy for gender dysphoria. Further research is needed to determine the optimal length of time these therapies should be discontinued to facilitate successful semen cryopreservation.

Annotation: Reports fertility-preservation outcomes in TGNB patients, including 2 who were < 18 years of age at the fertility preservation consult, 4 who were < 18 at the time of their initial GD consultation, and 7 who were < 18 at the time of GD onset.

Barthel EM, Werny DM, Hayden LL, Salehi P. Gender Affirming Hormone Replacement for the Adolescent and Young Adult Cancer Survivor with Hypogonadism. *J Adolesc Young Adult Oncol*. 2020;9(1):128-131. doi:10.1089/jayao.2019.0070 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31580768

Abstract: Hypogonadism is a known late effect of cancer treatment. Hypogonadism requires replacement of sex steroids to ensure appropriate development of secondary sex characteristics, growth, and other beneficial health effects. We present a cancer survivor with hypogonadotropic hypogonadism and gender dysphoria. The patient received gender affirming care in our gender clinic with a multidisciplinary team that included an endocrinologist. This is not an isolated case at our institution. Survivorship oncologists must include a discussion about gender concurrently with conversations about survivors' development of puberty. Conversations should start early to ensure appropriate referrals and gender affirming hormone replacement.

Annotation: A transgender female adolescent cancer survivor with hypogonadism in a pediatric gender specialty clinic (no IRB).

Bentsianov S, Gordon L, Goldman A, Jacobs A, Steever J. Use of Copper Intrauterine Device in Transgender Male Adolescents. *Contraception*. 2018;98(1):74-75. doi:10.1016/j.contraception.2018.02.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29490287

Abstract: Transgender men need contraception if engaging in intercourse with a cis-gender male partner. The copper IUD is an effective, non-hormonal contraceptive well suited for trans-males

even while utilizing gender affirming hormone therapy. A gender-neutral medical facility with well-trained and sensitive staff is the ideal setting to provide such contraceptive care.

Annotation: A trio of case reports on use of hormones and copper IUDs in transgender young men, including one that was age 17 upon presentation

Boris JR, McClain ZBR, Bernadzikowski T. Clinical Course of Transgender Adolescents with Complicated Postural Orthostatic Tachycardia Syndrome Undergoing Hormonal Therapy in Gender Transition: A Case Series. *Transgend Health*. 2019;4(1):331-334. doi:10.1089/trgh.2019.0041 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31754630

Abstract: Purpose: Postural orthostatic tachycardia syndrome (POTS), an increasingly recognized dysautonomia, may affect as many as 3,000,000 Americans. Concurrently, prevalence estimates suggest 10% of individuals identify as lesbian, gay, bisexual, transgender, or questioning/queer. The preponderance of female POTS patients implies hormonal differences between natal sexes and their role in POTS. Transgender POTS patients using hormone therapies may offer further insight into the mechanism of POTS. There have been no previously published studies of transgender patients with POTS undergoing gender-affirming hormone therapy. Methods: We reviewed our electronic health record for clinical histories of transgender patients in our POTS Database. Results: Three patients who transitioned from female to male demonstrated clinical improvement of their POTS symptoms with the addition of testosterone therapy. Conclusion: We present our clinical experience of three transgender POTS patients who transitioned from female to male with hormone therapy, all of whom demonstrated clinical improvement with testosterone. This may give further insight into the pathophysiology of POTS. However, the authors do not endorse the use of hormone therapy as primary therapy for the symptoms of POTS.

Annotation: Transgender adolescents presenting with complicated POTS and undergoing hormonal treatment

Campos-Munoz L, Lopez-De Lara D, Rodriguez-Rojo ML, Conde-Taboada A, Lopez-Bran E. Transgender adolescents and acne: A cases series. *Pediatr Dermatol*. 2018;35(3):e155-e158. doi:10.1111/pde.13448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29575091

Abstract: We describe the difficulties of treating acne in a series of female-to-male transgender adolescents, including concerns about potential hepatotoxicity with concomitant use of testosterone with isotretinoin or tetracyclines. Acne is a foreseeable adverse effect of testosterone treatment in transgender adolescents, so monitoring for acne is advised. The treatment of acne in transgender adolescents is important given that severe acne and transgenderism are associated with higher rates of depression and suicide.

Annotation: A pediatric case series reporting on transgender male adolescents presenting with acne (no IRB)

Cesur E, Yuksel S, Basar K, Kaptan S. Clinical Follow-up of Two Adolescents Diagnosed with Gender Dysphoria. *Turk Psikiyatri Derg*. 2022;33(3):214-219. doi:10.5080/u26795 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36148573

Abstract: Rapid physical, psychological and sexual changes in adolescents due to the developmental process differentiate the approach to adolescents with gender dysphoria (GD) from the approach to adults. In this article, two adolescents who applied for GD and followed up for a long time are presented. The first case was assigned male at birth and defined herself as female. At the age of fifteen, a gonadotropin-releasing hormone analog was started for puberty suppression, and sex hormone was started in the follow-up. The second case's assigned sex was female and defined himself as male. At the age of sixteen years and six months, puberty suppressive treatment was started, followed by sex hormones. Both cases were able to continue their psychosocial development without any problems after the psychiatric and physical treatments they could reach on time. Although GD in adolescents cannot be resolved with puberty suppression alone, it creates time to resolve the acute problems and to search for appropriate treatment approaches in the future. Puberty suppression partially relieves and prevents the exacerbation of the dysphoria experienced by the youth diagnosed as GD, and creates time to search appropriate treatment approaches in the follow-up. Through these two cases, it is aimed to introduce the gender affirmation processes of adolescents with GD, to discuss the medical interventions in adolescence and the psychosocial effects of the process on individuals. Keywords: Gender dysphoria, gender incongruence, adolescence, gender affirmation process, puberty supression, puberty blockers.

Annotation: A pair of case reports of Turkish, transgender adolescents with long-term follow-up

Chen D, Bernardi LA, Pavone ME, Feinberg EC, Moravek MB. Oocyte cryopreservation among transmasculine youth: a case series. *J Assist Reprod Genet*. 2018;35(11):2057-2061. doi:10.1007/s10815-018-1292-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30136015

Abstract: None

Annotation: Examines fertility preservation outcomes in transmasculine youths undergoing oocyte cryopreservation

Churcher Clarke A, Spiliadis A. 'Taking the lid off the box': The value of extended clinical assessment for adolescents presenting with gender identity difficulties. *Clin Child Psychol Psychiatry*. 2019;24(2):338-352. doi:10.1177/1359104518825288 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L627311211&from=export

Abstract: As the number of young people referred to specialist gender identity clinics in the western world increases, there is a need to examine ways of making sense of the range and diversity of their developmental pathways and outcomes. This article presents a joint case review of the authors caseloads over an 18-month period, to identify and describe those young people who presented to the Gender Identity Development Service (GIDS) with gender dysphoria (GD) emerging in adolescence, and who, during the course of assessment, ceased wishing to pursue medical (hormonal) interventions and/or who arrived at a different understanding of their embodied distress. From the 12 cases identified, 2 case vignettes are presented. Implications for the development of clinical practice, service delivery and research are considered.

Annotation: A case series reporting on TGNB patients seen in the UK's Tavistock & Portman Gender Identity Development Service (GIDS)

Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011;40(4):843-847. doi:10.1007/s10508-011-9758-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21503817

Abstract: Puberty suppression by means of gonadotropin releasing hormone (GnRH) analogs is considered a diagnostic aid in gender dysphoric adolescents. However, there are also concerns about potential risks, such as poor outcome or post-surgical regret, adverse effects on metabolic and endocrine status, impaired increment of bone mass, and interference with brain development. This case report is on a 22-year follow-up of a female-to-male transsexual, treated with GnRH analogs at 13 years of age and considered eligible for androgen treatment at age 17, and who had gender reassignment surgery at 20 and 22 years of age. At follow-up, he indicated no regrets about his treatment. He was functioning well psychologically, intellectually, and socially; however, he experienced some feelings of sadness about choices he had made in a long-lasting intimate relationship. There were no clinical signs of a negative impact on brain development. He was physically in good health, and metabolic and endocrine parameters were within reference ranges. Bone mineral density was within the normal range for both sexes. His final height was short as compared to Dutch males; however, his body proportions were within normal range. This first report on long-term effects of puberty suppression suggests that negative side effects are limited and that it can be a useful additional tool in the diagnosis and treatment of gender dysphoric adolescents.

Annotation: A case report following a Dutch adolescent who received puberty suppresion 22 years earlier.

Daniolos PT, Telingator CJ. Engendering identity. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1245-1247. doi:10.1016/j.jaac.2013.09.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24290454

Abstract: None

Annotation: Case report of the clinical findings in one transgender male adolescent

Day DS, Saunders JJ, Matorin A. Gender Dysphoria and Suicidal Ideation: Clinical Observations from a Psychiatric Emergency Service. *Cureus*. 2019;11(11):e6132. doi:10.7759/cureus.6132 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6903884/pdf/cureus-0011-00000006132.pdf

Abstract: Adolescent gender dysphoria is increasingly common. There has been documentation of the association of gender dysphoria with numerous other psychiatric conditions as well as attempted and completed suicide. The literature is unsettled on specific risk factors for self-harm within this population. Though there are published recommendations, there appears to be a need for additional clinical evidence for the determination of the safest and most effective treatment strategies for adolescent gender dysphoria. This clinical observation describes the unique case of an adolescent with gender dysphoria, severe body dysmorphia, and suicidal ideation who presented for emergency psychiatric evaluation. Gender-affirming hormone therapy had been administered to this patient at the age of 13, well earlier than published guidelines, though it was discontinued after a short course due to persistent gender uncertainty and distress. This case provides an opportunity to consider the complexity of adolescent gender dysphoria, including the unique individual features that affect the risk for self-harm and how

treatment history may be related. With an increasing prevalence of gender dysphoria in this population, it is essential that every provider who cares for adolescents be well informed and prepared to recognize and respond to these risks. Copyright © 2019, Day et al.

Annotation: A transgender boy presents to an academic emergency department with mental health crisis after detransitioning

Donaldson AA, Hall A, Neukirch J, et al. Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series. *Int J Eat Disord*. 2018;51(5):475-479. doi:10.1002/eat.22868 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29740834

Abstract: Gender nonconforming youth are at risk for body dissatisfaction and disordered eating. Currently, only a small body of literature addresses this high-risk group. The five cases in this series highlight important themes for this patient population from an interdisciplinary perspective. Identified themes include increased risk for self-harm/suicide, complex psychiatric, and medical implications of delay to treatment for either gender dysphoria or disordered eating, and the importance of collaborative management to maximize care and facilitate healthy development to adulthood. The purpose of this case series is to expand the interdisciplinary discussion regarding the breadth of presentation and management considerations for gender nonconforming adolescents with disordered eating. An interdisciplinary approach to care might enhance access to comprehensive, collaborative treatment for disordered eating, and gender dysphoria in this unique population.

Annotation: Eating disorders, suicidality, and self-harm behaviors in TGNB cases

Eisenberg L. Minor Patient, Major Decisions: Caring for a Rural Child With Gender Dysphoria. *Am J Bioeth*. 2019;19(7):64-65. doi:10.1080/15265161.2019.1619346 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31237514

Abstract: None

Annotation: A US-based case report of a transgender male adolescent (no IRB).

Expösito-Campos P, Gomez-Balaguer M, Hurtado-Murillo F, Garcia-Moreno RM, Morillas-Arino C. Medical detransition following transgender identity reaffirmation: two case reports. *Sex Health*. 2022;18(6):498-501. doi:10.1071/SH21089 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34883041

Abstract: Background Recently, increased social and scientific attention has been paid to gender detransition, a phenomenon in which individuals discontinue gender-affirming medical interventions (GAMI) aimed at alleviating gender dysphoria (GD). Yet, clinical knowledge of detransitioners and their experiences is still scarce. Case reports published in the literature suggest that both internal and external factors may influence this decision. Methods Two transgender individuals treated for GD at a gender identity unit presented with a desire to discontinue GAMI. A description of their clinical evolution is presented. Results Increased body satisfaction, self-esteem, self-acceptance, and self-empowerment with respect to their transgender identity were mentioned by the patients as reasons for discontinuing gender-affirming treatments. Coinciding factors included reduced GD, positive changes in social environments, better interpersonal functioning, and higher levels of psychological well-being in

general. Conclusions Gender detransition is an under-researched phenomenon. These cases highlight the need for a more nuanced approach to gender-related clinical presentations, which involves providing individuals the opportunity to work on their social ecosystems and explore alternative options to manage GD before initiating GAMI.

Annotation: Two case reports of Spanish transgender patients presenting for medical detransition, one of whom was an AMAB adolescent

Fan EM, Gordner C, Luty J. Venous Thromboembolism in a Transgender Adolescent on Testosterone Therapy: A Case Report and Literature Review. *J Pediatr Hematol Oncol*. 2020;42(5):e352-e354. doi:10.1097/MPH.0000000000001755 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32079984

Abstract: The incidence of pediatric venous thromboembolism (VTE) has been increasing in the past few decades and can be associated with significant mortality and morbidity. There are known risk factors associated with VTE, including estrogen therapy. However, the relationship between testosterone and VTE remains unclear. Here, we present a 17-year-old female-to-male transgender patient without a history of inherited thrombophilia, who developed pulmonary embolism while receiving testosterone injections for gender dysphoria. Despite the limited data on testosterone and the risk of VTE, health care providers should counsel patients and family about the possible increased risk of VTE when starting testosterone.

Annotation: A US-based case report of venous thromboembolism (VTE) in a transgender male adolescent on testosterone therapy (no IRB).

Fung R, Greenaway MK, McEvenue G. Gynecomastia in a Transgender Boy: A Case Report. *AACE clinical case reports*. 2021;7(6):350-352. doi:10.1016/j.aace.2021.05.003 Accessed September 15, 2023. Available at https://www.aaceclinicalcasereports.com/article/S2376-0605(21)00065-1/pdf

Abstract: OBJECTIVE: To describe the case of a 17-year-old transgender boy who experienced breast development while on testosterone, having been suppressed with a gonadotropin-releasing hormone (GnRH) agonist prior to testosterone therapy., CASE REPORT: A 17-year-old transgender boy presented with breast development after having been on a GnRH agonist and then testosterone since the age of 11 years, having never experienced breast development before, which was consistent with pubertal gynecomastia. A small decrease in the testosterone dose resulted in a significant reduction of gynecomastia. Despite the improvement, he went on to undergo chest surgery with the removal of the breast tissue., DISCUSSION: Pubertal gynecomastia is a common phenomenon in the cisgender male population. However, it has not been previously described in transgender boys. The potential mechanisms for its occurrence were discussed., CONCLUSION: Transgender boys who undergo GnRH agonist treatment for puberty suppression and subsequently receive testosterone therapy for puberty induction may develop gynecomastia. Judicious adjustment of the testosterone therapy may lead to an improvement.

Annotation: A Toronto-based case report of a 17-year-old transgender boy experiencing gynecomastia during ongoing testosterone therapy, after having received puberty suppression

Grimstad F, Moyer Q, Williams CR, Kremen J. A Body-Neutral and Gender-Neutral Modified Ferriman-Gallwey Diagram. *J Pediatr Adolesc Gynecol*. 2022;35(3):375-378.

doi:10.1016/j.jpag.2021.10.015 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34748917

Abstract: BACKGROUND: The modified Ferriman-Gallwey (mFG) diagram for scoring hirsutism uses images with traditionally Eurocentric feminine features. No reports have documented its utility in patients with other gender identities. CASE: A 16-year-old nonbinary masculine patient, assigned female sex at birth, was seen for hyperandrogenism and irregular menses. They declined an exam, citing body dysphoria, and declined self-documenting on the mFG diagram, expressing anxiety with gendered images. We subsequently developed a novel, gender-inclusive mFG diagram, which the patient was then comfortable using to document their hair pattern. SUMMARY AND CONCLUSION: This case documents how the binary gendered characteristics of the mFG diagram can impact the care of patients. As gender expression is highly individual, we created the first gender-inclusive version of the mFG diagram to enhance care for all patients.

Annotation: A US-based case report of hirsutism in a nonbinary masculine adolescent assigned female at birth (no IRB).

Insogna IG, Ginsburg E, Srouji S. Fertility Preservation for Adolescent Transgender Male Patients: A Case Series. *J Adolesc Health*. 2020;66(6):750-753. doi:10.1016/j.jadohealth.2019.12.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32001141

Abstract: This case series from a hospital-based academic in vitro fertilization clinic outlines the feasibility of oocyte cryopreservation for transgender male adolescents after varying degrees of exposure to pubertal blockers and/or testosterone. A description of each patient's oocyte cryopreservation cycle is reviewed, including prior exposure to pubertal blockers and/or testosterone, anti-Mullerian hormone level, stimulation medications, trigger injections, number of oocytes retrieved and cryopreserved, and complications. All patients tolerated stimulation and retrieval well and had mature oocytes cryopreserved in each cycle. There were no complications. Adolescent transgender males who choose to undergo oocyte cryopreservation tolerate the process well, reinforcing the importance of fertility preservation in providing comprehensive care for transgender patients.

Annotation: Describes fertility-preservation outcomes in transgender males presenting for a fertility consultation. Authors did not report gender identities for most subjects, but all subjects were AFAB.

Khazal S, Abdel-Azim H, Kapoor N, Mahadeo KM. Overcoming psychosocial and developmental barriers to blood and marrow transplantation (BMT) in an adolescent/young adult (AYA) transgender patient with chronic myelogenous leukemia. *Pediatr Hematol Oncol*. 2014;31(8):765-767. doi:10.3109/08880018.2014.909914 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24854505

Abstract: Adolescents/young adults (AYAs) afflicted with cancer face unique barriers to potentially standard curative therapies, such as blood and marrow transplantation (BMT). Transgender AYAs face additional barriers and there is a dearth of published literature regarding their oncology-related experience. We present the case of an AYA male-to-female (MTF) transgender patient on cross-sex hormone therapy, with a history of Chronic Myelogenous Leukemia (CML) and significant psychosocial barriers, which initially served as a barrier to BMT at two different centers; we modified our standard consent and education process and was able to successfully proceed with BMT and subsequently cure her CML. Despite unique challenges,

AYA and transgender patients with significant psychosocial barriers may achieve successful outcomes with BMT. Research is needed regarding guidelines for cross-sex hormone therapy administration for patients undergoing BMT and other issues, which may be unique to the transgender experience.

Annotation: A US-based case report on a transgender adolescent with chronic myelogenous leukemia (CML) (no IRB).

Lee G, Ferri-Huerta R, Greenberg KB, Somers KE. Acne fulminans in a transgender boy after an increase in testosterone dosage. *JAAD Case Rep*. 2022;21:32-34. doi:10.1016/j.jdcr.2021.11.029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35141385

Abstract: None

Annotation: Acne fulminans in a transgender boy receiving testosterone CSHT

Lin AJ, Baranski T, Chaterjee D, Chapman W, Foltz G, Kim H. Androgen-receptor-positive hepatocellular carcinoma in a transgender teenager taking exogenous testosterone. *Lancet*. 2020;396(10245):198. doi:10.1016/S0140-6736(20)31538-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32682485

Abstract: None

Annotation: A 17-year-old, testosterone-treated transgender male presenting with androgen-receptor positive hepatocellular carcinoma

Lopez X, Stewart S, Jacobson-Dickman E. Approach to Children and Adolescents with Gender Dysphoria. *Pediatr Rev*. 2016;37(3):89-96; quiz 97-88. doi:10.1542/pir.2015-0032 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26933223

Abstract: None

Annotation: A potential US-based case report of an adolescent presenting with gender dysphoria (no IRB).

Margolin EA, Mason RH. Female-to-male transgender patient with idiopathic intracranial hypertention. *J Neurol Sci*. 2020;415:116970. doi:10.1016/j.jns.2020.116970 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32521344

Abstract: None

Annotation: A Toronto-based case of a transgender male adolescent with idiopathic intracranial hypertension (no IRB).

Martin CE, Lewis C, Omurtag K. Successful oocyte cryopreservation using letrozole as an adjunct to stimulation in a transgender adolescent after GnRH agonist suppression. *Fertil Steril*. 2021;116(2):522-527. doi:10.1016/j.fertnstert.2021.02.025 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33795140

Abstract: OBJECTIVE: To report a successful case of ovarian hyperstimulation and oocyte cryopreservation in a transgender male adolescent after suppression with a gonadotropin-releasing hormone (GnRH) agonist while using the aromatase inhibitor letrozole to maintain low

serum estradiol. DESIGN: Case report. SETTING: Division of Reproductive Endocrinology and Infertility, Washington University in St. Louis School of Medicine, St Louis, Missouri. PATIENT(S): A 15-year-old Tanner II transgender male adolescent with a GnRH agonist implant. INTERVENTION(S): The GnRH agonist implant was removed. The patient was given letrozole (5 mg daily) while undergoing ovarian stimulation with an antagonist protocol. After oocyte retrieval, the patient began taking testosterone. MAIN OUTCOME MEASURE(S): Successful oocyte cryopreservation with minimal changes in breast budding. RESULT(S): The patient's peak serum estradiol concentration was 510 pg/mL. Twenty-two mature oocytes were cryopreserved. Small increases in breast budding occurred between baseline and the time of oocyte retrieval. CONCLUSION(S): We successfully used letrozole to maintain low serum estradiol in a transgender male adolescent during ovarian stimulation. Maintaining low estradiol to minimize pubertal development and possibly prevent gender dysphoria symptoms may make oocyte cryopreservation more desirable for transgender male adolescents.

Annotation: A US-based case report of successful oocyte cryopreservation in a transgender male adolescent (no IRB).

Maxwell S, Noyes N, Keefe D, Berkeley AS, Goldman KN. Pregnancy Outcomes After Fertility Preservation in Transgender Men. *Obstet Gynecol*. 2017;129(6):1031-1034. doi:10.1097/AOG.0000000000002036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28486372

Abstract: BACKGROUND: Transgender individuals, individuals whose gender identity does not align with their sex assigned at birth, undergoing gender-affirming hormonal or surgical therapies may experience loss of fertility. Assisted reproductive technologies have expanded family-building options for transgender men who were assigned female at birth. CASES: Three transgender men underwent oocyte cryopreservation before gender-affirming hormonal therapy. One patient underwent fertility preservation as an adolescent. Two adult patients had children using their cryopreserved oocytes, with the pregnancies carried by their sexually intimate partners. CONCLUSION: Transgender men with cryopreserved gametes can build families in a way that affirms their gender identity. Obstetrician-gynecologists should be familiar with the fertility needs of transgender patients so appropriate discussions and referrals can be made.

Annotation: A New York-based case series reporting on pregnancy outcomes in 3 transgender men (1 adolescent) who underwent fertility preservation

Millington K, Hayes K, Pilcher S, et al. A serous borderline ovarian tumour in a transgender male adolescent. *Br J Cancer*. 2021;124(3):567-569. doi:10.1038/s41416-020-01129-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106582

Abstract: Here we present a transgender male adolescent with an androgen receptor-positive serous borderline ovarian tumour in the setting of testosterone treatment for medical gender transition. To our knowledge, this is the second report of borderline tumour in a transgender individual and the first in an adolescent, an age group in which borderline tumours are extremely rare. We discuss the specific considerations of treating ovarian tumours in the transgender male population, the incompletely understood role of androgens in the genesis of ovarian epithelial neoplasia, and an emphasis on assessing cancer risk in transgender patients based on patient anatomy.

Annotation: A transgender male adolescent on CSHT with a serous borderline ovarian tumor

Nayman T, Hebert M, Ospina LH. Idiopathic intracranial hypertension in a pediatric transgender patient. *Am J Ophthalmol Case Rep*. 2021;24:101208. doi:10.1016/j.ajoc.2021.101208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34622090

Abstract: PURPOSE: Androgens given for gender affirmation have been implicated in the pathophysiology of idiopathic intracranial hypertension (IIH) in transgender patients. 10 cases of transgender adults with IIH have been published but this association has not been described in younger patients. Herein we describe the first case of IIH in an adolescent transgender patient. OBSERVATIONS: A 17-year-old non-obese female-to-male transgender patient on subcutaneous testosterone since age 13 presented with a two-month history of transient visual obscuration and frontal headaches. Ophthalmological examination revealed Frisen grade 2 papilledema with preserved visual function. Lumbar puncture confirmed elevated opening pressure. Papilledema resolved with oral acetazolamide and reduction of testosterone therapy. CONCLUSIONS AND IMPORTANCE: The use of cross-sex hormone therapy (CSH) for gender affirmation may increase the risk of IIH. Awareness of this association is important as the number of younger transgender patients seeking CSH is increasing significantly.

Annotation: A case report of intracranial hypertension in a 17-year-old transgender male

O'Connell MA, Nguyen TP, Ahler A, Skinner SR, Pang KC. Approach to the Patient: Pharmacological Management of Trans and Gender-Diverse Adolescents. *J Clin Endocrinol Metab*. 2022;107(1):241-257. doi:10.1210/clinem/dgab634 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34476487

Abstract: Internationally, increasing numbers of children and adolescents with gender dysphoria are presenting for care. In response, gender-affirming therapeutic interventions that seek to align bodily characteristics with an individual's gender identity are more commonly being used. Depending on a young person's circumstances and goals, hormonal interventions may aim to achieve full pubertal suppression, modulation of endogenous pubertal sex hormone effects, and/or development of secondary sex characteristics congruent with their affirmed gender. This is a relatively novel therapeutic area and, although short-term outcomes are encouraging, longer term data from prospective longitudinal adolescent cohorts are still lacking, which may create clinical and ethical decision-making challenges. Here, we review current treatment options, reported outcomes, and clinical challenges in the pharmacological management of trans and gender-diverse adolescents.

Annotation: A pair of case reports, including one transfeminine and one transmasculine adolescent

Pang KC, Nguyen TP, Upreti R. Case Report: Successful Use of Minoxidil to Promote Facial Hair Growth in an Adolescent Transgender Male. *Front Endocrinol (Lausanne)*. 2021;12:725269. doi:10.3389/fendo.2021.725269 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34659117

Abstract: Increasing numbers of trans and gender diverse young people are presenting to health services seeking gender-affirming medical care. While testosterone therapy in transgender males is generally effective in inducing masculinization, some adolescents encounter barriers to accessing such treatment or may not wish to experience all the changes that usually accompany

testosterone. Here, we describe the case of a 17 year old trans male who presented with gender dysphoria but was initially unable to start testosterone therapy. Due to a desire for facial hair, he was therefore treated with topical minoxidil, an easily accessible, over-the-counter medication that has been used to treat androgenic alopecia for several decades. In this case, minoxidil was applied regularly to the lower face and, after three months of treatment, he developed obvious pigmented facial hair that was sufficient to help him avoid being misgendered. The only reported side effect was excessive skin dryness. Unexpectedly, despite no direct application to other areas, there was also an increase in pigmented body hair, suggestive of systemic absorption and effect. Given its long-standing use and safety record in the management of alopecia, minoxidil might thus represent a useful treatment option for trans males who desire an increase in facial hair.

Annotation: A case report of minoxidil use to promote facial hair growth in a transgender male adolescent

Pang KC, Notini L, McDougall R, et al. Long-term Puberty Suppression for a Nonbinary Teenager. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1606 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974217

Abstract: Many transgender and gender-diverse people have a gender identity that does not conform to the binary categories of male or female; they have a nonbinary gender. Some nonbinary individuals are most comfortable with an androgynous gender expression. For those who have not yet fully progressed through puberty, puberty suppression with gonadotrophin-releasing hormone agonists can support an androgynous appearance. Although such treatment is shown to ameliorate the gender dysphoria and serious mental health issues commonly seen in transgender and gender-diverse young people, long-term use of puberty-suppressing medications carries physical health risks and raises various ethical dilemmas. In this Ethics Rounds, we analyze a case that raised issues about prolonged pubertal suppression for a patient with a nonbinary gender.

Annotation: A case report describing outcomes in a nonbinary patient receiving long-term puberty suppression

Parikh N, Chattha A, Gargollo P, Granberg C. Fertility Preservation: A Tale of Two Testicles. *Urology*. 2021;153:298-300. doi:10.1016/j.urology.2020.11.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33221414

Abstract: OBJECTIVE: The transgender population has long been marginalized by society. Societal stigmata, fear to seek care, and dearth of provider knowledge regarding transgender health issues has caused disparities to widen. The purpose of this case study is to call to attention the often-overlooked aspect of transgender care: the importance of fertility preservation prior to undergoing therapy. METHODS: 13 and 16-year old genetically XY patients presented to a tertiary care facility for gender affirmation. Both self-identified as female since a young age and successfully socially transitioned. Impending onset and/or progression of puberty prompted patients to seek hormonal therapy. Fortunately, physicians in transgender clinic were aware of fertility struggles after undergoing hormone therapy and referred for consultation. RESULTS: Sperm cryopreservation via open gonadal biopsy, tissue cryopreservation, and semen sample were discussed. Though invasive, biopsy relieves patients of the psychological impact of sample production and is indicated in pubertal immaturity. After further discussion with

patients and parents, the 13-year-old decided to undergo testicular biopsy while the 16-year old opted for semen sample. Both patients had success and their genetic material was cryopreserved for future assisted reproduction. CONCLUSION: Gender affirming procedures and hormone therapy affect the long-term reproductive potential of transgender individuals. While cost concerns and insurance coverage regarding oncofertility is a prominent area of discussion, the transgender community is often excluded. With more individuals beginning medical and surgical therapy at a younger age, fertility preservation discussions are essential but often overlooked, depriving these individuals the joy of becoming a biological parent.

Annotation: Transgender females undergoing sperm cryopreservation

Penney SW, Jung JH, Ballantyne AJ, Parekh DS, Klein DA, Viola SA. Affirming Hormone Treatment for a Transgender Adolescent After a Venous Thromboembolic Event. *J Pediatr Hematol Oncol*. 2022;44(5):E892-E895. doi:10.1097/MPH.0000000000002442 Accessed September 15, 2023. Available at https://www.ingentaconnect.com/content/wk/jpho/2022/00000044/00000005/art00019

Abstract: Background: Medical affirmation, including gender-affirming hormones, is an essential component in the treatment of many transgender and gender-diverse youth. The risk of venous thromboembolism (VTE) during testosterone therapy for gender-affirming care is not fully elucidated. Observation: The case describes a 17-year-old transgender male treated with testosterone therapy who presented with an occlusive deep vein thrombosis of right axillary and subclavian veins. Testosterone level was 920 ng/dL at the time of the deep vein thrombosis, and he had no risk factors for VTE. A complete hypercoagulable workup was negative. Conclusions: The possibility of testosterone therapy as a risk factor for VTE may suggest the need to include this information during informed consent discussions. Long-term anticoagulation may be considered for those restarting testosterone therapy.

Annotation: A 17 year-old transgender male diagnosed with VTE who went on to receive testosterone therapy

Pham A, Kasenic A, Hayden L, et al. A Case Series on Disordered Eating Among Transgender Youth With Autism Spectrum Disorder. *J Adolesc Health*. 2021;68(6):1215-1219. doi:10.1016/j.jadohealth.2020.12.143 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33707147

Abstract: Transgender youth with autism spectrum disorder (ASD) may experience complex relationships with eating because of cognitive rigidity, including inflexible thoughts and behaviors around food and/or their body. Yet, there is no research that provides guidance to clinicians providing care for youth with the unique triad of gender dysphoria, ASD, and disordered eating. This case series discusses trends in presentation and management of three cases from a multidisciplinary gender care clinic. All three individuals endorsed rigid thoughts around food and/or body appearance, which affected nutritional intake; however, their presenting eating disorder behaviors, described etiology for disordered thoughts, diagnosis, and level of engagement in a multidisciplinary treatment model varied. Based on these cases we hypothesize several strategies including early engagement with ASD specialists, proactive screening and discussions around eating with all transgender youth with suspected/confirmed ASD, continued discussions throughout care, as disordered eating behaviors may change after the initiation of gender-affirming medications, dietician visits early in treatment regardless of

endorsed thoughts and behaviors, tailored management to the unique needs of each individual and their eating thoughts/behaviors, and consistent multidisciplinary collaboration.

Annotation: A trio of clinical cases of autistic, transgender, pediatric patients with eating disorders

Ristori J, Fisher AD, Castellini G, et al. Gender Dysphoria and Anorexia Nervosa Symptoms in Two Adolescents. *Arch Sex Behav*. 2019;48(5):1625-1631. doi:10.1007/s10508-019-1396-7 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s10508-019-1396-7

Abstract: The co-occurrence of gender dysphoria and anorexia nervosa has been described in the scientific literature. This paper presents two adolescents with gender dysphoria and pathological eating behaviors and questions with longitudinal observations the clinical meaning of anorexia nervosa symptoms (e.g., restricting eating behaviors and fear of gaining weight) in adolescents with gender dysphoria. Both received psychological evaluations at different times: at first admission to the gender dysphoria clinic (T0) and 6 months after starting treatment with gonadotropin-releasing analogues (GnRHa; T1). In both cases, treatment with GnRHa not only improved psychological functioning, but also resolved pathological eating behaviors. In fact, both adolescents reported quick restoring of healthy food habits with restricting eating behaviors as well as intensive exercise no longer needed after treatment with GnRHa. Therefore, pathological eating behaviors (e.g., food avoidance and weight loss) could be assessed as a dysfunctional coping strategy adopted to gain control over a body developing in an unwanted direction and to block irreversible physical pubertal changes. This psychopathological conceptualization of pathological eating behaviors in adolescents with gender dysphoria stresses the importance of providing, in selected cases, early medical intervention such as pubertal suppression with GnRHa. Mental health professionals should therefore perform a specific and detailed assessment on gender identity within the evaluation of apparent eating disorders in adolescents. Restrictive eating behaviors as well as the intense fear of gaining weight or of becoming fat may, in fact, be considered secondary to a gender dysphoria diagnosis instead of anorexia nervosa symptoms.

Annotation: A pair of case reports about the occurrence of anorexia nervosa in TGNB adolescents

Salvatore L, Dancyger I, Shadianloo S, Fornari V. Caring for Transgender Youth with Eating Disorders in a Day Treatment Program. *Adolesc Psychiatry*. 2022;12(3):196-206. doi:10.2174/2210676613666221027124554 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2018683391&from=export

Abstract: Background: The treatment of transgender youth with an eating disorder presents particular considerations due to the unique combination of body dissatisfaction, drive for thinness, malnutrition coupled with the evolving gender identity in the midst of biological and physical changes. At this time, public awareness, societal acknowledgment and legislative initiatives have led to wider acceptance of Lesbian, Gay, Bi-sexual and Transgender rights. However, at the same time, transgender youth are at increased risk for mental health problems, including eating disorders. Objective: To describe two cases of trans adolescents with anorexia nervosa treated in a day treatment program. Methods: This paper will discuss the two clinical vignettes of the transgender adolescent with anorexia nervosa. The focused care included

specific attention to the initial disclosure of gender identity in a safe space, name and pronoun preferences, and wardrobe and hairstyle changes. In addition, treatment focused on the reduction of social anxiety around meal consumption, with special attention given to the impact of weight on the development of secondary sex characteristics. Themes of identity, rejection and secrecy were explored. Conclusion: In summary, treating transgender youth with anorexia nervosa requires additional considerations is more complex than treating cis gender youth. Additional issues, such as hormonal treatments, the development of secondary sexual characteristics, and social and cultural factors, can exacerbate eating disorder symptoms. Treatment should focus on understanding the disorder's etiology and trajectory within this lens.

Annotation: Anorexia nervosa in transgender females who were ages < 18 years when they first sought treatment, but who were seen for eating disorders in a tertiary care center

Sanchez Lorenzo I, Mora Mesa JJ, Oviedo de Lucas O. Psychomedical care in gender identity dysphoria during adolescence. *Revista de psiquiatria y salud mental*. 2017;10(2):96-103. doi:10.1016/j.rpsm.2015.04.002 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26055932

Abstract: INTRODUCTION: In the clinical literature, the term gender dysphoria is used to define the perception of rejection that a person has to the fact of being male or female. In children and adolescents, gender identity dysphoria is a complex clinical entity. The result of entity is variable and uncertain, but in the end only a few will be transsexuals in adulthood., OBJECTIVES: METHODOLOGY: RESULTS AND CONCLUSIONS.

Annotation: A Spanish clinical case report on the presentation, assessment, findings, and treatment of a 16-year-old transgender boy

Sayeem M, Carter B, Phulwani P, Zempsky WT. Gender Dysphoria and Chronic Pain in Youth. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2021-050128 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34561268

Abstract: Chronic pain in youth with gender dysphoria (GD) is poorly understood. The aim of our study was to review the clinical presentation of 8 youth with GD in a multidisciplinary chronic pain clinic. A single center retrospective chart review was conducted to obtain information on demographics, clinical care, previous diagnoses, and validated clinical measures. We present the trajectory of pain in this population with treatment of GD. Recognition and treatment of GD in youth with pain may improve pain outcomes.

Annotation: Describes pain and functionality outcomes in TGNB youths with gender dysphoria presenting in a pain clinic

Schneider MA, Spritzer PM, Soll BMB, et al. Brain Maturation, Cognition and Voice Pattern in a Gender Dysphoria Case under Pubertal Suppression. *Front Hum Neurosci*. 2017;11:528. doi:10.3389/fnhum.2017.00528 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29184488

Abstract: Introduction: Gender dysphoria (GD) (DMS-5) is a condition marked by increasing psychological suffering that accompanies the incongruence between one's experienced or expressed gender and one's assigned gender. Manifestation of GD can be seen early on during

childhood and adolescence. During this period, the development of undesirable sexual characteristics marks an acute suffering of being opposite to the sex of birth. Pubertal suppression with gonadotropin releasing hormone analogs (GnRHa) has been proposed for these individuals as a reversible treatment for postponing the pubertal development and attenuating psychological suffering. Recently, increased interest has been observed on the impact of this treatment on brain maturation, cognition and psychological performance. Objectives: The aim of this clinical report is to review the effects of puberty suppression on the brain white matter (WM) during adolescence. WM Fractional anisotropy, voice and cognitive functions were assessed before and during the treatment. MRI scans were acquired before, and after 22 and 28 months of hormonal suppression. Methods: We performed a longitudinal evaluation of a pubertal transgender girl undergoing hormonal treatment with GnRH analog. Three longitudinal magnetic resonance imaging (MRI) scans were performed for diffusion tensor imaging (DTI), regarding Fractional Anisotropy (FA) for regions of interest analysis. In parallel, voice samples for acoustic analysis as well as executive functioning with the Wechsler Intelligence Scale (WISC-IV) were performed. Results: During the follow-up, white matter fractional anisotropy did not increase, compared to normal male puberty effects on the brain. After 22 months of pubertal suppression, operational memory dropped 9 points and remained stable after 28 months of follow-up. The fundamental frequency of voice varied during the first year; however, it remained in the female range. Conclusion: Brain white matter fractional anisotropy remained unchanged in the GD girl during pubertal suppression with GnRHa for 28 months, which may be related to the reduced serum testosterone levels and/or to the patient's baseline low average cognitive performance.Global performance on the Weschler scale was slightly lower during pubertal suppression compared to baseline, predominantly due to a reduction in operational memory. Either a baseline of low average cognition or the hormonal status could play a role in cognitive performance during pubertal suppression. The voice pattern during the follow-up seemed to reflect testosterone levels under suppression by GnRHa treatment.

Annotation: Describes brain maturation, cognition, and voice pattern in a patient with GD receiving GnRH agonist therapy for puberty suppression

Shumer DE, Tishelman AC. The Role of Assent in the Treatment of Transgender Adolescents. *Int J Transgend*. 2015;16(2):97-102. doi:10.1080/15532739.2015.1075929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27175107

Annotation: Ethics of assent to treatment in a transgender female patient.

Silverstein L, Zander E, Middleman AB. Adolescent identity: The importance of the social history. *SAGE Open Med Case Rep*. 2020;8:2050313X20952980. doi:10.1177/2050313X20952980 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32922796

Abstract: This is a unique case of a patient with trichotillomania, depression, and anxiety for 2 years, serving as coping strategies for underlying gender dysphoria. To our knowledge, a case of a patient presenting with this unique constellation of comorbid conditions has not previously been reported. This case stresses the importance of providers obtaining a full social history consistently and repeatedly while providing a nonjudgmental environment for patients to disclose sensitive and potentially fluid information related to gender identity and sexuality.

Annotation: A transmasculine adolescent with gender dysphoria and comorbid trichotillomania, depression, and anxiety

Stanley K, Cooper J. Hormone Therapy and Venous Thromboembolism in a Transgender Adolescent. *J Pediatr Hematol Oncol*. 2018;40(1):e38-e40. doi:10.1097/MPH.0000000000000984 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945660

Abstract: Venous thromboembolism can be precipitated by both genetic and acquired factors, but the role of testosterone therapy is less clear. Here, we present a 17-year-old transgender adolescent, transitioning from female to male, receiving both estrogen and testosterone therapy, who developed a pulmonary embolism without an underlying genetic thrombophilic condition. As transgender medical care evolves, the use of testosterone as cross-sex hormone therapy in adolescents is likely to increase. Our review suggests that care must be taken when initiating treatment with testosterone, and modification of other thrombophilic risks should be explored before starting therapy in this population.

Annotation: A 17-year-old transgender male presenting with venous thromboembolism

Turban JL, Carswell J, Keuroghlian AS. Understanding Pediatric Patients Who Discontinue Gender-Affirming Hormonal Interventions. *JAMA Pediatr*. 2018;172(10):903-904. doi:10.1001/jamapediatrics.2018.1817 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30178056

Abstract: None

Annotation: A transfeminine child's clinical presentation and treatment with histrelin for puberty suppression at age 15 and estrogen CSHT at age 16

Wolf-Gould CS, Riley MR, Carswell JM. A Trans-Feminine Youth with a BRCA1 Mutation: Case Study. *LGBT health*. 2018;5(4):270-272. doi:10.1089/lgbt.2017.0148 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626215648&from=export

Annotation: Reports on one US-based, transfeminine youth with a BRCA-1 mutation

Zupanič S, Kruljac I, Sostaric Zvonar M, Drobnic Radobuljac M. Case Report: Adolescent With Autism and Gender Dysphoria. *Front Psychiatry*. 2021;12:671448. doi:10.3389/fpsyt.2021.671448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34122187

Abstract: There is increasing clinical evidence of an association between gender variability, gender dysphoria (GD), and autism spectrum disorder (ASD). This seems to be a two-way relationship, a person with GD is more likely to be diagnosed with ASD and vice versa. In youth, it is important to distinguish whether the presented symptoms are a manifestation of ASD focus on special interests or symptoms of co-occurring GD. This distinction is crucial in the process of planning reversible and especially irreversible medical procedures in the context of treatment. We present the case of a birth-assigned female adolescent with GD, who enrolled in our clinic at the age of 16.5 years with "being transgender" as her main complaint accompanied by a wish for surgical breast removal. His (as the patient prefers to use male pronouns) medical and developmental history involved obesity, hyperlipidemia, delays in social and language development and specific interests and rituals. He presented with half a year of untreated

depression, suicidal thoughts and non-suicidal self-injuring, social phobia and relative social isolation. Comprehensive clinical assessments revealed a female karyotype (46, XX), normal female genitalia and unremarkable hormonal status. Clinical psychological assessments reported GD, ASD with average intellectual abilities and co-occurring symptoms of depression and anxiety. Other disorders, such as psychosis, personality disorder and dysmorphophobia, were excluded during longer-term diagnostic and psychotherapeutic processes. Our first aim was to build a good therapeutic alliance with the patient and treat depression and suicidality. He refused to take sertraline, but took a St. John's Wort over-the-counter peroral preparation in the form of infusions. His mood improved, he was no longer suicidal and started social transitioning, yet he remained socially phobic. At the time of writing, he is 20 years old, waiting for bilateral mastectomy and receiving regular triptorelin depot and testosterone depot intramuscular injections. Even though the diagnostic procedures and transition process in autistic gender diverse adolescents may take longer than in non-autistic individuals, ASD is not a contraindication to the gender transition process. We present a well-documented case of a slow social and medical transition resulting in gradual improvement of co-occurring symptoms of GD.

Annotation: A case report of a transgender male adolescent with autism

Eligible Studies Lacking High-priority Comparisons: Descriptive Studies without Pre-post Comparisons (Bibliography Only)

Abu-Ghname A, Grome L, Raj S, Axelrad ME, Chapman SG. Health Care Services Utilization by Transgender Patients in a Medicaid Managed Program. *J Health Care Poor Underserved*. 2021;32(1):435-448. doi:10.1353/hpu.2021.0033 Accessed September 15, 2023. Available at https://muse.jhu.edu/article/783119

Abstract: While challenges related to health care utilization among transgender individuals have been discussed, studies examining health services under Medicaid are limited. A retrospective review was performed on all patients who presented with Gender Dysphoria from 2013-2018 to one Medicaid managed program. Utilization rates of distinct services and interventions were analyzed. A total of 192 patients, with 787 encounters, were identified. Mean patient age was 15 years old. Mean number of encounters per patient was 4.1. The average number of distinct specialties seen was 1.4. Behavioral health (BH) services were most commonly utilized (50%). Endocrinology and surgical services were encountered less frequently. Medications were prescribed for 25% of patients; hormonal treatment was prescribed for 6.7%. This study highlights the deficiencies in services this population is receiving under one managed Medicaid program. While behavioral health services are widely employed, underutilization of medical and surgical consultations compromises patient awareness of available interventions.

Annotation: Examines GD-related utilization in a cohort of TGNB adolescents seen in a state-managed Medicaid program. Affirmed genders were not reported, only natal sexes (N = 70 AMAB and N = 122 AFAB).

Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav*. 2020;49(7):2611-2618. doi:10.1007/s10508-020-01660-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32152785

Abstract: Gonadotropin-releasing hormone analogues (GnRHa) are recommended as initial treatment for adolescents diagnosed with gender dysphoria, providing time to follow gender identity development and consider further treatment wishes without distress caused by unwanted pubertal changes. This has been described as an extended diagnostic phase. However, there are also concerns about the physical, neurocognitive, and psychosocial effects of this treatment. In this retrospective study, we document trajectories after the initiation of GnRHa and explore reasons for extended use and discontinuation of GnRHa. Treatment was considered appropriate in 143 (67%) of the 214 adolescents eligible for GnRHa treatment by virtue of their age/pubertal status, and all started GnRHa (38 transgirls, 105 transboys; median age, 15.0 years [range, 11.1-18.6] and 16.1 years [range, 10.1-17.9]). After a median duration of 0.8 years (0.3-3.8) on GnRHa, 125 (87%) started gender-affirming hormones (GAH). Nine (6%) discontinued GnRHa, five of whom no longer wished gender-affirming treatment. Thirteen had used GnRHa for longer than required by protocol for reasons other than logistics and regularly met with a mental health professional during this time, supporting the use of GnRHa treatment as an extended diagnostic phase. In conclusion, the vast majority who started GnRHa proceeded to GAH, possibly due to eligibility criteria that select those highly likely to pursue further gender-affirming treatment. Due to the observational character of the study, it is not possible to say if GnRHa treatment itself influenced the outcome. Few individuals discontinued GnRHa, and only 3.5% no longer wished gender-affirming treatment.

Annotation: A Dutch descriptive study examining GnRHa treatment trajectories in n=143 TGNB adolescents

Brik T, Vrouenraets L, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of Fertility Preservation Among a Cohort of Transgirls in the Netherlands. *J Adolesc Health*. 2019;64(5):589-593. doi:10.1016/j.jadohealth.2018.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691936

Abstract: PURPOSE: The primary aims of the study are to examine the rate of attempted fertility preservation (FP) among a Dutch cohort of transgirls who started gonadotropin-releasing hormone analog treatment and the reasons why adolescents did or did not choose to attempt FP. METHODS: The study was a single-center retrospective review of medical records of 35 transgirls who started gonadotropin-releasing hormone analog treatment between 2011 and 2017. RESULTS: Ninety-one percent of adolescents were counseled on the option of FP. Thirty-eight percent of counseled adolescents attempted FP, and 75% of them were able to cryopreserve sperm suitable for intrauterine insemination or intracytoplasmic sperm injection. Younger and Caucasian transgirls were less likely to attempt FP. No specific reason for declining FP was known in 33% adolescents, 32% of adolescents were not able to produce a semen sample because of early puberty, 17% felt uncomfortable with masturbation, 17% did not want to have children, and 13% wanted to adopt. CONCLUSIONS: One third of adolescents attempted FP, which is much more than the percentage reported in previous studies from the United States. One third of the transgirls could not make use of FP because they were unable to produce a semen sample because of early pubertal stage. For these adolescents, alternatives need to be explored.

Annotation: Examines use of fertility preservation among transgender girls

Butler G, Adu-Gyamfi K, Clarkson K, et al. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child*.

2022;107(11):1018-1022. doi:10.1136/archdischild-2022-324302 Accessed September 15, 2023. Available at https://adc.bmj.com/content/107/11/1018

Abstract: Introduction The destination of transgender and gender variant young people referred by the National Health Service (NHS) Gender Identity Development Service (GIDS) to, and discharged from the two English paediatric endocrine liaison clinics is not known. Methods 1151 young people referred after full assessment by the GIDS; 827 to University College London Hospital since 2008; 324 to Leeds Children's Hospital since 2013. Discharge categorisation was by agreed criteria. Eleven emigrated and 51 self-discharged. 1089 had known outcomes. Results 999/1089 (91.7%) continued identifying as gender variant. 867/999 (86.8%) were discharged to adult gender identity clinics (GICs). 166/867 (19.1%) of these were <16 years and 701/867 (80.9%) ≥16 years at initial endocrine referral. No sex differences were seen. 38/999 (3.8%) opted for non-NHS services. 90/1089 ceased identifying as gender variant. In 32/1089 (2.9%), this was subsequent to their first clinic appointment. 58/1089 (5.3%) stopped treatment either with the gonadotropin releasing hormone analogue (GnRHa) or gender-affirming hormones (GAH) and reverted to their birth gender: <16 years (20/217; 9.2%); ≥16 years (38/872; 4.4%). Subdividing further, 16/217 (7.4%) <16 years ceased GnRHa and 4/217 (1.8%) after GAH. Of those ≥16 years, 33/872 (3.8%) ceased GnRHa and 5/872 (0.6%) GAH. Conclusions At discharge, 91.7% continued as transgender or gender variant, 86.8% sought ongoing care through NHS GICs. 2.9% ceased identifying as transgender after an initial consultation prior to any endocrine intervention and 5.3% stopped treatment either with GnRHa or GAH, a higher proportion in the <16 year compared with the ≥16 year groups.

Annotation: A descriptive study examining gender identities of TGNB adolescents after discharge from 2 English children's hospitals for GD-related treatments. Only natal genders were reported: 329 AMAB and 651 AFAB adolescents < 18 years.

Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. *J Adolesc Health*. 2017;61(1):120-123. doi:10.1016/j.jadohealth.2017.01.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28363716

Abstract: PURPOSE: To describe fertility preservation (FP) utilization by transgender adolescents within a pediatric gender clinic between July 2013 and July 2016. METHODS: A retrospective chart review was conducted to abstract demographic and clinical information among adolescents initiating gender-affirming hormones, including patient age at initial FP consultation, birth-assigned sex, race/ethnicity, and outcome of FP consultation. RESULTS: In our sample of 105 transgender adolescents, a total of 13 (seven transgender men and six transgender women) between the age of 14.2 and 20.6 years were seen in formal consultation for FP before initiating hormones. Of these adolescents, four completed sperm cryopreservation and one completed oocyte cryopreservation. CONCLUSIONS: Rates of FP utilization among transgender youth were low, which is consistent with a recently published report of FP utilization among transgender youth at another pediatric institution. Identified barriers to FP in our sample included cost, invasiveness of procedures, and desire not to delay medical transition.

Annotation: Examines fertility consultation outcomes in TGNB adolescents

Clark BA, Marshall SK, Saewyc EM. Hormone therapy decision-making processes: Transgender youth and parents. *J Adolesc*. 2020;79:136-147. doi:10.1016/j.adolescence.2019.12.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31972534

Abstract: INTRODUCTION: This study explored how transgender (trans) youth and parents of trans youth made decisions around hormone therapy initiation as well as trans youth experiences of barriers to care. METHODS: Participants included 21 trans youth (ages 14-18) and 15 parents of trans youth who resided in British Columbia, Canada. Data for this grounded theory research consisted of transcripts and lifeline drawings collected through semi-structured interviews conducted August 2016 through February 2017. RESULTS: The decision-making processes of youth and of parents are illustrated in three-phase temporal models, starting with discovery, leading to (inter)action while seeking care, and reflection after hormone therapy initiation. Youth who sought hormone therapy were clear about their decision to access this care. Throughout these processes, youth experienced numerous parent- and system-related barriers to care. Youth with the lowest levels of parent support experienced more system barriers, with non-binary/genderfluid youth experiencing greater barriers and less support for hormone therapy than youth with binary genders. A new barrier identified in this study was health care provider imposed requirements for parental involvement and/or approval, which rendered some youth unable access to hormone therapy. CONCLUSIONS: Health care providers should be aware of the deliberation and information-seeking in which youth engage prior to seeking care as well as the temporally misaligned decision-making processes of youth and parents. Understanding the challenges trans youth experience due to insufficient parental support and system barriers can provide important context for health care providers striving to provide accessible, gender-affirming care and decision-making support for trans youth.

Annotation: A Canadian descriptive study examining the hormone treatment decision-making process with TGNB adolescents and their parents

Clark BA, Virani A, Marshall SK, Saewyc EM. Conditions for shared decision making in the care of transgender youth in Canada. *Health Promot Int*. 2021;36(2):570-580. doi:10.1093/heapro/daaa043 Accessed September 15, 2023. Available at https://academic.oup.com/heapro/article-abstract/36/2/570/5864519?redirectedFrom=fulltext

Abstract: Information is lacking on the role shared decision making plays in the care of transgender (trans) youth. This qualitative, descriptive study explored how trans youth, parents and health care providers engaged or did not engage in shared decision-making practices around hormone therapy initiation and what conditions supported shared decision-making approaches in clinical practice. Semi-structured interviews were conducted with 47 participants in British Columbia, Canada, and analyzed using a constructivist grounded theory approach. While formal shared decision-making models were not used in practice, many participants described elements of such approaches when asked about their health care decision-making processes. Others described health care interactions that were not conducive to a shared decision-making approach. The key finding that emerged through this analysis was a set of five conditions for supporting shared decision making when making decisions surrounding initiation of hormone therapy with trans youth. Both supportive relationships and open communication were necessary among participants to support shared decision making. All parties needed to agree regarding what decisions were to be made and what role each person would play in the process. Finally, adequate time was needed for decision-making processes to unfold. When stakeholders meet these five conditions, a gender-affirming and culturally safer shared decision-making approach may be used to support decision making about gender-affirming care. Implications for clinical practice and future research are discussed.

Annotation: A qualitative descriptive study examining aspects of decision-making in TGNB youths

Daley T, Grossoehme D, McGuire JK, Corathers S, Conard LA, Lipstein EA. "I Couldn't See a Downside": Decision-Making About Gender-Affirming Hormone Therapy. *J Adolesc Health*. 2019;65(2):274-279. doi:10.1016/j.jadohealth.2019.02.018 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31196783

Abstract: PURPOSE: The aim of the article was to understand adolescents' and parents' decision-making process related to gender-affirming hormone therapy (GAHT). METHODS: We conducted qualitative semistructured interviews with transgender adolescents who began testosterone for GAHT in the prior year and the parents of such adolescents. Questions focused on decision-making roles, steps in the decision process, and factors considered in the decision. Participants used pie charts to describe the division of responsibility for the decision. All interviews were coded by at least two members of the research team with disagreements resolved through discussion. Thematic analysis was used to analyze the data. RESULTS: Seventeen adolescents and 13 parents were interviewed (12 dyads). The process of deciding about GAHT involves a series of small conversations, typically with the adolescent advocating to start treatment and the parent feeling hesitant. In most cases, after seeking information from the Internet, healthcare providers and personal contacts move toward acceptance and agree to start treatment. Although adolescents have some short-term concerns, such as about needles, parents' concerns relate more to long-term risks. Ultimately, for both parents and adolescents, the benefits of treatment outweigh any concerns, and they are in agreement about the goals of personal confidence, comfort in one's body and happiness. CONCLUSIONS: To the extent that the decision about GAHT is a medical decision, the decision process is similar to others. However, decisions about GAHT are much more about gender identity than medical risks, suggesting that interventions based in a medical framework may not aid in supporting decision-making.

Annotation: A qualitative study of pediatric transmasculine patients and their parents, focusing on decision-making around the initiation GAHT

de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010;40(8):930-936. doi:10.1007/s10803-010-0935-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20094764

Abstract: Only case reports have described the co-occurrence of gender identity disorder (GID) and autism spectrum disorders (ASD). This study examined this co-occurrence using a systematic approach. Children and adolescents (115 boys and 89 girls, mean age 10.8, SD = 3.58) referred to a gender identity clinic received a standardized assessment during which a GID diagnosis was made and ASD suspected cases were identified. The Dutch version of the Diagnostic Interview for Social and Communication Disorders (10th rev., DISCO-10) was administered to ascertain ASD classifications. The incidence of ASD in this sample of children and adolescents was 7.8% (n = 16). Clinicians should be aware of co-occurring ASD and GID and the challenges it generates in clinical management.

Annotation: Examines the prevalence of autism and autism traits in TGNB children and adolescents. Only natal sex reported: 115 AMAB and 89 AFAB

Garborcauskas G, Boskey ER, Guss CE, Grimstad FW. Retrospective Review of Sexual and Reproductive Health Conversations During Initial Visits of Adolescents Seeking Gender-Affirming Testosterone. *J Pediatr Adolesc Gynecol*. 2023;36(1):25-32. doi:10.1016/j.jpag.2022.09.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36162722

Abstract: STUDY OBJECTIVE: To use a retrospective review of sexual and reproductive health (SRH) counseling that occurred during initial visits of adolescents seeking testosterone gender-affirming hormone therapy to determine the feasibility of using such visits to manage SRH DESIGN: Retrospective chart review SETTING: Children's hospital, multidisciplinary gender clinic PARTICIPANTS: Transgender male and nonbinary patients assigned female at birth (TGD-M) aged 15-17 seen for initiation of testosterone between January 1, 2010, and December 31, 2019 INTERVENTIONS: Not applicable MAIN OUTCOME MEASURE(S): Counseling on (1) testosterone impact on fertility and (2) fertility preservation; assessment of (3) desire for gender-affirming surgery, (4) sexual activity, (5) sexual orientation, and (6) human papilloma virus vaccination as documented during the initial visit. RESULTS: Of 195 patients who met the inclusion criteria, only 3 (1.5%) had all 6 measures addressed. The median number addressed was 4 out of 6 (IQR = 2-5/6), with fertility counseling (95.9%, n = 187) being most common, followed by assessment of surgery desire (74.4%, n = 145), sexual orientation (69.2%, n = 135), and sexual activity (69.2%, n = 135). The odds of being asked about sexual orientation were 5.3 times higher in patients who endorsed sexual activity than in those who did not (P < .001; 95% CI, 9.8-10.3). CONCLUSION: Providers of adolescent gender-affirming hormone therapy regularly assess and counsel on certain aspects of SRH as part of their initial visits for those seeking testosterone. Our data suggest that these initial visits for patients seeking testosterone represent an opportunity to expand SRH assessment and counseling among TGD-M adolescents.

Annotation: Examines characteristics and counseling topics in TGNB adolescents seeking testosterone CSHT

Gawlik A, Antosz A, Kasparek K, Nowak Z, Grabski B. Gender confirmation hormonal treatment use in young Polish transgender binary and non-binary persons. *Endokrynol Pol*. 2022;73(6):922-927. doi:10.5603/EP.a2022.0088 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36519648

Abstract: INTRODUCTION: Gender confirmation hormonal treatment (GCHT) is a cornerstone of medical treatments for persistent gender dysphoria, which is expected and required by many transgender binary and non-binary individuals. Many protocols have been published, and the qualification process is guided by the World Professional Association for Transgender Health Standards of Care. The standards and other documents such as the Endocrine Society Clinical Practice Guideline provide gender confirmation hormonal care also for minors. However, the issue of starting these treatments in younger populations is still marked by controversy. This preliminary study aimed to inquire into GCHT (medications used, timing of its initiation, its tolerance, and sources of information on the treatment) in a convenience sample of young Polish transgender binary and non-binary persons. MATERIAL AND METHODS: A total of 166 adult transgender participants answered our online questionnaire between November 2020 and December 2021. The population was divided into 2 groups: assigned male at birth (AMB, n = 37) and assigned female at birth (AFB, n = 126). Subsequently, division into binary and non-binary was applied to these groups. RESULTS: Most patients (91.9% AMB and 92.2% AFB) did not use gender confirmation medical treatments before the age of 18 years. The most common medication used for GCHT before the age of 18 was cyproterone acetate for AMB and

testosterone for AFB. When asked about their opinion on the timing (age) of initiating GCHT, 73.1% of the AMB and 59.2% of the AFB participants shared the view that it had been initiated much too late. By far the most common source of information on GCHT and gender confirmation surgery (GCS) was the Internet (92.2%). CONCLUSIONS: These treatments (including pubertal blocking) seem to be rarely commenced in Poland before the age of 18 years. In adults, treatment consists mostly of either testosterone or oestradiol, and cyproterone acetate and, more seldom, spironolactone are used as antiandrogens in persons assigned male at birth. In turn, gonadotropin-releasing hormone agonists are barely used at all. Specialists need to be more aware that withholding treatment in minors with gender dysphoria is not a health-neutral option. Gonadotropin-releasing hormone agonists should also be more often considered as an alternative to cyproterone acetate in the context of long-term safety.

Annotation: A survey-based, descriptive study of Polish TGNB young adults with self-reported testosterone and GnRH analogue treatment initiation before age 16, before age 18, and current use.

Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in Referrals to a Pediatric Transgender Clinic. *Pediatrics*. 2019;144(5)doi:10.1542/peds.2019-1368 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31619510

Abstract: OBJECTIVES: We characterized referral trends over time at a transgender clinic within an integrated health system in Northern California. We identified the transition-related requests of pediatric transgender and gender-nonconforming patients and evaluated differences in referrals by age group. METHODS: Medical records were analyzed for all patients <18 years of age in the Kaiser Permanente Northern California health system who were referred to a specialty transgender clinic between February 2015 and June 2018. Trends in treatment demand, demographic data, service requests, and surgical history were abstracted from medical charts and analyzed by using descriptive statistics. RESULTS: We identified 417 unique transgender and gender-nonconforming pediatric patients. The median age at time of referral was 15 years (range 3-17). Most (62%) identified on the masculine spectrum. Of the 203 patients with available ethnicity data, 68% were non-Hispanic. During the study period, the clinic received a total of 506 referrals with a significant increase over time ($P < .001$). Most referrals were for requests to start cross-sex hormones and/or blockers (34%), gender-affirming surgery (32%), and mental health (27%). Transition-related requests varied by age group: younger patients sought more mental health services, and older patients sought hormonal and surgical services. Eighty-nine patients underwent gender-affirming surgeries, mostly before age 18 and most frequently mastectomies (77%). CONCLUSIONS: The increase in referrals supports the need for expanded and accessible health care services for this population. The transition-related care of patients in this large sample varied by age group, underscoring the need for an individualized approach to gender-affirming care.

Annotation: A California-based descriptive study examining trends in TGNB referrals and requests for cross-sex hormones, puberty blockers, and surgery.

Harris RM, Kolaitis IN, Frader JE. Ethical issues involving fertility preservation for transgender youth. *J Assist Reprod Genet*. 2020;37(10):2453-2462. doi:10.1007/s10815-020-01873-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550448/pdf/10815_2020_Article_1873.pdf

Abstract: Purpose: To investigate ethical issues associated with fertility preservation (FP) in transgender youth based on reports of patients and their parents. Methods: Our qualitative study involved in-person interviews with 54 subjects (35 patients and 19 parents). Interviews were audio recorded, transcribed, and verified. Each subject completed a demographic questionnaire, and each patient's medical chart was reviewed for additional information. We analyzed the data using inductive thematic content analysis. Results: Themes that emerged included a range of desires and ambivalence about having genetically related children, variability in understanding the potentially irreversible impact of gender affirming hormones (GAHs) on fertility, use of adoption, and the impact of age on decision-making. Subjects (patients and parents) noted barriers to FP, such as cost and insurance coverage. Several parents expressed concern that their transgender children may have future regret about not attempting FP. Both transgender youth and their parents felt FP was an important precaution. Conclusions: Our study took advantage of the richness of personal narratives to identify ongoing ethical issues associated with fertility preservation in transgender youth. Transgender youth and their parents did not fully understand the process of FP, especially regarding the effects of GAHs, had fears that FP could reactivate gender dysphoria, and noted barriers to FP, such as cost, highlighting economic disparity and lack of justice. These findings highlight ethical issues involving the adequacy of informed consent and economic injustice in access to FP despite expressed interest in the topic.

Annotation: A qualitative, descriptive interview study examining ethical considerations related to fertility preservation in TGNB youth and their parents

Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust*. 2012;196(9):578-581. doi:10.5694/mja12.10222 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22621149

Abstract: OBJECTIVE: To describe the experience of hormone treatment of gender identity disorder (GID) in children and adolescents within a specialist clinic. DESIGN, PATIENTS AND SETTING: Cohort study by medical record review of children aged 0-17 years referred during 2003-2011 for management at the GID clinic in a tertiary paediatric referral centre - the Royal Children's Hospital, Melbourne, Victoria. MAIN OUTCOME MEASURES: Clinical characteristics of the patient population, hormone treatment provided, frequency of referrals with time. RESULTS: Thirty-nine children and adolescents were referred for gender dysphoria. Seventeen individuals were pubertal with persistent GID, and were considered eligible for hormone treatment. Seven patients, comprising three biological males and four biological females, had legally endorsed hormone treatment. In this group, gender dysphoria was first noted at 3-6 years of age. Hormone treatment with GnRH analogue to suppress pubertal progression (phase 1) was given at 10-16 years of age. Treatment with cross-sex hormones (phase 2) was given at 15.6-16 years. One patient purchased cross-sex hormone treatment overseas. One patient received oestrogen and progesterone for menstrual suppression before phase 1. The annual frequency of new referrals increased continuously over the study period. CONCLUSIONS: Hormone treatment for pubertal suppression and subsequent gender transition needs to be individualised within stringent protocols in multidisciplinary specialist units.

Annotation: An Australia-based descriptive study reporting on pediatric TGNB cases and their treatments.

Hobson BJ, Lett E, Hawkins LA, Swendiman RA, Nance ML, Dowshen NL. Transgender Youth Experiences with Implantable GnRH Agonists for Puberty Suppression. *Transgend Health*. 2022;7(4):364-368. doi:10.1089/trgh.2021.0006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36033209

Abstract: This descriptive study reports caregiver experiences with GnRH agonist implants among a cohort of youth followed in a pediatric hospital-based gender clinic. We administered a survey to 36 of 55 eligible caregivers ascertaining demographics and satisfaction, with a medical record review of any surgical complications. The overwhelming majority (97.1%) reported satisfaction with the procedure and would undergo the implant procedure again (94.4%). The most frequent challenges noted were about affordability (39.8%) and insurance denials (39.8%). Implantable GnRH agonist can be used successfully in pediatric patients with gender dysphoria. Future policy should seek to address concerns regarding insurance approval and reimbursement.

Annotation: A qualitative study examining patient and parent preferences in TGNB patients with implantable GnRH agonists for puberty suppression. Investigators did not report affirmed gender identities; only natal sex reported (N = 15 AMAB and N = 21 AFAB).

Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. *Int J Transgend*. 2019;20(4):413-420. doi:10.1080/15532739.2019.1631929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999626

Abstract: Aims: To describe the use of hormonal contraceptives for menstrual management and/or pregnancy prevention in a clinic-based series of transgender adolescents and young adults who were assigned female at birth (transmasculine identity). Methods: We performed a chart review of post-menarchal transgender assigned-female-at-birth (AFAB) patients, age 10-25 years, seen at CCHMC Transgender Health Clinic for at least 2 visits between July 1, 2013 and September 17, 2016, and who were not on a puberty suppression method. We collected data including choice of hormonal contraceptive and indication (menstrual suppression, pregnancy prevention, or both), duration of use, initiation of sexual activity, reported sexual partners, and use of gender-affirming hormone therapy (i.e., testosterone). We present simple descriptive statistics. Results: A total of 231 patients met inclusion criteria, with ages from 11 to 25 years. Of those, 135 (59%) were using a hormonal contraceptive method. Most patients (67%) used hormonal contraception for the indication of menstrual suppression. Most commonly used method was depot medroxyprogesterone (DMPA) (49 patients), followed by combined oral contraceptives (COC) and norethindrone (progestin-only pill, POP) (34 patients each). Thirteen patients used 52 mg levonorgestrel IUD (LNG-IUD). Of the total sample (n = 231), 82 (36%) reported sexual activity, 35 of whom (43% of sexually active patients) reported sexual intercourse with assigned-male-at-birth (AMAB) partners and/or penile-vaginal intercourse. Among 35 patients at risk for pregnancy, only 21 (60%) were using hormonal contraception. Over half (54%) of sexually active patients taking testosterone discontinued their hormonal contraceptive method once they stopped having menses. Discussion: Within a sample of transgender AFAB adolescents, half of whom were taking testosterone, a variety of contraceptives were used, including depot medroxyprogesterone, combined oral contraceptives, and levonorgestrel IUD. Among those taking testosterone, many patients discontinued contraception once they stopped having menses.

Annotation: Examines oral contraceptive use in transgender males

Kerman HM, Pham A, Crouch JM, et al. Gender Diverse Youth on Fertility and Future Family: A Qualitative Analysis. *J Adolesc Health*. 2021;68(6):1112-1120. doi:10.1016/j.jadohealth.2021.01.002 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(21)00004-5/fulltext

Abstract: Purpose: Gender-affirming treatment for transgender and nonbinary adolescents has been shown to decrease anxiety, depression, and suicidality, but treatments have medical consequences. Specifically, hormone replacement and pubertal blocking may impact patients' fertility and childbearing capabilities. We interviewed gender diverse adolescents regarding their thoughts on family and fertility. Methods: We completed semistructured interviews with 23 gender diverse adolescents recruited from the Seattle Children's Gender Clinic. Interviewees included transfeminine, transmasculine, and nonbinary youth. Interviews were recorded, transcribed, and analyzed using Braun and Clarke's theory of thematic analysis, a flexible framework for qualitative analysis. Results: Gender diverse adolescents have myriad views on fertility, but four main themes were identified: (1) an interest in future family, including ideas regarding adoption and biological children; (2) barriers to fertility, including cost and procedure-related dysphoria; (3) factors unique to the developmental stage of adolescents, including the age discordance of making fertility decisions as a teenager and parental influence on decision-making; and (4) suggestions for clinicians approaching fertility counseling with adolescents considering hormone therapy. Conclusions: Many gender diverse youth asserted an interest in building families, although the process of fertility preservation remains fraught. Relative to other studies, our participants were hopeful, imaginative, and interested in having children. Participants wanted to receive specific counseling on fertility, to receive help navigating the logistics of fertility preservation, and to be listened to when their hopes for children (or no children) were stated. Further research is needed to create care paradigms that address fertility of transgender youth in an affirming, developmentally appropriate manner.

Annotation: A qualitative survey study examining fertility attitudes among TGNB children seen in a pediatric gender clinic

Krishna V, Lee SL, DeUgarte DA. Optimizing pediatric histrelin implantation to improve success rates in clinic without sedation. *J Pediatr Endocrinol Metab*. 2021;34(11):1443-1448. doi:10.1515/jpem-2021-0432 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34407329

Abstract: OBJECTIVES: The purpose of this study was to review our success rate performing the histrelin implant procedure in clinic without sedation. METHODS: A retrospective study was performed for histrelin implant procedures done at our institution from 2008 to 2020. Wilcoxon rank-sum test or Fisher's exact test was utilized to identify significant differences ($p<0.05$). RESULTS: A total of 73 patients underwent 184 histrelin implant procedures from 2008 to 2020. In the past few years, there has been a decrease in procedures for precocious puberty and an increase for gender dysphoria. The majority of procedures were performed in clinic without sedation (82%). The only risk factor associated with requiring sedation was younger age (median 9 vs. 10 years; $p<0.003$). Complications (i.e. implant fracture or need for counter-incision) were noted in 10 of the procedures (5%). The only risk factor identified for a procedural complication during implant removal/replacement was interval time from insertion (21 vs. 13 months; $p<0.01$). The only documented wound problem reported was dermatitis in 1 patient (no suture

granuloma, dehiscence, or implant extravasation). CONCLUSIONS: Procedural refinements and distraction therapy have enabled us to perform the majority of procedures in clinic without sedation. In our experience, procedural difficulty and complications appear to increase with prolonged implant duration. Histrelin implantation is increasingly being performed for gender dysphoria.

Annotation: Examines on characteristics and temporal trends in use of histrelin implants in pediatric patients, including patients with GD

Lopez CM, Solomon D, Boulware SD, Christison-Lagay E. Trends in the "Off-Label" Use of GnRH Agonists Among Pediatric Patients in the United States. *Clin Pediatr (Phila)*. 2018;57(12):1432-1435. doi:10.1177/0009922818787260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30003804

Abstract: BACKGROUND: Gonadotropin-releasing hormone (GnRH) agonists are FDA approved for the treatment of precocious puberty. The therapy consists of histrelin acetate (Supprelin), a surgically implanted device, or Lupron injections. In recent years, the use of these agents has been extended to include the off-label treatment of children with normally timed puberty. Trends in the off-label use of GnRH agonists in children across the U.S. have not been previously described in the literature. METHODS: We analyzed data on the use of Supprelin and Lupron reported to the Pediatric Health Information System (PHIS) from 2013 to 2016 to determine the trends in both the FDA-approved and off-label uses of these medications. RESULTS: We identified a stable cohort of 39 children's hospitals administering GnRH agonist therapies from 2013 to 2016. During this period, the annual number of children treated with these medications for precocious puberty increased modestly, from 283 to 303; meanwhile, the fraction of children receiving therapy for an off-label indication more than doubled, from 12% (39 of 322 total patients) to 29% (125 of 428 total patients). Privately insured patients were more likely to be treated for an off-label indication (13%; 119 out of 883 patients) than Medicaid patients (8%; 58 out of 706 patients; chi(2)[1] = 10.97, P = .00093). CONCLUSION: From 2013 to 2016, the proportion of children treated with GnRH agonists for an off-label indication notably increased. The number of children treated for precocious puberty modestly increased. Private insurance coverage was associated with higher rates of off-label use.

Annotation: Examines off-label use of GnRH agonists among pediatric patients with GD or developmental sex disorders. Neither affirmed genders nor birth-assigned sexes were reported.

Lopez CM, Solomon D, Boulware SD, Christison-Lagay ER. Trends in the use of puberty blockers among transgender children in the United States. *J Pediatr Endocrinol Metab*. 2018;31(6):665-670. doi:10.1515/jpem-2018-0048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29715194

Abstract: BACKGROUND: The objective of the study was to identify national trends in the utilization of histrelin acetate implants among transgender children in the United States. METHODS: We analyzed demographic, diagnostic and treatment data from 2004 to 2016 on the use of histrelin acetate reported to the Pediatric Health Information System (PHIS) to determine the temporal trends in its use for transgender-related billing diagnoses, e.g. "gender identity disorder". Demographic and payer status data on this patient population were also collected. RESULTS: Between 2004 and 2016, the annual number of implants placed for a transgender-related diagnosis increased from 0 to 63. The average age for placement was 14 years.

Compared to natal females, natal males were more likely to receive implants (57 vs. 46) and more likely to have implants placed at an older age (62% of natal males vs. 50% of natal females were >/=;13 years; p<0.04). The majority of children were White non-Hispanic (White: 60, minority: 21). When compared to the distribution of patients treated for precocious puberty (White: 1428, minority: 1421), White non-Hispanic patients were more likely to be treated with a histrelin acetate implant for a transgender-related diagnosis than minority patients (p<0.001). This disparity was present even among minority patients with commercial insurance (p<0.001). CONCLUSIONS: Utilization of histrelin acetate implants among transgender children has increased dramatically. Compared to natal females, natal males are more likely to receive implants and also more likely to receive implants at an older age. Treated transgender patients are more likely to be White when compared to the larger cohort of patients being treated with histrelin acetate for central precocious puberty (CPP), thus identifying a potential racial disparity in access to medically appropriate transgender care.

Annotation: Examines use of GnRH analogues in pediatric patients, including TGNB children and cis children with CPP. Authors did not report affirmed gender ratios, only natal sex (N = 52 AMAB, N = 39 AFAB, and 1 whose natal sex was unknown).

Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child*. 2022;107(11):1012-1017. doi:10.1136/archdischild-2022-324283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35902230

Abstract: OBJECTIVES: Some gender-diverse young people (YP) who experience clinically significant gender-related distress choose to pursue endocrine treatment alongside psychotherapeutic support to suppress pubertal development using gonadotropin-releasing hormone analogues (GnRHa), and then to acquire the secondary sex characteristics of their identified gender using gender affirming hormones (GAH). However, little is known about the demographics of transgender adolescents accessing paediatric endocrinology services while under the specialist Gender Identity Development Service (GIDS) in England. DESIGN: Demographics of referrals from the GIDS to affiliated endocrinology clinics to start GnRHa or GAH between 2017 and 2019 (cohort 1), with further analysis of a subgroup of this cohort referred in 2017-2018 (cohort 2) were assessed. RESULTS: 668 adolescents (227 assigned male at birth (AMAB) and 441 assigned female at birth (AFAB)) were referred to endocrinology from 2017 to 2019. The mean age of first GIDS appointment for cohort 1 was 14.2 (+/-2.1) years and mean age of referral to endocrinology postassessment was 15.4 (+/-1.6) years. Further detailed analysis of the trajectories was conducted in 439 YP in cohort 2 (154 AMAB; 285 AFAB). The most common pathway included a referral to access GnRHa (98.1%), followed by GAH when eligible (42%), and onward referral to adult services when appropriate (64%). The majority (54%) of all adolescents in cohort 2 had a pending or completed referral to adult services. CONCLUSIONS: This study highlights the trajectories adolescents may take when seeking endocrine treatments in child and adolescent clinical services and may be useful for guiding decisions for gender-diverse YP and planning service provision.

Annotation: A London-based descriptive study examining treatment trajectories in TGNB adolescents referred for treatment with GnRHa and cross-sex hormones.

McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr*.

2021;180(9):2969-2976. doi:10.1007/s00431-021-04075-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33855617

Abstract: The clinical needs of young people with gender dysphoria (GD) have outpaced the capacity of health services to provide appropriate care. The study aimed to explore the interface of Paediatric Endocrinology and young people with GD, detailing the clinical characteristics and the clinical care provided, in order to inform future service development. Medical records of all young people with GD (n=91, 59 (65%) birth-assigned females and 32 (35%) birth-assigned males) referred to Paediatric Endocrinology during 2011-2019 for puberty suppression were reviewed. Median age at initial assessment was 14.6 years (range 8.8-17.6 years). There was a threefold increase from 2016 (n=22) to 2019 (n=73). Mental health disorders were present in 34 (37%) and autistic spectrum disorder in 21 (23%), while 54 (59%) had at least one comorbidity. Sixty-four (70%) young people fulfilled the criteria for consideration of fertility preservation, with 6 (9%) of them preserving their gametes. Seventy-nine (87%) young people commenced treatment with gonadotrophin-releasing hormone analogue, at a median age of 14.8 years (range 9.7-18.0 years). Six (8%) of those discontinued treatment, following a median duration of 6 months (range 6-18 months). Forty-one young people commenced gender-affirming hormones. One (2%) of those who started gender-affirming hormones discontinued treatment.Conclusions: We have witnessed increasing numbers of young people with GD attending Paediatric Endocrinology, with an over-representation of comorbidities, necessitating provision of an individualised approach to treatment. Addressing young people's acceptability of fertility services and ongoing close collaboration between endocrinology and mental health professionals require innovative models of multidisciplinary care. What is Known: * A worldwide increase in presentation of gender dysphoria has been mirrored in our service, with majority assigned female at birth and post-pubertal. * An over-representation of comorbidities exists, notably mental health disorders and autistic spectrum disorder. What is New: * Coordination of interprofessional care to meet complex needs, at an individual level, while improving efficiency of working, at a systemic level, can be met by the development of specialist centres. * The reasons for low uptake of fertility services demand further exploration.

Annotation: A Scotland-based descriptive study of characteristics of pediatric patients referred to a pediatric gender care clinic.

Morrison A, Olezeski C, Cron J, Kallen AN. A Pilot Study to Assess Attitudes Toward Future Fertility and Parenthood in Transgender and Gender Expansive Adolescents. *Transgender Health*. 2020;5(2):129-137. doi:10.1089/trgh.2019.0075 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L632152015&from=export

Abstract: Purpose: In this pilot study, we sought to characterize the knowledge about fertility and attitudes about future parenthood in a sample of transgender and gender expansive (TGE) youth attending an academic, university-affiliated adolescent gender program. Methods: A 22-item cross-sectional survey assessing knowledge of fertility issues and attitudes toward future parenthood was administered to 23 transgender adolescents, 12-22 years of age, who reported gender identity incongruent with birth-assigned sex, and who were seen at our university-affiliated clinic during an 11-month period between October 2016 and August 2017. Knowledge scores and ranked responses on selected topics in fertility and reproduction were evaluated. Results: Participants were well informed overall about fertility topics related to their gender care (mean score of 3.8±0.8 out of 5), but over half of participants lacked specific knowledge regarding basic fertility principles and overestimated the ability of physicians to predict the

effects of gender-affirming hormone therapy on fertility. The majority of participants (15/23) preferred nonbiological parenthood in the form of adoption. Participants who ranked future parenthood as unimportant had the greatest concern about becoming a parent ($p<0.05$), and over one-third were also concerned about interrupting their gender-affirming hormone therapy to preserve fertility. Conclusion: TGE youth would benefit from fertility-related counseling that both assesses baseline understanding of reproduction and also acknowledges the limitations of current data on gender-affirming hormones and future fertility. Counseling should also be comprehensive and explore both biological and nonbiological forms of parenthood.

Annotation: A US-based descriptive study reporting on survey results about fertility preference in N=23 transgender children seen at a university-affiliated clinic.

Nahata L, Chen D, Quinn GP, et al. Reproductive Attitudes and Behaviors Among Transgender/Nonbinary Adolescents. *J Adolesc Health*. 2020;66(3):372-374. doi:10.1016/j.jadohealth.2019.09.008 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(19)30451-3/fulltext

Abstract: Purpose: The aim of the study was to examine reproductive health attitudes and behaviors related to contraception use, provider counseling, parenthood goals, and fertility preservation (FP) in TNB adolescents. Methods: A 24-item survey was administered to 44 TNB adolescents aged 12–19 years. Results: Contraceptive use was variable even among the 46% who reported sexual activity. Half denied or were unsure if they had been offered options from their provider to prevent sexually transmitted infections, and more than one third denied or were unsure about the offer of pregnancy prevention options. Importantly, the majority did not desire more information about contraceptive options. Few used FP, although many thought their feelings about parenthood may change in the future. Conclusions: TNB adolescents are at risk for sexually transmitted infections, unplanned pregnancies, and future infertility, yet many do not desire more information about contraception or FP. Tailored counseling strategies should be developed and researched to protect this vulnerable group of youth.

Annotation: Examines gender identity, sexual orientation, contraception counseling, and attitudes towards fertility among TGNB adolescents seen in 4 gender clinics across 3 states

O'Bryan J, Leon K, Wolf-Gould C, Scribani M, Tallman N, Gadomski A. Building a Pediatric Patient Registry to Study Health Outcomes Among Transgender and Gender Expansive Youth at a Rural Gender Clinic. *Transgend Health*. 2018;3(1):179-189. doi:10.1089/trgh.2018.0023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30581991

Abstract: Purpose: Significant knowledge gaps regarding outcomes of gender-affirming therapy in transgender (TG) and gender expansive (GE) youth impede an evidence-based approach to these patients. The Gender Wellness Center (GWC) Pediatric Patient Registry was established in 2017 to enable systematic, longitudinal research to describe the physical, mental, and quality-of-life outcomes of these youth. Methods: All TG/GE youth, ages 8-21 years, presenting to the GWC were recruited on site. Ten research questions guided the creation of data fields. The following 131 variables were abstracted from electronic medical records: demographics, weight, height, body mass index, gender identity, sexual orientation, coexisting diagnoses, substance use, Tanner stage, sexual activity, medications, fertility preservation, Gonadotropin Releasing Hormone (GnRH) analog use, hormone therapy, surgery, and related outcomes. Health-related quality of life is assessed using the Child Health Questionnaire-87 for ages <18 and the Short

Form-36 for ages 18-21. Results: To date, 139 TG and GE youth (90% white and 93% non-Hispanic), have enrolled in the registry. Average age at enrollment was 17.5 years (+/-3.1, range: 8-21). Two-thirds of youth identified on the trans masculine spectrum (n=90), 28.8% identified on the trans feminine spectrum (n=40), and 6.5% identified as nonbinary/gender nonconforming (n=9). Nearly, all youth had socially transitioned (n=121, 87.7%) and were medically transitioning (n=123, 89.1%). Conclusion: As one of the first rural-based registries, the GWC Registry has helped to delineate health outcomes attributable to gender-affirming care in a unique patient population of TG/GE youth. Our results will be used to describe treatment outcomes that will contribute to evidence-based guidelines.

Annotation: A US-based descriptive study examining characteristics (including medication use) in a cohort of TGNB adolescents.

Olson KR, Durwood L, Horton R, Gallagher NM, Devor A. Gender Identity 5 Years After Social Transition. *Pediatrics*. 2022;150(2)doi:10.1542/peds.2021-056082 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35505568

Abstract: BACKGROUND AND OBJECTIVES: Concerns about early childhood social transitions among transgender youth include that these youth may later change their gender identification (ie, retransition), a process that could be distressing. The current study aimed to provide the first estimate of retransitioning and to report the current gender identities of youth an average of 5 years after their initial social transitions. METHODS: The current study examined the rate of retransition and current gender identities of 317 initially transgender youth (208 transgender girls, 109 transgender boys; M = 8.1 years at start of study) participating in a longitudinal study, the Trans Youth Project. Data were reported by youth and their parents through in-person or online visits or via e-mail or phone correspondence. RESULTS: We found that an average of 5 years after their initial social transition, 7.3% of youth had retransitioned at least once. At the end of this period, most youth identified as binary transgender youth (94%), including 1.3% who retransitioned to another identity before returning to their binary transgender identity. A total of 2.5% of youth identified as cisgender and 3.5% as nonbinary. Later cisgender identities were more common among youth whose initial social transition occurred before age 6 years; their retransitions often occurred before age 10 years. CONCLUSIONS: These results suggest that retransitions are infrequent. More commonly, transgender youth who socially transitioned at early ages continued to identify that way. Nonetheless, understanding retransitions is crucial for clinicians and families to help make retransitions as smooth as possible for youth.

Annotation: A nationwide survey study examining gender identities 5 years after initial presentation

Parks MA, Zwayne N, Temkit M. Bleeding Patterns among Adolescents Using the Levonorgestrel Intrauterine Device: A Single Institution Review. *J Pediatr Adolesc Gynecol*. 2020;33(5):555-558. doi:10.1016/j.jpag.2020.04.006 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(20)30223-0/fulltext

Abstract: Study Objective: To describe the bleeding patterns associated with the use of the levonorgestrel intrauterine device (IUD) in adolescents. Design, Setting, and Participants: A retrospective chart review of postmenarchal adolescent patients ages 8-19 years who had the levonorgestrel IUD inserted at Phoenix Children's Hospital from 2012 to 2018. Interventions: Insertion of the 52-mg and 13.5-mg levonorgestrel IUD. Main Outcome Measures: The rate of

amenorrhea and other bleeding patterns after insertion of the levonorgestrel IUD and the factors that might predict those bleeding patterns. Results: A total of 260 charts were identified with 221/260 (85.0%) patients choosing the 52-mg IUD and 39/260 (15.0%) patients choosing the 13.5-mg IUD to be inserted. Follow-up data were available for 166 patients. The overall rate of amenorrhea among IUD users was 39.8% (n = 66) with no difference between 52-mg and 13.5-mg IUD users (P = .656). Regularity and flow of menstrual cycle, history of bleeding disorder, history of developmental delay, and current treatment with testosterone for gender dysphoria before IUD insertion did not appear to have a significant effect on the rate of amenorrhea or bleeding patterns post-IUD insertion. Conclusion: The levonorgestrel IUD can be successfully used to control abnormal uterine bleeding and suppress menses in adolescents. Menstrual cycle characteristics pre-IUD insertion did not result in predictable post-IUD bleeding patterns.

Annotation: Examines menstrual outcomes in adolescents who received levonorgestrel IUDs, including transgender male patients

Persky RW, Gruschow SM, Sinaii N, Carlson C, Ginsberg JP, Dowshen NL. Attitudes Toward Fertility Preservation Among Transgender Youth and Their Parents. *J Adolesc Health*. 2020;67(4):583-589. doi:10.1016/j.jadohealth.2020.02.027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32359942

Abstract: PURPOSE: While gender-affirming hormones (GAH) may impact the fertility of transgender and gender diverse (TGGD) youth, few pursue fertility preservation (FP). The objective of this study is to understand youth and parent attitudes toward FP decision-making. METHODS: This study is a cross-sectional survey of youth and parents in a pediatric, hospital-based gender clinic from April to December 2017. Surveys were administered electronically, containing 34 items for youth and 31 items for parents regarding desire for biological children, willingness to delay GAH for FP, and factors influencing FP decisions. RESULTS: The mean age of youth (n = 64) was 16.8 years, and 64% assigned female at birth; 46 parents participated. Few youth (20%) and parents (13%) found it important to have biological children or grandchildren, and 3% of youth and 33% of parents would be willing to delay GAH for FP. The most common factor influencing youth FP decision-making was discomfort with a body part they do not identify with (69%), and for the parents, whether it was important to their child (61%). In paired analyses, youth and their parents answered similarly regarding youth desire for biological children and willingness to delay GAH for FP. CONCLUSIONS: The majority of TGGD youth and parents did not find having biological offspring important and were not willing to delay GAH for FP. Discomfort with reproductive anatomy was a major influencing factor for youth FP decision-making and their child's wishes was a major factor for parents. Future qualitative research is needed to understand TGGD youth and parent attitudes toward FP and to develop shared decision-making tools.

Annotation: A US-based descriptive study examining characteristics, attittudes, and beliefs about fertility and GAH in N=41 TGNB youth/parent pairs.

Pullen Sansfaçon A, Temple Newhook J, Douglas L, et al. Experiences and Stressors of Parents of Trans and Gender-Diverse Youth in Clinical Care from Trans Youth CAN! *Health Soc Work*. 2022;47(2):92-101. doi:10.1093/hsw/hlac003 Accessed September 15, 2023. Available at https://academic.oup.com/hsw/article-abstract/47/2/92/6544691?redirectedFrom=fulltext

Abstract: Parents of trans and gender-diverse youth can experience challenges navigating gender-affirming (GA) care such as stigma, transphobia, and lack of support. There is little information available about stressors, worries, and positive feelings of parents as they try to support their youth accessing GA care. This article presents baseline survey data on experiences and stressors of 160 parents/caregivers in the Trans Youth CAN! cohort study, which examined medical, social, and family outcomes in youth age 16 years or younger considering puberty blockers or GA hormones. Data were collected at 10 Canadian gender clinics. Authors report on participating parents' characteristics, levels of support toward youth, stressors, worries, concerns, and positive feelings related to youth's gender. Most parent participants were White (85.1 percent), female (85.1 percent), birth or adoptive parents (96.1 percent), and reported strong support for youth's gender. Participants' concerns included their youth facing rejection (81.9 percent), generalized transphobia (74.6 percent), or encountering violence (76.4 percent). Parents also reported positive feelings about seeing their youth grow more confident. Most parental worries and stressors were situated outside the family, reflecting the systemic discrimination faced by youth and their families. Social workers could address these by developing systems-focused interventions and by further taking into account intersectional health disparities.

Annotation: A Canada-based, descriptive survey study (Trans Youth CAN!) examining stressors in TGNB adolescents who were referred for puberty suppression and/or hormones and their parents

Pullen Sansfaçon A, Temple-Newhook J, Suerich-Gulick F, et al. The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. *Int J Transgend*. 2019;20(4):371-387. doi:10.1080/15532739.2019.1652129 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999623

Abstract: Background: Canadian specialty clinics offering gender-affirming care to trans and gender diverse children and youth have observed a significant increase in referrals in recent years, but there is a lack of information about the experiences of young people receiving care. Furthermore, treatment protocols governing access to gender-affirming medical interventions remain a topic of debate. Aims: This qualitative research aims to develop a deeper understanding of experiences of trans youth seeking and receiving gender-affirming care at Canadian specialty clinics, including their goals in accessing care, feelings about care and medical interventions they have undergone, and whether they have any regrets about these interventions. Methods: The study uses an adapted Grounded Theory methodology from social determinants of health perspective. Thirty-five trans and gender diverse young people aged 9 to 17 years were recruited to participate in semi-structured interviews through the specialty clinics where they had received or were waiting for gender-affirming medical interventions such as puberty blockers, hormone therapy, and surgery. Results: Young people felt positively overall about the care they had received and the medical interventions they had undergone, with many recounting an improvement in their well-being since starting care. Most commonly shared frustrations concerned delays in accessing interventions due to clinic waiting lists or treatment protocols. Some youth described unwanted medication side-effects and others said they had questioned their transition trajectory at certain moments in the past, but none regretted their choice to undergo the interventions. Discussion : The results suggest that trans youth and gender diverse children are benefiting from medical gender-affirming care they receive at specialty clinics, providing valuable insight into their decision-making processes in seeking care

and specific interventions. Providers might consider adjusting aspects of treatment protocols (such as age restrictions, puberty stage, or mental health assessments) or applying them on a more flexible, case-by-case basis to reduce barriers to access.

Annotation: A Canadian, multi-province, interview-based, qualitative, descriptive study examining the decision and initiation of GD treatment

Razzak M. Pediatrics: evaluation and management of gender identity disorder--an American tale. *Nat Rev Urol*. 2012;9(4):175. doi:10.1038/nrurol.2012.36 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22410681

Abstract: None

Annotation: A research letter describing the experience of a pediatric gender specialty clinic, and the Tanner stages of children presenting for care. Investigators did not report the affirmed gender of their patients, only natal sex (N = 43 AMAB and N = 54 AFAB).

Riggs DW, Bartholomaeus C, Sansfacon AP. 'If they didn't support me, I most likely wouldn't be here': Transgender young people and their parents negotiating medical treatment in Australia. *International journal of transgender health*. 2020;21(1):3-15. doi:10.1080/15532739.2019.1692751 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430428/pdf/WIJT_21_1692751.pdf

Abstract: Background: It is increasingly recognized that transgender young people require affirming medical care, however the provision of such care may be mitigated by the availability of services and the views of parents. Aims: This study aimed to explore the views of Australian transgender young people (aged 11-17) and their parents with regards to medical treatment. Methods: Ten qualitative interviews were conducted with parent-child dyads in two Australian states. Thematic analysis was undertaken on responses to interview questions related to family relationships, views about medical treatment (specifically hormone blockers and hormones), and the relationship between medical treatment and sense of self. Results: Themes developed focused on the importance of strong supportive parent-child relationships, the meaning of and access to hormone blockers, and the meaning of and access to hormones. Discussion: The paper concludes by discussing the implications of the findings for clinical services, particularly in relation to supporting parents to be affirming of a transgender child, the need to prepare transgender young people and their parents for the passage of time in regards to medical treatment, and the need to focus on expectations in regards to sense of self in relation to medical treatment. Copyright © 2019 Taylor & Francis Group, LLC.

Annotation: A qualitative, descriptive interview study that examined the views of TGNB adolescents and their parents about medical treatments.

Shim JY, Laufer MR, Grimstad FW. Dysmenorrhea and Endometriosis in Transgender Adolescents. *J Pediatr Adolesc Gynecol*. 2020;33(5):524-528. doi:10.1016/j.jpag.2020.06.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32535219

Abstract: STUDY OBJECTIVE: To study the presentation of dysmenorrhea and endometriosis in transmasculine adolescents and review their treatment outcomes. DESIGN: A retrospective review. SETTING: Boston Children's Hospital. PARTICIPANTS: Transmasculine persons younger than 26 years old who were diagnosed with dysmenorrhea and treated between January 1, 2000

and March 1, 2020. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: An electronic medical record review of the clinical characteristics, transition-related care, and treatment outcomes. RESULTS: Dysmenorrhea was diagnosed in 35 transmasculine persons. Mean age was 14.9 years +/- 1.9 years. Twenty-nine (82.9%) were diagnosed after social transition. Twenty-three of 35 (65.7%) were first treated with combined oral contraceptives, but 14/23 (61%) discontinued or transitioned to alternative therapy. Twelve patients with dysmenorrhea alone initiated testosterone treatment, and 4/12 (33.3%) experienced persistent symptoms. Seven of 35 patients with dysmenorrhea (20.0%) were laparoscopically evaluated for endometriosis, and it was confirmed in all seven. Six had stage I disease, and one had stage II. Three of the 7 (42.9%) were diagnosed after social transition, with one diagnosed 20 months after initiating testosterone treatment. Their endometriosis was treated with combined oral contraceptives, danazol, or progestins; four experienced suboptimal response during treatment with these therapies alone. Two of those with suboptimal response subsequently resolved their dysmenorrhea when using testosterone. Five patients with endometriosis initiated testosterone treatment, and of the 5 (40%) experienced persistent symptomatology with combined testosterone and progestin therapies. CONCLUSION: To our knowledge, this is the first study to characterize endometriosis in transmasculine persons. Evaluation for endometriosis was underutilized in transmasculine persons with dysmenorrhea, despite those who underwent laparoscopic evaluation and had disease confirmation. Although testosterone treatment can resolve symptoms in some, others might require additional suppression. Endometriosis should be considered in transmasculine persons with symptoms even when they are using testosterone.

Annotation: Examining treatment trajectories, risk factors, and endometriosis in transgender males with dysmenorrhea

Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3):418-425. doi:10.1542/peds.2011-0907 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22351896

Abstract: OBJECTIVES: To describe the patients with gender identity disorder referred to a pediatric medical center. We identify changes in patients after creation of the multidisciplinary Gender Management Service by expanding the Disorders of Sex Development clinic to include transgender patients. METHODS: Data gathered on 97 consecutive patients <21 years, with initial visits between January 1998 and February 2010, who fulfilled the following criteria: long-standing cross-gender behaviors, provided letters from current mental health professional, and parental support. Main descriptive measures included gender, age, Tanner stage, history of gender identity development, and psychiatric comorbidity. RESULTS: Genotypic male:female ratio was 43:54 (0.8:1); there was a slight preponderance of female patients but not significant from 1:1. Age of presentation was 14.8 +/- 3.4 years (mean +/- SD) without sex difference (P = .11). Tanner stage at presentation was 4.1 +/- 1.4 for genotypic female patients and 3.6 +/- 1.5 for genotypic male patients (P = .02). Age at start of medical treatment was 15.6 +/- 2.8 years. Forty-three patients (44.3%) presented with significant psychiatric history, including 20 reporting self-mutilation (20.6%) and suicide attempts (9.3%). CONCLUSIONS: After establishment of a multidisciplinary gender clinic, the gender identity disorder population increased fourfold. Complex clinical presentations required additional mental health support as the patient population grew. Mean age and Tanner Stage were too advanced for pubertal suppressive therapy to be an affordable option for most patients. Two-thirds of patients were started on cross-sex hormone therapy. Greater awareness of the benefit of early medical

intervention is needed. Psychological and physical effects of pubertal suppression and/or cross-sex hormones in our patients require further investigation.

Annotation: A US-based descriptive study reporting on characteristics and treatment tragjectory of N=97 patients with gender dysphoria, including percentages starting cross-sex hormone treatment.

Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. doi:10.1177/1359104510378303 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21216800

Abstract: The aim of this qualitative study was to obtain a better understanding of the developmental trajectories of persistence and desistence of childhood gender dysphoria and the psychosexual outcome of gender dysphoric children. Twenty five adolescents (M age 15.88, range 14-18), diagnosed with a Gender Identity Disorder (DSM-IV or DSM-IV-TR) in childhood, participated in this study. Data were collected by means of biographical interviews. Adolescents with persisting gender dysphoria (persisters) and those in whom the gender dysphoria remitted (desisters) indicated that they considered the period between 10 and 13 years of age to be crucial. They reported that in this period they became increasingly aware of the persistence or desistence of their childhood gender dysphoria. Both persisters and desisters stated that the changes in their social environment, the anticipated and actual feminization or masculinization of their bodies, and the first experiences of falling in love and sexual attraction had influenced their gender related interests and behaviour, feelings of gender discomfort and gender identification. Although, both persisters and desisters reported a desire to be the other gender during childhood years, the underlying motives of their desire seemed to be different.

Annotation: A interview-based, qualitatively-analyzed descriptive study of desisting or persisting Dutch TGNB adolescents

Stevens J, Gomez-Lobo V, Pine-Twaddell E. Insurance Coverage of Puberty Blocker Therapies for Transgender Youth. *Pediatrics*. 2015;136(6):1029-1031. doi:10.1542/peds.2015-2849 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26527547

Abstract: None

Annotation: Examines insurance barriers to treatment access among TGNB children seen in 2 University-based pediatric clinics (MedStar Washington Hospital Center and Chase Brexton Health Care)

Strang JF, Jarin J, Call D, et al. Transgender Youth Fertility Attitudes Questionnaire: Measure Development in Nonautistic and Autistic Transgender Youth and Their Parents. *J Adolesc Health*. 2018;62(2):128-135. doi:10.1016/j.jadohealth.2017.07.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29033160

Abstract: PURPOSE: The objective of this study was to assess transgender youth and parent attitudes regarding (1) the potential impact of gender-affirming hormone therapy on fertility and (2) fertility preservation (FP) options. METHODS: The Transgender Youth Fertility Attitudes Questionnaire was developed through a multistage participatory process with gender specialists and key stakeholders (transgender youth and their parents, N = 35). As up to 25% of youth

gender referrals have co-occurring autism, measure development included a well-characterized supplementary sample of autistic transgender youth to maximize the applicability of the questionnaire. Following its development and refinement, the Transgender Youth Fertility Attitudes Questionnaire was pilot tested with transgender youth (nonautistic and autistic) and their parents (N = 51). RESULTS: The participatory process produced parallel child and parent questionnaires addressing fertility and FP knowledge and attitudes. In the pilot trial, youth and parents expressed generally similar attitudes about fertility and FP. Most youth (92%) reported learning about gender-affirming hormone therapy-related fertility issues online. Although many transgender youth endorsed a wish to parent children at some point, few (24%) expressed desire to have their own biological child. However, many youth wondered, or did not know, if their feelings about having a biological child might change in the future. CONCLUSIONS: This study presents a novel procedure for developing instruments for use with transgender youth. Although a majority of transgender youth in this study were uninterested in using FP, extending exploration of this topic with young people may be useful given findings of their openness to the idea that fertility attitudes may change in adulthood.

Annotation: A qualitative comparison of attitudes about fertility preservation between autistic and allistic TGNB youths

van der Loos M, Klink DT, Hannema SE, et al. Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol. *J Sex Med*. 2023;20(3):398-409. doi:10.1093/jsxmed/qdac029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36763938

Abstract: BACKGROUND: Twenty years ago, the Dutch Protocol-consisting of a gonadotropin-releasing hormone agonist (GnRHa) to halt puberty and subsequent gender-affirming hormones (GAHs)-was implemented to treat adolescents with gender dysphoria. AIM: To study trends in trajectories in children and adolescents who were referred for evaluation of gender dysphoria and/or treated following the Dutch Protocol. METHODS: The current study is based on a retrospective cohort of 1766 children and adolescents in the Amsterdam Cohort of Gender Dysphoria. OUTCOMES: Outcomes included trends in number of intakes, ratio of assigned sex at birth, age at intake, age at start of GnRHa and GAH, puberty stage at start of GnRHa, proportions of adolescents starting and stopping GnRHa, reasons for refraining from GnRHa, and proportions of people undergoing gender-affirming surgery. RESULTS: A steep increase in referrals was observed over the years. A change in the AMAB:AFAB ratio (assigned male at birth to assigned female at birth) was seen over time, tipping the balance toward AFAB. Age at intake and at start of GnRHa has increased over time. Of possibly eligible adolescents who had their first visit before age 10 years, nearly half started GnRHa vs around two-thirds who had their first visit at or after age 10 years. The proportion starting GnRHa rose only for those first visiting before age 10. Puberty stage at start of GnRHa fluctuated over time. Absence of gender dysphoria diagnosis was the main reason for not starting GnRHa. Very few stopped GnRHa (1.4%), mostly because of remission of gender dysphoria. Age at start of GAH has increased mainly in the most recent years. When a change in law was made in July 2014 no longer requiring gonadectomy to change legal sex, percentages of people undergoing gonadectomy decreased in AMAB and AFAB. CLINICAL IMPLICATIONS: A substantial number of adolescents did not start medical treatment. In the ones who did, risk for retransitioning was very low, providing ongoing support for medical interventions in comprehensively assessed gender diverse adolescents. STRENGTHS AND LIMITATIONS: Important topics on transgender health care for children and adolescents were studied in a large cohort over an unprecedented time span, limited by the retrospective design.

CONCLUSION: Trajectories in diagnostic evaluation and medical treatment in children and adolescents referred for gender dysphoria are diverse. Initiating medical treatment and need for surgical procedures depends on not only personal characteristics but societal and legal factors as well.

Annotation: Examines characteristics, treatment trajectories, and temporal trends in TGNB adolescents over 20 years of applying the Dutch protocol in an Amsterdam clinic. Authors did not specify affirmed gender identities, only natal sex: N = 689 AMAB and N = 1077 AFAB. Reports the size of the ACOG as 8831 patients in 2018, up from 8210 in previous publication.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. *Arch Sex Behav*. 2016;45(7):1697-1703. doi:10.1007/s10508-016-0764-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27251640

Abstract: International guidelines recommend the use of Gonadotropin-Releasing Hormone (GnRH) agonists in adolescents with gender dysphoria (GD) to suppress puberty. Little is known about the way gender dysphoric adolescents themselves think about this early medical intervention. The purpose of the present study was (1) to explicate the considerations of gender dysphoric adolescents in the Netherlands concerning the use of puberty suppression; (2) to explore whether the considerations of gender dysphoric adolescents differ from those of professionals working in treatment teams, and if so in what sense. This was a qualitative study designed to identify considerations of gender dysphoric adolescents regarding early treatment. All 13 adolescents, except for one, were treated with puberty suppression; five adolescents were trans girls and eight were trans boys. Their ages ranged between 13 and 18 years, with an average age of 16 years and 11 months, and a median age of 17 years and 4 months. Subsequently, the considerations of the adolescents were compared with views of clinicians treating youth with GD. From the interviews with the gender dysphoric adolescents, three themes emerged: (1) the difficulty of determining what is an appropriate lower age limit for starting puberty suppression. Most adolescents found it difficult to define an appropriate age limit and saw it as a dilemma; (2) the lack of data on the long-term effects of puberty suppression. Most adolescents stated that the lack of long-term data did not and would not stop them from wanting puberty suppression; (3) the role of the social context, for which there were two subthemes: (a) increased media-attention, on television, and on the Internet; (b) an imposed stereotype. Some adolescents were positive about the role of the social context, but others raised doubts about it. Compared to clinicians, adolescents were often more cautious in their treatment views. It is important to give voice to gender dysphoric adolescents when discussing the use of puberty suppression in GD. Otherwise, professionals might act based on assumptions about adolescents' opinions instead of their actual considerations. We encourage gathering more qualitative research data from gender dysphoric adolescents in other countries.

Annotation: Examines perceptions and attitudes about gender in transgender youths

Vrouenraets LJJJ, de Vries ALC, Arnoldussen M, et al. Medical decision-making competence regarding puberty suppression: perceptions of transgender adolescents, their parents and clinicians. *Eur Child Adolesc Psychiatry*. 2022;32(11):2343-2361. doi:10.1007/s00787-022-02076-6 Accessed September 15, 2023. Available at https://link.springer.com/content/pdf/10.1007/s00787-022-02076-6.pdf

Abstract: According to international transgender care guidelines, transgender adolescents should have medical decision-making competence (MDC) to start puberty suppression (PS) and halt endogenous pubertal development. However, MDC is a debated concept in adolescent transgender care and little is known about the transgender adolescents', their parents', and clinicians' perspectives on this. Increasing our understanding of these perspectives can improve transgender adolescent care. A qualitative interview study with adolescents attending two Dutch gender identity clinics (eight transgender adolescents who proceeded to gender-affirming hormones after PS, and six adolescents who discontinued PS) and 12 of their parents, and focus groups with ten clinicians was conducted. From thematic analysis, three themes emerged regarding transgender adolescents' MDC to start PS: (1) challenges when assessing MDC, (2) aspects that are considered when assessing MDC, and (3) MDC's relevance. The four criteria one needs to fulfill to have MDC—understanding, appreciating, reasoning, communicating a choice—were all, to a greater or lesser extent, mentioned by most participants, just as MDC being relative to a specific decision and context. Interestingly, most adolescents, parents and clinicians find understanding and appreciating PS and its consequences important for MDC. Nevertheless, most state that the adolescents did not fully understand and appreciate PS and its consequences, but were nonetheless able to decide about PS. Parents' support of their child was considered essential in the decision-making process. Clinicians find MDC difficult to assess and put into practice in a uniform way. Dissemination of knowledge about MDC to start PS would help to adequately support adolescents, parents and clinicians in the decision-making process.

Annotation: A qualitative interview/focus group study of TGNB adolescents who either continued or discontinued treatment, and their parents. TGNB natal sexes reported only: 5 AMAB and 9 AFAB.

Vrouenraets LJJJ, de Vries MC, Hein IM, Arnoldussen M, Hannema SE, de Vries ALC. Perceptions on the function of puberty suppression of transgender adolescents who continued or discontinued treatment, their parents, and clinicians. *International journal of transgender health*. 2022;23(4):428-441. doi:10.1080/26895269.2021.1974324 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9621271/pdf/WIJT_23_1974324.pdf

Abstract: Purpose: Treatment of transgender adolescents with puberty suppression (PS) was developed to provide time for exploration before pursuing gender affirming medical treatment (GAMT) with irreversible effects. It may also result in a more satisfactory physical outcome for those who continue with GAMT. Despite being the current first choice treatment, little research has examined the function of PS from the perspectives of transgender adolescents, their parents, and clinicians. Insight into the perceived functions of PS will help to adequately support adolescents in their decision-making process and give them the care they need. Methods: Qualitative study using interviews with eight transgender adolescents who proceeded with GAMT after PS ("continuers"), six adolescents who discontinued PS ("discontinuers") and 12 parents, and focus groups with ten clinicians. Results: All informants considered inhibition of development of secondary sex characteristics an important function of PS. Most continuers saw PS as the first step of GAMT. Nevertheless, some were glad that the effects were reversible even if they didn't expect to change their minds. Some discontinuers did experience PS as an expanded diagnostic phase. One continuer used the time on PS to get used to living in the affirmed gender role, and several parents found the time helpful to adapt to their child's new gender role. PS provided clinicians more time for diagnostic assessment. Conclusions: Adolescents, parents and clinicians do not all report the same functions of PS. Although

international guidelines emphasize providing time for exploration of gender identity as an important reason for PS, many adolescents nowadays seem to have clear ideas about their gender identity and treatment wishes, and experience PS as the first step of GAMT. For some discontinuers however, PS offered a valued period of exploration. Guidelines could be modified to provide more customized care, taking adolescents' and parents' ideas about the functions of PS into account.

Annotation: A qualitative study examining perceptions about the function of puberty suppression in TGNB adolescents who continued vs discontinued treatment, their parents, and clinicians. TGNB natal sexes reported only: 5 AMAB and 9 AFAB.

Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. *Transgender Health*. 2023;8(1):84-88. doi:10.1089/trgh.2021.0102 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0102

Abstract: Background: Puberty suppression is a standard of care for gender-affirming therapy in gender-diverse youth. Leuprolide acetate is a gonadotropin-releasing hormone agonist (GnRHa) commonly used for pubertal suppression. There are concerns that GnRHa agents prolong the rate-corrected QT interval (QTc) when used as androgen deprivation therapy in management of prostate cancer; however, there is a paucity of literature regarding the effect of leuprolide acetate on QTc intervals in gender-diverse youth. Aim: To determine the proportion of gender-diverse youth with QTc prolongation on leuprolide acetate therapy. Methods: A retrospective chart review of gender-diverse youth initiated on leuprolide acetate between July 1, 2018 and December 31, 2019 was conducted at a tertiary care pediatric hospital in Alberta, Canada. Youth aged 9–18 years were included if a 12-lead electrocardiogram was completed after initiating leuprolide acetate. The proportion of adolescents with clinically significant QTc prolongation was assessed, defined as QTc > 460 milliseconds (ms). Results: Thirty-three pubertal youth were included. The cohort had a mean age of 13.7 years (standard deviation [SD] 2.1) and 69.7% identified as male (assigned female at birth). The mean post-leuprolide acetate QTc was 415 ms (SD 27, range 372–455). Twenty-two (66.7%) of youth were prescribed concomitant medications, including QTc-prolonging medications in 15.2%. None of the 33 youth on leuprolide acetate had QTc prolongation. Only 24.2% patients had a borderline QTc (QTc 440–460 ms). Conclusion: No gender-diverse youth on leuprolide acetate demonstrated clinically significant QTc prolongation.

Annotation: A descriptive study examining QTc intervals of TGNB youths on leuprolide acetate

Warwick RM, Araya AC, Shumer DE, Selkie EM. Transgender Youths' Sexual Health and Education: A Qualitative Analysis. *J Pediatr Adolesc Gynecol*. 2022;35(2):138-146. doi:10.1016/j.jpag.2021.09.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34619356

Abstract: STUDY OBJECTIVE: To characterize transgender adolescents' sexual behaviors, identities, and their perceived experiences with sex education. DESIGN: Semi-structured interviews were conducted and addressed sexual experiences and perceptions of sex education received from family, school educators, and healthcare providers. Interviews were audio recorded, transcribed, and analyzed utilizing NVivo 12 software for thematic analysis. SETTING: Child and adolescent gender services clinic at a Midwestern university-based medical center in

the United States. PARTICIPANTS: 30 transgender adolescents between the ages of 15 to 20. INTERVENTIONS AND MAIN OUTCOME MEASURES: Themes generated during semi-structured interviews. RESULTS: Sexual orientations were inclusive of attractions to a spectrum of gender identities. Libido was perceived to be impacted by gender-affirming hormone therapy, which was unanticipated for some adolescents. Family and school-based sex education was perceived to be relevant only for heterosexual and cisgender adolescents. Inclusive education for transgender adolescents was desired. Counseling provided by gender-affirming providers on sexual health was trusted and other healthcare providers were perceived to lack training on gender-inclusive care. CONCLUSION: This study demonstrated that families and school educators did not provide sex education perceived to be applicable to transgender adolescents. Similarly, healthcare providers of transgender adolescents were perceived to not provide inclusive or comprehensive medical care in comparison to physicians who routinely provide gender-affirming care. Gaps in education and healthcare could be improved with sex education outreach or training for families and school educators as well as the development and implementation of professional competencies for pediatricians on transgender adolescent healthcare.

Annotation: Qualitative study examining sexual health and education outcomes in transgender adolescents

Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *J Sex Med*. 2018;15(4):582-590. doi:10.1016/j.jsxm.2018.01.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463477

Abstract: BACKGROUND: Over the past decade, the number of people referred to gender identity clinics has rapidly increased. This raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions. AIM: To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment. METHODS: The medical files of all people who attended our gender identity clinic from 1972 to 2015 were reviewed retrospectively. OUTCOMES: The number of (and change in) people who applied for transgender health care, the percentage of people starting with gender-affirming hormonal treatment (HT), the estimated prevalence of transgender people receiving gender-affirming treatment, the percentage of people who underwent gonadectomy, and the percentage of people who regretted gonadectomy, specified separately for each year. RESULTS: 6,793 people (4,432 birth-assigned male, 2,361 birth-assigned female) visited our gender identity clinic from 1972 through 2015. The number of people assessed per year increased 20-fold from 34 in 1980 to 686 in 2015. The estimated prevalence in the Netherlands in 2015 was 1:3,800 for men (transwomen) and 1:5,200 for women (transmen). The percentage of people who started HT within 5 years after the 1st visit decreased over time, with almost 90% in 1980 to 65% in 2010. The percentage of people who underwent gonadectomy within 5 years after starting HT remained stable over time (74.7% of transwomen and 83.8% of transmen). Only 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy were identified as experiencing regret. CLINICAL IMPLICATIONS: Because the transgender population is growing, a larger availability of transgender health care is needed. Other health care providers should familiarize themselves with transgender health care, because HT can influence diseases and interact with medication. Because not all people apply for the classic treatment approach, special attention should be given to those who choose less common forms of treatment.

STRENGTHS AND LIMITATIONS: This study was performed in the largest Dutch gender identity clinic, which treats more than 95% of the transgender population in the Netherlands. Because of the retrospective design, some data could be missing. CONCLUSION: The number of people with gender identity issues seeking professional help increased dramatically in recent decades. The percentage of people who regretted gonadectomy remained small and did not show a tendency to increase. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018;15:582-590.

Annotation: First describes the Dutch ACOG cohort, adults, adolescents, and children with a GD/TGNB diagnosis and at least one CEGD visit. Examines temporal trends in diagnosis, treatment, and surgical interventions, as well as reporting on the proportions of subjects who reported regret after gonadectomy in N=6793 transgender patients, including N=812 adolescents.

Eligible Studies Lacking High-priority Comparisons: Observational Studies of TGNB Youth versus Special Populations (Bibliography Only)

Dilday EA, Bukulmez O, Saner K, Lopez X, Jarin J. Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy. *Transgend Health*. 2022;7(6):528-532. doi:10.1089/trgh.2021.0037 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644123

Abstract: PURPOSE: The target population for fertility preservation recently has been expanded from adolescents with cancer undergoing gonadotoxic chemotherapy to include transgender youth before initiating gender-affirming hormone therapy. Patients and providers may have knowledge deficits regarding options for fertility preservation, accessibility, and feasibility of its techniques, and impact of treatment on future fertility. This study describes outcomes of sperm cryopreservation in transgender male-to-female (affirmed female) youth and compares semen parameters with adolescents diagnosed with cancer. METHODS: Medical records of transgender-affirmed female adolescents and adolescent males diagnosed with cancer who underwent sperm cryopreservation at the Fertility and Advanced Reproductive Medicine clinic of the University of Texas (UT) Southwestern Medical Center between March 2015 and March 2020 were reviewed. Demographic data were recorded and values for sperm parameters (volume, count, total count, motility (%), total motile) were collected. When available, hormone levels (luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol) and Tanner stages were also assessed. The two populations were compared using chi-square analysis and two-sample student's t-test. Data are presented as mean+/-standard deviation. RESULTS: While semen quality parameters trended lower in transgender youth compared with adolescents with cancer, there was no statistically significant difference between groups. While four out of 18 patients in the transgender group had azoospermia, mean semen quality parameters fell within normal adult reference ranges for both groups. CONCLUSION: Sperm cryopreservation for transgender youth and adolescents with cancer is feasible, inexpensive, and does not result in significant treatment delays. This information can improve counseling and access to these procedures, particularly in the transgender population.

Annotation: A US-based cross-sectional study comparing sperm quality outcomes between transgender females vs a special population (ie, cisgender males with cancer) at baseline (before initiating treatment with gender-affirming hormones).

Mejia-Otero JD, White P, Lopez X. Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth. *Transgend Health*. 2021;6(1):31-35. doi:10.1089/trgh.2020.0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33614957

Abstract: Purpose: To analyze the effectiveness of gonadotropin-releasing hormone agonists (GnRHa) in suppressing the hypothalamic-pituitary gonadal (HPG) axis in transgender adolescents. Methods: Retrospective review of electronic medical records of transgender youth and children with central precocious puberty (CPP) treated with GnRHa. Blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and/or estradiol at baseline and during treatment were compared between groups. Results: Data from 30 transgender and 30 patients with CPP were analyzed. Transgender patients were older with a mean age of 13.0+/-2.1 years versus 7.7+/-2.3 years in the CPP group, p<0.001. There were more patients assigned male at birth (AMAB) in the transgender group (56.7%) than males in the CPP group (30%), p<0.001. The transgender group had more patients with advanced puberty with 56% of patients having a Tanner stage of IV-V, versus none in the CPP group, p<0.01. GnRHa treatment resulted in LH, FSH, and testosterone levels that were similar in males with CPP versus transgender patients AMAB; suppression of LH and FSH levels was similar in females with CPP versus transgender patients assigned female at birth, but estradiol levels were higher in the latter (1.8+/-1.8 pg/mL vs. 9.4+/-9.7 pg/mL, respectively, p<0.001). FSH levels were lower in the transgender group treated with histrelin (0.8+/-0.8 mIU/mL vs. 1.9+/-1.2 mIU/mL in the leuprolide group, p=0.004). Conclusions: GnRHa are effective in suppressing the HPG axis in transgender youth, similar to that observed in children with CPP.

Annotation: Compares puberty suppression outcomes in TGNB youth versus those with central precocious puberty (CPP).

Van Donge N, Schvey NA, Roberts TA, Klein DA. Transgender Dependent Adolescents in the U.S. Military Health Care System: Demographics, Treatments Sought, and Health Care Service Utilization. *Mil Med*. 2019;184(5-6):e447-e454. doi:10.1093/milmed/usy264 Accessed September 15, 2023. Available at https://watermark.silverchair.com/usy264.pdf

Abstract: INTRODUCTION: Transgender and gender-diverse (TGD) youth are at greater risk for mental health and medical conditions than their cisgender peers; however, poor health outcomes and identity-based discrimination can be minimized in the context of optimal support. Approximately 1.7 million youth may be eligible for care covered by the Military Health System, which includes mental health and gender-affirming medications. The purpose of the current study is to identify sociodemographic characteristics, the psychosocial and behavioral risk profile, and health care utilization patterns of TGD dependent youth cared for in the U.S. military system to inform provider training and resource allocation. MATERIALS AND METHODS: We performed a retrospective chart review by searching all medical records between July 1, 2014 and July 1, 2017 for diagnoses suggesting visits for TGD-services at a regional referral-based adolescent medicine clinic which cares for dependent children of active duty, activated selected reserve, and retired military service members between the ages of 9 and 24 years for a wide range of health care needs. RESULTS: Fifty-three participants were included in this study.

Sixty-four percent reported a transmasculine identity, 21% a transfeminine identity, and 15% a non-binary or undecided identity. The mean age at first gender-related visit was 14.5 years (SD 3.2). The mean number of primary care physicians and specialists seen by a given individual in a military treatment facility for any visit type since the implementation of the medical record system in 2005 was 12 (SD 6.8) and 10.2 (SD 7.8), respectively. Thirty-three percent of all patients assigned as female at birth were on testosterone therapy and 23% of all patients assigned as male at birth were on estrogen therapy at their most recent clinic visit. Twelve patients were undergoing pubertal suppression with an injectable or implantable gonadotropin-releasing hormone agonist. Seventy percent reported a history of suicidal ideation, 42% self-harm, 21% at least one suicide attempt, and 33% psychiatric hospitalization. Having strongly supportive parents was significantly associated with recognizing, disclosing and seeking treatment for gender nonconformity at an earlier age (ps ≤ 0.03) and marginally associated with less likelihood of current suicidal ideation (p = 0.06) compared to those with less supportive parents. CONCLUSIONS: This study elucidated the sociodemographic and behavioral risk profile of a sample of TGD youth in the MHS. Military and non-military health care providers across a broad spectrum of specialties should be knowledgeable about the unique psychosocial and medical needs, requisite sensitivity, and available referral options in the care of TGD youth. Assumptions about one's gender identity, sexual orientation, gender expression, or behaviors cannot be made based on birth-assigned sex. Further research is needed to investigate the health and wellbeing of TGD military-affiliated youth over time and to determine quality transgender-related services in support of this vulnerable and underserved population.

Annotation: A cross-sectional study examining mental health outcomes in TGNB adolescent dependents of active-duty or retired US military personnel

Eligible Studies without High-priority Outcomes (Bibliography Only)

Akgül S, Bonny AE, Ford N, Holland-Hall C, Chelvakumar G. Experiences of Gender Minority Youth With the Intrauterine System. *J Adolesc Health*. 2019;65(1):32-38. doi:10.1016/j.jadohealth.2018.11.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691940

Abstract: PURPOSE: The aim of the study was to evaluate the experience of menstruating adolescents identifying as male or gender nonconforming with the levonorgestrel-releasing intrauterine system (LNG-IUS) as a method of menstrual suppression and compare to that of cisgender youth (CGY) using the LNG-IUS for noncontraceptive indications. METHODS: A retrospective chart review of gender minority youth (GMY), aged 12-22 years, who self-selected the 52 mg LNG-IUS for menstrual suppression between June 2014 and January 2018. GMY were then matched for age and time of insertion with CGY. Subjects were contacted by telephone to further explore LNG-IUS experience such as if the device was still in place, method satisfaction, current bleeding patterns, and for GMY improvement in menstrual distress. RESULTS: Thirty GMY had the LNG-IUS inserted during the study period, and 20 GMY were matched with CGY for age and time of insertion. GMY were significantly more likely to receive sedation for LNG-IUS insertion (50% vs. 15%, p = .04). Otherwise, the LNG-IUS experience was similar between groups, including mean number of telephone/office visit encounters for an LNG-IUS concern, expulsion and reinsertion rates, and need for additional medications to control bleeding. On average, the mean months of use was 14.5 +/- 8.6 months in GMY and 14.6+/-11.5 in CGY (p = .97). LNG-IUS removal was documented in three (15%) of GMY and five (25%) of CGY.

Improvement in menstrual distress was reported by 80% of GMY after the insertion of the LNG-IUS. CONCLUSIONS: Overall experience with the LNG-IUS was similar for GMY and CGY, and menstrual distress and bleeding pattern improved in the majority of GMY who self-selected this method for menstrual suppression.

Annotation: A US cohort study examining menstrual suppression in transmasculine versus cisgender adolescents.

Alaniz VI, Sheeder JL, Whitmore GT, et al. Menstrual Suppression in Adolescent and Young Adult Transgender Males. *J Pediatr Adolesc Gynecol*. 2023;36(2):116-121. doi:10.1016/j.jpag.2022.10.007 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2021591277&from=export

Abstract: Objective: To describe time to cessation of menses in adolescent and young adult transgender males with testosterone and/or other hormonal therapies Design: Retrospective chart review Setting: Tertiary children's hospital Participants: Patients, aged 10-24, who began gender-affirming hormonal therapy between January 2013 and January 2019 (n = 220) Intervention(s): None Main Outcome Measure(s): Time to cessation of menses Results: Most patients identified as transgender male or transmasculine (211/220, 95.9%), with an average age of 15.8 (±1.9) years. Approximately 53.6% (118/220) of patients reported regular menstrual cycles; 18.2% (40/220) reported irregular cycles. Median time to cessation of menses for all patients was 182 days. Patients treated with testosterone alone (n = 105) reported a median time to cessation of menses of 151 days. Patients who concurrently began testosterone and norethindrone acetate (NETA) (n = 5) had a median time to cessation of menses of 188 days, compared with 168 days for those on testosterone and depot medroxyprogesterone acetate (DMPA, n = 15). In 15 patients who began testosterone, a progestin therapy was later added to induce menstrual suppression, and the median time to cessation of menses was 168 days (+DMPA, n = 4) or 56 days (+NETA, n = 11). Patients treated with NETA (n = 14) or depot leuprolide (n = 11) reported a median time to cessation of menses of 78 days or 77 days, respectively. Considerable variability in prescribing patterns was noted in the remaining 36.4% of patients (n = 80). Conclusion: Patients used a variety of different hormonal regimens for menstrual suppression. Less than half achieved cessation of menses within 6 months. NETA and depot leuprolide users reported the most rapid cessation of menses.

Annotation: Examines time to menstrual suppression in transmasculine and gender expansive youths receiving GAHT, including testosterone

Baram S, Myers SA, Yee S, Librach CL. Fertility preservation for transgender adolescents and young adults: a systematic review. *Hum Reprod Update*. 2019;25(6):694-716. doi:10.1093/humupd/dmz026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31633751

Abstract: BACKGROUND: Many transgender individuals choose to undergo gender-affirming hormone treatment (GAHT) and/or sex reassignment surgery (SRS) to alleviate the distress that is associated with gender dysphoria. Although these treatment options often succeed in alleviating such symptoms, they can also negatively impact future reproductive potential. OBJECTIVE AND RATIONALE: The purpose of this systematic review was to synthesize the available psychosocial and medical literature on fertility preservation (FP) for transgender

adolescents and young adults (TAYAs), to identify gaps in the current research and provide suggestions for future research directions. SEARCH METHODS: A systematic review of English peer-reviewed papers published from 2001 onwards, using the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) guidelines, was conducted. Four journal databases (Ovid MEDLINE, PubMed Medline, Ovid Embase and Ovid PsychINFO) were used to identify all relevant studies exploring psychosocial or medical aspects of FP in TAYAs. The search strategy used a combination of subject headings and generic terms related to the study topic and population. Bibliographies of the selected articles were also hand searched and cross-checked to ensure comprehensive coverage. All selected papers were independently reviewed by the co-authors. Characteristics of the studies, objectives and key findings were extracted, and a systematic review was conducted. OUTCOMES: Included in the study were 19 psychosocial-based research papers and 21 medical-based research papers that explore fertility-related aspects specific for this population. Key psychosocial themes included the desire to have children for TAYAs; FP discussions, counselling and referrals provided by healthcare providers (HCPs); FP utilization; the attitudes, knowledge and beliefs of TAYAs, HCPs and the parents/guardians of TAYAs; and barriers to accessing FP. Key medical themes included fertility-related effects of GAHT, FP options and outcomes. From a synthesis of the literature, we conclude that there are many barriers preventing TAYAs from pursuing FP, including a lack of awareness of FP options, high costs, invasiveness of the available procedures and the potential psychological impact of the FP process. The available medical data on the reproductive effects of GAHT are diverse, and while detrimental effects are anticipated, the extent to which these effects are reversible is unknown. WIDER IMPLICATIONS: FP counselling should begin as early as possible as a standard of care before GAHT to allow time for informed decisions. The current lack of high-quality medical data specific to FP counselling practice for this population means there is a reliance on expert opinion and extrapolation from studies in the cisgender population. Future research should include large-scale cohort studies (preferably multi-centered), longitudinal studies of TAYAs across the FP process, qualitative studies of the parents/guardians of TAYAs and studies evaluating the effectiveness of different strategies to improve the attitudes, knowledge and beliefs of HCPs.

Annotation: A systematic review examining fertility outcomes in TGNB adolescents and young adults.

Burke SM, van Heesewijk JO, Menks WM, et al. Postnatal Effects of Sex Hormones on Click-Evoked Otoacoustic Emissions: A Study of Adolescents with Gender Dysphoria. *Arch Sex Behav*. 2020;49(2):455-465. doi:10.1007/s10508-020-01652-8 Accessed September 15, 2023. Available at https://orbi.uliege.be/bitstream/2268/259356/1/BurkeArchSexBehav%202020.pdf

Abstract: Click-evoked otoacoustic emissions (CEOAEs) are echo-like sounds, generated by the inner ear in response to click-stimuli. A sex difference in emission strength is observed in neonates and adults, with weaker CEOAE amplitudes in males. These differences are assumed to originate from testosterone influences during prenatal male sexual differentiation and to remain stable throughout life. However, recent studies suggested activational, postnatal effects of sex hormones on CEOAEs. Adolescents diagnosed with gender dysphoria (GD) may receive gonadotropin-releasing hormone analogs (GnRHa) in order to suppress endogenous sex hormones and, therefore, pubertal maturation, followed by cross-sex hormone (CSH) treatment. Using a cross-sectional design, we examined whether hormonal interventions in adolescents diagnosed with GD (62 trans boys, assigned female at birth, self-identifying as male; 43 trans girls, assigned male at birth, self-identifying as female), affected their CEOAEs compared to age-

and sex-matched controls (44 boys, 37 girls). Sex-typical differences in CEOAE amplitude were observed among cisgender controls and treatment-naïve trans boys but not in other groups with GD. Treatment-naïve trans girls tended to have more female-typical CEOAEs, suggesting hypomasculinized early sexual differentiation, in support of a prominent hypothesis on the etiology of GD. In line with the predicted suppressive effects of androgens, trans boys receiving CSH treatment, i.e., testosterone plus GnRHa, showed significantly weaker right-ear CEOAEs compared with control girls. A similar trend was seen in trans boys treated with GnRHa only. Unexpectedly, trans girls showed CEOAE masculinization with addition of estradiol. Our findings show that CEOAEs may not be used as an unequivocal measure of prenatal androgen exposure as they can be modulated postnatally by sex hormones, in the form of hormonal treatment.

Annotation: A cross-sectional study examining the effect of GnRH agonists and sex hormones on click-evoked otoacoustic emissions in TGNB adolescents. Also compares TGNB adolescents to cisgender peers.

Chen D, Matson M, Macapagal K, et al. Attitudes Toward Fertility and Reproductive Health Among Transgender and Gender-Nonconforming Adolescents. *J Adolesc Health*. 2018;63(1):62-68. doi:10.1016/j.jadohealth.2017.11.306 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29503031

Abstract: PURPOSE: Little is known about the reproductive desires of transgender and gender-nonconforming (TGNC) adolescents who may seek gender-affirming medical care that leads to infertility. The current study addressed this gap by examining attitudes toward fertility and family formation in a diverse sample of TGNC youth. METHOD: An online survey about sexual/reproductive health in sexual and gender minority (SGM) adolescents ages 14-17 years was conducted from September to October 2016. RESULTS: A total of 156 TGNC adolescents (M(age) = 16.1 years; 83.3% assigned female at birth; 58.3% youth of color) responded. Overall, 70.5% of TGNC adolescents were interested in adoption and 35.9% in biological parenthood; more gender-nonconforming youth (43.8%) than transgender youth (25.8%) expressed interest in biological fertility. Discussions with health-care providers about fertility and reproductive health were uncommon-only 20.5% of youth had discussed fertility in general and only 13.5% had discussed effects of hormones on fertility. However, 60.9% of respondents were interested in learning more about their fertility and family building options. Key themes emerging from qualitative comments included concerns related to fertility/reproductive health (e.g., stigma of SGM parenthood, effect of gender-affirming treatments on fertility), and the need for additional reproductive health information both tailored to their individual experience and for SGM individuals more generally. DISCUSSION: TGNC adolescents expressed interest in multiple family building options, including adoption and biological parenthood, and identified a need for more information about these options. Thus, clinicians working with adolescents should be aware of the unique fertility and reproductive health needs of TGNC youth.

Annotation: A survey study examining attitudes about fertility among TGNB adolescents who were participants in a larger study about sexual health and HIV prevention

Chiniara LN, Viner C, Palmert M, Bonifacio H. Perspectives on fertility preservation and parenthood among transgender youth and their parents. *Arch Dis Child*. 2019;104(8):739-744. doi:10.1136/archdischild-2018-316080 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30894340

Abstract: OBJECTIVE: The aim of this study was to investigate the views of young people (YP) with gender dysphoria and their parents concerning fertility preservation and reproductive and life priorities. DESIGN: A cross-sectional questionnaire-based study assessed knowledge of potential effects of treatments for gender dysphoria on fertility, current and future life priorities and preferences regarding future fertility/parenting options among YP and parents. RESULTS: A total of 79 YP (81% assigned female at birth [AFAB], 19% assigned male at birth [AMAB], aged 12-18 years, 68% between ages 16 years and 18 years) and 73 parents participated. The top current life priority for YP among eight options was being in good health; the least important priority was having children. Anticipated life priorities 10 years from now were ranked similarly. Parents' rankings paralleled the YP responses; however, parents ranked having children as a significantly higher priority for AFAB compared with AMAB YP in 10 years. The majority of YP (66% AFAB, 67% AMAB) want to be a parent in the future. However, most do not envision having a biological child. A large majority (72% AFAB, 80% AMAB) were open to adoption. None of the YP surveyed pursued fertility preservation. CONCLUSION: Fertility is a low current and future life priority for transgender YP. The majority of YP wish to become parents but are open to alternative strategies for building a family. These data may explain in part the reported low rates of fertility preservation among this population. Further studies are needed to assess if life priorities change over time.

Annotation: A Toronto-based cross-sectional study of TGNB adolescents and their parents examining fertility- and treatment-related questionnaire responses

Chu L, Gold S, Harris C, et al. Incidence and Factors Associated With Acne in Transgender Adolescents on Testosterone: A Retrospective Cohort Study. *Endocr Pract*. 2023;29(5):353-355. doi:10.1016/j.eprac.2023.02.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36889581

Abstract: OBJECTIVE: This retrospective cohort study aimed to assess incidence and predictors of acne among transgender adolescents receiving testosterone. METHODS: We analyzed records of patients aged <18 years, assigned female at birth, seen at Children's Healthcare of Atlanta Pediatric Endocrinology clinic for testosterone initiation between January 1, 2016, and January 1, 2019, with at least 1-year follow-up documented. Bivariable analyses to determine the association of clinical and demographic factors with new acne diagnosis were performed. RESULTS: Of 60 patients, 46 (77%) did not have baseline acne, but of those 46 patients, 25 (54%) developed acne within 1 year of testosterone initiation. Overall incidence proportion was 70% at 2 years; patients who used progestin prior to or during follow-up were more likely to develop acne than nonusers (92% vs 33%, P <.001). CONCLUSION: Transgender adolescents starting testosterone, particularly those taking progestin, should be monitored for acne development and treated proactively by hormone providers and dermatologists.

Annotation: Examines acne outcomes in transmasculine adolescents receiving testosterone in a pediatric endocrinology clinic

Cohen A, Gomez-Lobo V, Willing L, et al. Shifts in Gender-Related Medical Requests by Transgender and Gender-Diverse Adolescents. *J Adolesc Health*. 2023;72(3):428-436. doi:10.1016/j.jadohealth.2022.10.020 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36529618

Abstract: PURPOSE: Gender-affirming hormones and/or surgeries seeking to change the body can have potentially lasting effects. Changes in requests for these therapies among gender-diverse youth are not well-understood. The study aim is to characterize factors associated with shifts in gender-related medical requests. METHODS: This mixed-methods study used retrospective chart review and qualitative interviews with clinicians. Of 130 youth receiving clinical gender care at Children's National Hospital, 68 met inclusion criteria. Qualitative interview analysis was performed to identify patterns and themes around shifts in gender-related medical requests over time. Statistical analysis employed chi-square and t-tests to compare characteristics in the shift versus no-shift groups and kappa statistics to calculate qualitative coding agreement. RESULTS: Of the 68 youth followed over time (mean age 15.11 years, 47% autistic, 22% nonbinary), 20 (29%) reported a shift in request. No significant differences were found by age, autism status, or designated sex at birth. More youth with shifts were nonbinary (p = .012). Six shift profiles were identified from qualitative interviews with excellent reliability (kappa = 0.865). Four of the profiles reflect shifts in request prior to starting treatment (85% sample); two involved shifts after commencing treatment (15%). The most common profile reflected a medical request that was made, withdrawn, and re-requested (45%). DISCUSSION: Shifts in gender-affirming medical requests by gender-diverse youth may not be uncommon during the adolescent's gender discernment process, and may more likely occur among nonbinary youth. Many individuals who experience shifts away from medical treatment may later resume the request.

Annotation: A case-control study examining potential predictors of GD treatment discontinuation in TGNB adolescents in a gender services program. Only natal sex (29 AMAB and 39 AFAB) and transbinary/nonbinary were reported.

de Nie I, Mulder CL, Meissner A, et al. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. *Hum Reprod*. 2022;37(2):297-308. doi:10.1093/humrep/deab240 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34791270

Abstract: STUDY QUESTION: Can transgender women cryopreserve germ cells obtained from their orchiectomy specimen for fertility preservation, after having used puberty suppression and/or hormonal treatment? SUMMARY ANSWER: In the vast majority of transgender women, there were still immature germ cells present in the orchiectomy specimen, and in 4.7% of transgender women-who all initiated medical treatment in Tanner stage 4 or higher-mature spermatozoa were found, which would enable cryopreservation of spermatozoa or testicular tissue after having used puberty suppression and/or hormonal treatment. WHAT IS KNOWN ALREADY: Gender affirming treatment (i.e. puberty suppression, hormonal treatment, and subsequent orchiectomy) impairs reproductive function in transgender women. Although semen cryopreservation is generally offered during the transition process, this option is not feasible for all transgender women (e.g. due to incomplete spermatogenesis when initiating treatment in early puberty, in case of inability to masturbate, or when temporary cessation of hormonal treatment is too disruptive). Harvesting mature spermatozoa, or testicular tissue harboring immature germ cells, from orchiectomy specimens obtained during genital gender-affirming surgery (gGAS) might give this group a chance of having biological children later in life. Previous studies on spermatogenesis in orchiectomy specimens showed conflicting results, ranging from complete absence of germ cells to full spermatogenesis, and did not involve transgender women who initiated medical treatment in early- or late puberty. STUDY DESIGN, SIZE, DURATION: Histological and immunohistochemical analyses were performed on orchiectomy specimens

from 214 transgender women who underwent gGAS between 2006 and 2018. Six subgroups were identified, depending on pubertal stage at initiation of medical treatment (Tanner stage 2-3, Tanner stage 4-5, adult), and whether hormonal treatment was continued or temporarily stopped prior to gGAS in each of these groups. PARTICIPANTS/MATERIALS, SETTING, METHODS: All transgender women used a combination of estrogens and testosterone suppressing therapy. Orchiectomy specimen sections were stained with Mayer's hematoxylin and eosin and histologically analyzed to assess the Johnsen score and the ratio of most advanced germ cell types in at least 50 seminiferous tubular cross-sections. Subsequently, immunohistochemistry was used to validate these findings using spermatogonia, spermatocytes or spermatids markers (MAGE-A3/A4, gammaH2AX, Acrosin, respectively). Possibilities for fertility preservation were defined as: preservation of spermatozoa, preservation of spermatogonial stem cells or no possibilities (in case no germ cells were found). Outcomes were compared between subgroups and logistic regression analyses were used to assess the association between the duration of hormonal treatment and the possibilities for fertility preservation. MAIN RESULTS AND THE ROLE OF CHANCE: Mature spermatozoa were encountered in 4.7% of orchiectomy specimens, all from transgender women who had initiated medical treatment in Tanner stage 4 or higher. In 88.3% of the study sample orchiectomy specimens only contained immature germ cells (round spermatids, spermatocytes or spermatogonia, as most advanced germ cell type). In 7.0%, a complete absence of germ cells was observed, all these samples were from transgender women who had initiated medical treatment in adulthood. Cessation of hormonal treatment prior to gGAS did not affect the presence of germ cells or their maturation stage, nor was there an effect of the duration of hormonal treatment prior to gGAS. LIMITATIONS, REASONS FOR CAUTION: Since data on serum hormone levels on the day of gGAS were not available, we were unable to verify if the transgender women who were asked to temporarily stop hormonal treatment 4 weeks prior to surgery actually did so, and if people with full spermatogenesis were compliant to treatment. WIDER IMPLICATIONS OF THE FINDINGS: There may still be options for fertility preservation in orchiectomy specimens obtained during gGAS since a small percentage of transgender women had full spermatogenesis, which could enable cryopreservation of mature spermatozoa via a testicular sperm extraction procedure. Furthermore, the vast majority still had immature germ cells, which could enable cryopreservation of testicular tissue harboring spermatogonial stem cells. If maturation techniques like in vitro spermatogenesis become available in the future, harvesting germ cells from orchiectomy specimens might be a promising option for those who are otherwise unable to have biological children. STUDY FUNDING/COMPETING INTEREST: None. TRIAL REGISTRATION NUMBER: N/A.

Annotation: A cohort study comparing potential for fertility preservation in transgender women, including adolescents, who initiated cross-sex hormones at different pubertal stages at a gender specialty clinic

Garborcauskas G, McCabe E, Boskey ER, Grimstad FW. Family Building Perspectives of Assigned Female at Birth Transgender and Gender Diverse Adolescents Seeking Testosterone Gender-Affirming Hormone Therapy. *LGBT Health*. 2022;9(7):463-470. doi:10.1089/lgbt.2022.0004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35802494

Abstract: Purpose: The purpose of this study was to assess the future family building desires of assigned female at birth (AFAB) transgender and gender diverse (TGD) adolescents initiating hormone therapy, and to characterize the individuals interested in adoption. Methods: This was a retrospective chart review of AFAB TGD adolescents ages 15-17 years old initiating testosterone gender-affirming hormone therapy between 2010 and 2019, analyzing interest in

adoption, demographics, and gender-affirming care. Results: Of 195 AFAB TGD adolescents asked about family planning goals, 58% (n = 113) indicated desire for adoption in their future, and 13.3% (n = 26) had no desire for children. There was no difference between those who did and did not want to adopt in terms of age at time of first visit (p = 0.22), or race distribution (p = 0.45); however, straight-identified patients were more likely to desire adoption (p = 0.02) than people with other sexual orientations. Fifty-nine percent (n = 110) of those who did not have a history of adoption and/or experience with the child welfare system desired adoption, compared with 22% (n = 2) of those with a history (odds ratio, 5.14; 95% confidence interval, 1.04-25.39; p = 0.05). Conclusion: Some AFAB TGD adolescents endorse adoption as their desired pathway to parenthood. Clinicians should be sensitive to the complexities of parenthood desires of AFAB TGD patients and have resources to direct patients to more information. Further research is needed to better understand why many AFAB TGD adolescents desire adoption, how this changes with age, and the barriers they face in achieving their goals.

Annotation: Cohort study examining predictors of fertility beliefs and attitudes in testosterone-treated TGNB adolescents ages 15-17 years

Gilani M, Wallach P, Kyriakou A. Levels of physical activity and barriers to sport participation in young people with gender dysphoria. *J Pediatr Endocrinol Metab*. 2021;34(6):747-753. doi:10.1515/jpem-2021-0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33818040

Abstract: OBJECTIVES: To determine the levels of physical activity (PA) in young people with gender dysphoria (GD) and help identify factors which deter participation. METHODS: Fifty-six young people who attended paediatric endocrinology because of GD, June to October 2019, and were on treatment with gonadotrophin-releasing hormone (GnRH) analogue were approached to participate in a survey. RESULTS: A total of 55 young people (98%) responded to the survey. Thirty-eight (69%) participated in PA for >1 h/week. Thirty-two (58%) reported high motivation level for exercise. Those had median age of 15.9 years (10.7, 18.7) at the time of survey, and 13.6 years (9.7, 17.6) at start of GnRH analogue compared to 16.7 years (13.9, 18.5) (p, 0.047) and 15.4 years (11.2, 18.0) (p, 0.009) of the 23 (42%) who reported low motivation. Forty-one (74.5%) reported barriers when accessing PA, such as not being as good as others (75%), revealing sports clothing (73%) and not satisfied with body image (47%). Those were older (16.4 years [10.9, 18.7] vs. 14.7 years [10.7, 18.4] [p, 0.011]) at the time of survey and at start of GnRH analogue (14.9 years [9.7, 18.0] vs. 12.5 years [10.6, 15.2] [p, 0.0001]) than those 14 (25.5%) who reported facing no barriers. Twelve (85.7%) of those reporting no barriers stated high motivation levels compared to 20 (48.8%) of those reporting barriers (p, 0.026). CONCLUSIONS: Strategies aimed at improving participation are twofold: first to improve motivation, especially in post-pubertal young people, and secondly to achieve societal change to help eliminate barriers.

Annotation: A Scotland-based cross-sectional study examining sports participation and motivation levels in TGNB adolescents treated with GnRHa and a subset with cross-sex hormones.

Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. *Headache*. 2023;63(4):517-522. doi:10.1111/head.14493 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36988085

Abstract: OBJECTIVE: Assess the prevalence of headache in transgender and gender-diverse adolescents, comparing prevalence with and without exposure to gender-affirming hormone therapy. BACKGROUND: Transgender and gender-diverse youth are an understudied group in whom we can study the effects of sex steroids on adolescents' development of headache. We hypothesized that transfeminine adolescents treated with estrogen would have higher odds of headache than those not treated, and that transmasculine adolescents treated with testosterone would have lower odds of headache than those not treated. METHODS: This retrospective case-control study analyzed all patients seen at the Boston Children's Hospital Gender Multispecialty Service clinic from 2007 to 2017. Cases were defined as patients with headache, controls as those without headache, and exposure as treatment with gender-affirming hormone therapy (i.e., estrogen or testosterone). A computerized search identified cases that were then validated by chart review. RESULTS: Fifty-two of the 763 transgender and gender-diverse patients seen were confirmed to have headache. Of 273 transfeminine patients 45% (123/273) received estrogen treatment. Transfeminine patients receiving estrogen were more likely to have headache than those not receiving estrogen (7% [9/123] vs. 1% [2/150]; odd ratio [OR] 5.84 (95% confidence interval [CI] 1.24-27.6), p = 0.026). Of 490 transmasculine patients, 46% (227/490) received testosterone. Transmasculine patients receiving testosterone were more likely to have headache than those not receiving testosterone (12% [28/227] vs. 5% (13/263); OR 2.71 (95% CI 1.37-5.4), p = 0.005). CONCLUSION: Among transfeminine and transmasculine youth, those who received gender-affirming hormone therapy had higher odds of headache compared to those not taking gender-affirming hormone therapy. Further prospective studies to guide headache care of transgender and gender-diverse youth and adults are needed. Our results could be generalizable to other pediatric gender management clinics and may be worth discussing with patients considering treatment.

Annotation: A cumulative case-control study comparing risks of headache in TGNB patients receiving testosterone/estrogen versus not.

James HA, Chang AY, Imhof RL, et al. A community-based study of demographics, medical and psychiatric conditions, and gender dysphoria/incongruence treatment in transgender/gender diverse individuals. *Biol Sex Differ*. 2020;11(1):55. doi:10.1186/s13293-020-00332-5 Accessed September 15, 2023. Available at https://bsd.biomedcentral.com/counter/pdf/10.1186/s13293-020-00332-5.pdf

Abstract: BACKGROUND: Current understanding about health care in the gender diverse population is limited by the lack of community-based, longitudinal data, especially in the USA. We sought to characterize a community-based cohort of transgender individuals including demographics, gender identities, social characteristics, psychiatric and medical conditions, and medical therapy for gender dysphoria/incongruence. PATIENTS AND METHODS: We performed a retrospective chart review of gender diverse residents of Olmsted County, Minnesota, who sought gender-specific healthcare from January 1, 1974, through December 31, 2015, using an infrastructure that links medical records of Olmsted County residents from multiple institutions. RESULTS: The number of patients seeking gender-specific healthcare increased from 1 to 2 per 5-year interval during the 1970s-1990s to 41 from 2011 to 2015 (n = 82). Forty-nine (59.8%) were assigned male sex at birth (AMAB), 31 (37.8%) were assigned female (AFAB), and 2 (2.4%) were intersex. Gender identities evolved over time in 16.3% and 16.1% of patients AMAB and AFAB, respectively, and at most recent follow-up, 8.2% and 12.9% of patients AMAB and AFAB, respectively, were non-binary. Depression affected 78%, followed by anxiety (62.2%), personality disorder (22%), and post-traumatic stress disorder (14.6%). 58.5% experienced

suicidal ideation, 22% attempted suicide, and 36.6% were victims of abuse. The most prevalent medical conditions and cardiovascular (CV) risk factors included obesity (42.7%), tobacco use (40.2%), fracture [34.1% (86.2% traumatic)], hypertension (25.6%), hyperlipidemia (25.6%), and hypertriglyceridemia (15.9%). 67.3% of patients AMAB used feminizing and 48.4% of patients AFAB used masculinizing hormone therapy. When compared to US CDC National Health Statistics, there was a significantly greater prevalence of depression and anxiety but no difference in the prevalence of obesity, hypertension, hypercholesterolemia, type 2 diabetes, or stroke. CONCLUSION: Transgender and gender diverse individuals represent a population who express various gender identities and are seeking gender-specific healthcare at increasing rates. Psychiatric illness is highly prevalent compared to the US population but there is no difference in the prevalence of CV risk factors including obesity, type 2 diabetes, hypertension, and dyslipidemia.

Annotation: Examines changes in gender identity between AFAB and AMAB TGNB patients, including adolescents. Outcomes of interest were not reported separately for adolescents.

Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. *Transgend Health*. 2019;4(1):300-303. doi:10.1089/trgh.2018.0061 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31663037

Abstract: This retrospective chart review aims to address gaps in the literature regarding the efficacy and interaction of gonadotropin-releasing hormone agonists (GnRHa) and gender-affirming hormone therapies in medical transition regimens in transgender adolescents. We abstracted and reviewed data from 83 patients at our pediatric gender clinic, and found that patients who initiated treatment with GnRHa before gender-affirming hormones (estrogen, testosterone) required lower doses of those hormones than those who did not use GnRHa. The results of this preliminary research provide a foundation for future long-term prospective studies aimed to better understand these relationships.

Annotation: A cohort study comparing demographic characteristics, adverse effects, and estrogen/testosterone dosages between transgender patients receiving GnRH agonists versus not.

Komorowski AS, Fisher AR, Jungheim ES, Lewis CS, Omurtag KR. Fertility preservation discussions, referral and follow-up in male-to-female and female-to-male adolescent transgender patients. *Hum Fertil (Camb)*. 2021, 10.1080/14647273.2021.2015804:1-5. doi:10.1080/14647273.2021.2015804 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34915792

Abstract: The number of patients seeking transgender healthcare is growing, and there is a potential impact of gender-affirming therapies on fertility. The use of fertility preservation (FP), particularly among transgender adolescents, has been limited. We aimed to examine differences in FP counselling, referral and utilisation between male-to-female (MtF) and female-to-male (FtM) transgender adolescents. A retrospective review of the medical records of patients ages 12-17 seen at an academic medical centre between 2012 and 2017 with a diagnosis of gender dysphoria was conducted. A total of 22 MtF and 45 FtM adolescents were included. The counselling on the potential fertility impact of gender-affirming therapy was documented in

55%, and of those counselled, 73% were counselled before receiving medication. There was no significant difference between the timing of counselling for MtF versus FtM adolescents. Of patients with documented reproductive wishes, 77% reported either desire for adopted children or no desire for biological children. Among patients offered FP referral, 2 (22.2%) MtF and 3 (12.5%) FtM patients accepted; both MtF patients cryopreserved sperm. While most adolescents were counselled on the fertility impact of gender-affirming therapy, there is room for improvement as 45% of patients had no documented counselling. The rate of transgender adolescents pursuing FP consultation and gamete cryopreservation was low, consistent with prior studies in this population.

Annotation: A US-based cohort study examining fertility-related outcomes in n=67 TGNB adolescents seen in a specialty clinic.

Kyweluk MA, Sajwani A, Chen D. Freezing for the future: Transgender youth respond to medical fertility preservation. *International Journal of Transgenderism*. 2018;19(4):401-416. doi:10.1080/15532739.2018.1505575 Accessed September 15, 2023. Available at https://doi.org/10.1080/15532739.2018.1505575

Annotation: A qualitative, descriptive interview study examining ethical considerations related to fertility preservation in TGNB youth and their parents

Lambert A, Pratt A, Conard LAE, et al. Supporting Gender-Related Medical Decision Making for Transgender and Gender-Diverse Individuals: A Scoping Review. *Transgend Health*. 2023;8(2):113-123. doi:10.1089/trgh.2021.0030 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37013094

Abstract: PURPOSE: Transgender and gender-diverse (TGD) individuals and their families face numerous challenging decisions. To better understand their decision processes, we conducted a scoping review of the existing literature and of decision-support tools in use at pediatric gender-care clinics. METHODS: We searched PubMed, EMBASE, Scopus CINAHL, PsychINFO, and EBM Reviews for studies that were original research focused on decisions, decision making, or decision support for TGD individuals and/or their families. All studies were reviewed for inclusion by at least two researchers. Additionally, we reviewed clinical tools used to support decision making by TGD youth and their families. RESULTS: We retrieved 3306 articles. Thirty-two met criteria for data extraction. Studies focused on three major decisions: gender-confirming surgery, fertility preservation, and gender-affirming hormone therapy. Several themes that cut across clinical topics emerged: decision-making processes, decision-making roles, and sources of decision support. Only three articles focused on decision-support interventions, two of which discussed development of support tools and one evaluated a class designed to help with surgical decision making. None of the clinical tools reviewed met criteria for a decision aid. CONCLUSIONS: There is a dearth of studies related to decision support interventions, an absence validated by the resources currently in clinical use. This scoping review suggests an opportunity for the development of tools to aid in the decision-making processes for TGD youth and their families.

Annotation: A scoping review examining components of decision-making for TGNB individuals.

Lawlis SM, Donkin HR, Bates JR, Britto MT, Conard LAE. Health Concerns of Transgender and Gender Nonconforming Youth and Their Parents Upon Presentation to a Transgender Clinic. *J Adolesc*

Health. 2017;61(5):642-648. doi:10.1016/j.jadohealth.2017.05.025 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(17)30254-9/fulltext

Abstract: Purpose The purpose of the study was to determine the frequency of specific health concerns identified by transgender and gender nonconforming patients and their parents at initial clinic visit. Methods Checklists were developed in an iterative process and distributed to both patients and parents at their initial visit to a transgender clinic. Retrospective chart review and secondary data analyses were performed to determine the number of items endorsed, frequency with which each item was endorsed, and provider domain of each item endorsed: physician, social work, or both physician and social work. Results Checklists were collected from 118 patients and 103 parents. Patients endorsed a mean of 8.4 concerns (range 0–22) and parents 7.9 concerns (range 0–20). The most commonly endorsed patient concerns included use of gender-affirming hormones, steps for transition, gender-affirming surgery, restroom/dressing room use, and legal issues. Common parent concerns included general resources, child safety at school, acute mental health concerns, restroom/dressing room use, and steps for transition. Of the concerns endorsed by patients, 44% were in the social work domain, 37% in the physician domain, and 19% in both the social work and physician domain. Of the concerns endorsed by parents, 40% were in the social work domain, 31% in the physician domain, and 29% in the social work and physician domain. Conclusions Although patients and parents had similar numbers of concerns, they primarily focused on different topics. Youth were more interested in hormones and transition, while parents were more interested with transition and acceptance. Many concerns for both patients and parents fell within the social work domain.

Annotation: A cross-sectional study comparing attitudes about GD drug treatments between TGNB youths and their parents

Lee WG, Butler G, Carmichael P, et al. Urological and Gynaecological Considerations for the Use of Gonadotropin-releasing Hormone Analogues in Transgender and Nonbinary Adolescents: A Narrative Review. *Eur Urol Focus*. 2023;9(1):35-41. doi:10.1016/j.euf.2022.11.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36396559

Abstract: CONTEXT: Gonadotropin-releasing hormone analogues (GnRHAs) delay the progression of puberty in transgender and nonbinary (TGNB) adolescents and reduce the impact of dysphoria due to ongoing physical development. The intervention remains contentious despite growing evidence to support this practice. OBJECTIVE: To stimulate discussion on this topical issue in the urological and gynaecological community given potential ramifications for future fertility, physical development, and options for gender affirmation surgery (GAS). EVIDENCE ACQUISITION: We conducted searches of the MEDLINE (from 1946) and Embase (from 1974) databases for the benefits and potential challenges of hormone blockade in TGNB adolescents on February 1, 2022. Evidence with a primary focus on clinical issues of interest to urologists and gynaecologists was objectively synthesised and reported. EVIDENCE SYNTHESIS: The onset of puberty represents a period of distress for TGNB adolescents as secondary sexual characteristics develop. GnRHAs are prescribed to inhibit sex hormone production, but the decision to treat should be balanced against the known (and unknown) adverse effects. Fertility preservation is more likely to be successful if GnRHA treatment is delayed for as long as possible. Some adolescents may decide to stop GnRHA use to harvest spermatozoa or oocytes before starting gender-affirming hormone treatment. Transfeminine individuals should consider that options for genital GAS may become more limited, as vaginoplasty with penile skin inversion requires an adequate stretched penile length. Transmasculine individuals may no

longer require chest reconstruction for breast development. CONCLUSIONS: Offers of GnRHA treatment to TGNB adolescents should be balanced by careful preparation and counselling. Urologists and gynaecologists can complement the expertise of specialist psychosocial and adolescent endocrinology teams, and should be involved early in and throughout the treatment pathway to maximise future functional and surgical outcomes. PATIENT SUMMARY: Puberty blockers for transgender and nonbinary adolescents have benefits, but timing is important to preserve fertility and surgical options.

Annotation: A systematic review examining fertility outcomes associated with GnRH analogues in TGNB adolescents.

Maschião LF, Bastos FI, Wilson E, et al. Nonprescribed Sex Hormone Use Among Trans Women: The Complex Interplay of Public Policies, Social Context, and Discrimination. *Transgend Health*. 2020;5(4):205-215. doi:10.1089/trgh.2020.0012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644312

Abstract: Purpose: Trans women are systematically excluded from basic human rights, possibly due to social contexts of transphobia. In health care, such barriers may result in nonprescribed sex hormone use and lead to significant health complications. As few studies investigated this phenomenon, we analyzed factors associated with nonprescribed sex hormone use by trans women in seven municipalities of Sao Paulo, Brazil. Methods: Muriel was a cross-sectional study (2014/2015), in which 673 transgender people answered a face-to-face survey. This analysis focused on trans women (n=616). Poisson regression models were used to assess factors associated with nonprescribed sex hormone use. A direct acyclic graph was built with a priori knowledge on the matter and was used for covariate selection. Results: A total of 90.7% of participants reported ever taking sex hormones. Most of those detailed nonprescribed use, which was associated with sex work, starting to use hormones before 18, identifying as travesti and lower education. Having the chosen name honored in public health services was found to be protective against this outcome. Conclusion: A high proportion of nonprescribed sex hormone use was observed in our sample. Our findings suggest barriers to health care and the need for trans women to resort to medically unsupervised transition procedures. Among sex workers, this may also be due to higher economic and access needs than other groups. Ensuring social rights and providing adequate health care services may lessen nonprescribed sex hormone use, preventing subsequent risks and resulting in better health outcomes for trans women.

Annotation: A Brazil-based cross-sectional study examining correlates (ie, "risk factors") for use of non-prescribed sex hormones.

Nasomyont N, Meisman AR, Ecklund K, et al. Changes in Bone Marrow Adipose Tissue in Transgender and Gender Non-Conforming Youth Undergoing Pubertal Suppression: A Pilot Study. *J Clin Densitom*. 2022;25(4):485-489. doi:10.1016/j.jocd.2022.06.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36064698

Abstract: Pubertal suppression with gonadotropin-releasing hormone (GnRH) agonists in transgender and gender non-conforming (TGNC) youth may affect acquisition of peak bone mass. Bone marrow adipose tissue (BMAT) has an inverse relationship with bone mineral density (BMD). To evaluate the effect of pubertal suppression on BMAT, in this pilot study we prospectively studied TGNC youth undergoing pubertal suppression and cisgender control

participants with similar pubertal status over a 12-month period. BMD was measured by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography. Magnetic Resonance T1 relaxometry (T1-R) and spectroscopy (MRS) were performed to quantify BMAT at the distal femur. We compared the change in BMD, T1-R values, and MRS lipid indices between the two groups. Six TGNC (two assigned female and four assigned male at birth) and three female control participants (mean age 10.9 and 11.7 years, respectively) were enrolled. The mean lumbar spine BMD Z-score declined by 0.29 in the TGNC group, but increased by 0.48 in controls (between-group difference 0.77, 95% CI: 0.05, 1.45). Similar findings were observed with the change in trabecular volumetric BMD at the 3% tibia site (-4.1% in TGNC, +3.2% in controls, between-group difference 7.3%, 95% CI: 0.5%-14%). Distal femur T1 values declined (indicative of increased BMAT) by 7.9% in the TGNC group, but increased by 2.1% in controls (between-group difference 10%, 95% CI: -12.7%, 32.6%). Marrow lipid fraction by MRS increased by 8.4% in the TGNC group, but declined by 0.1% in controls (between-group difference 8.5%, 95% CI: -50.2%, 33.0%). In conclusion, we observed lower bone mass acquisition and greater increases in BMAT indices by MRI and MRS in TGNC youth after 12 months of GnRH agonists compared with control participants. Early changes in BMAT may underlie an alteration in bone mass acquisition with pubertal suppression, including alterations in mesenchymal stem cells within marrow.

Annotation: Examines changes in bone marrow adipose tissue among TGNB youths undergoing puberty suppression. Also an observational study comparing findings to controls not undergoing puberty suppression. Only natal sexes were reported (N = 4 AMAB and N = 2 AFAB).

Ni J, Chi C, Aye T. Review of implant gonadotrophin-releasing hormone agonist use: experience in a single academic center. *Horm Res Paediatr*. 2023, 10.1159/000529733doi:10.1159/000529733 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36791687

Abstract: BACKGROUND: Gonadotrophin-releasing hormone agonists (GnRHa) are used for puberty suppression in central precocious puberty (CPP) and gender dysphoria (GD). Guidelines on biochemical monitoring are not defined. OBJECTIVES: To evaluate the utility of biochemical monitoring of GnRHa therapy in patients with CPP or GD. METHODS: Retrospective chart review of patients 18 years or younger who received GnRHa therapy from 1/1/2018 to 3/2/2021. RESULTS: 103 patients were evaluated, 43 with CPP and 60 with GD. Using thresholds of basal luteinizing hormone (LH) <2 IU/L and stimulated LH <4 IU/L, biochemical pubertal suppression occurred in all but two patients. Basal LH frequently remained above prepubertal range. CONCLUSIONS: Laboratory assessment for puberty suppression on GnRHa therapy may be unnecessary in CPP and GD patients monitored with physical exams.

Annotation: Examining endogenous hormone levels associated with implantable GnRH agonist therapy in TGNB adolescents. Only natal sex reported (N = 63 AFAB and N = 40 AMAB).

Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. *J Sex Med*. 2021;18(3):632-645. doi:10.1016/j.jsxm.2020.12.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33642235

Abstract: BACKGROUND: The number of adolescents presenting with gender dysphoria (GD) in healthcare services has increased significantly, yet specialized services offering transition-

related care (TRC) for trans youth is lacking. AIM: To investigate satisfaction with TRC, regret, and reasons for (dis)satisfaction with transition-related medical interventions (TRMIs) in trans adolescents who had presented to the Hamburg Gender Identity Service for children and adolescents (Hamburg GIS). METHODS: Data were collected from a clinical cohort sample of 75 adolescents and young adults diagnosed with GD (81% assigned female at birth) aged 11 to 21 years (M = 17.4) at baseline and follow-up (on a spectrum of ongoing care, on average 2 years after initial consultation). To determine progress of the youth's medical transitions, an individual treatment progress score (ITPS) was calculated based on number of desired vs received TRMIs. OUTCOMES: Main outcome measures were satisfaction with TRC at the time of follow-up, ITPS, social support, reasons for regret and termination of TRC, and (dis)satisfaction with TRMIs. RESULTS: Participants underwent different stages of TRMIs, such as gender-affirming hormone treatment or surgeries, and showed overall high satisfaction with TRC received at the Hamburg GIS. Regression analysis indicated that a higher ITPS (an advanced transition treatment stage) was predictive of higher satisfaction with TRC. Sex assigned at birth, age, and time since initial consultation at the clinic showed no significant effects for satisfaction with TRC, while degree of social support showed a trend. No adolescents regretted undergoing treatment at follow-up. Additional analysis of free-text answers highlighted satisfaction mostly with the physical results of TRMI. CLINICAL IMPLICATIONS: Because youth were more satisfied with TRC when their individual transition (ITPS) was more progressed, treatment should start in a timely manner to avoid distress from puberty or long waiting lists. STRENGTHS AND LIMITATIONS: This study is one of the first to report on treatment satisfaction among youth with GD from Europe. The ITPS allowed for a more detailed evaluation of TRMI wishes and experiences in relation to satisfaction with TRC and may close a gap in research on these treatments in adolescent populations. However, all participants were from the same clinic, and strict treatment eligibility criteria may have excluded certain trans adolescents from the study. Low identification rates with non-binary identities prevented comparisons between non-binary and binary genders. CONCLUSION: The study highlights the role of TRMI and individual treatment or transition progress for youth's overall high satisfaction with TRC received at the Hamburg GIS. Nieder TO, Mayer TK, Hinz S, et al. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. J Sex Med 2021;18:632-645.

Annotation: A Germany-based cohort study examining patients satisfaction with transition-related care (TRC) over time and with various treatments.

Nos AL, Klein DA, Adirim TA, et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. *JAMA Netw Open*. 2022;5(11):e2239758. doi:10.1001/jamanetworkopen.2022.39758 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36318207

Abstract: IMPORTANCE: Gonadotropin-releasing hormone analogue (GnRHa) use during puberty improves mental health among transgender and gender-diverse (TGD) adolescents. In previous studies, most (96.5%-98.1%) TGD adolescents who started GnRHa subsequently started gender-affirming hormones (GAH), raising concerns that GnRHa use promotes later use of GAH. OBJECTIVE: To determine whether GnRHa use among TGD adolescents is associated with increased subsequent GAH use. DESIGN, SETTING, AND PARTICIPANTS: This is a retrospective cohort study of administrative records collected between 2009 and 2018. The current analysis was completed in August 2022. Participants were enrolled in the US Military Healthcare System (MHS) with an initial TGD-related encounter occurring between ages 10 and 17 years.

EXPOSURES: GnRHa use. MAIN OUTCOMES AND MEASURES: Initiation of GAH. RESULTS: The 434 patients were a mean (SD) of 15.4 (1.6) years old at the time of their first TGD-related encounter; 312 (71.9%) were assigned female at birth, and 300 (69.1%) had an enlisted insurance sponsor. GnRHa use was more common among patients who were assigned male at birth (28 patients [23.0%]) than those assigned female (42 patients [13.5%]), but GAH use was not. Socioeconomic status was not associated with GnRHa or GAH use. Compared with older patients (aged 14-17 years), those who were younger (aged 10-13 years) at the time of the initial TGD-related encounter had a higher rate of GnRHa use (32 patients [57.1%] vs 38 patients [10.1%]) and a longer median time to starting GAH. The median interval from the date of the initial encounter to starting GAH decreased over time, from 2.3 years (95% CI, 1.7-2.8 years) between October 2009 and December 2014 to 0.6 years (95% CI, 0.5-0.6 years) between September 2016 and April 2018. Patients who were prescribed GnRHa had a longer median time to starting GAH (1.8 years; 95% CI, 1.1-2.4 years) than patients who were not (1.0 years; 95% CI, 0.8-1.2 years) and were less likely to start GAH during the 6 years after their first TGD-related encounter (hazard ratio, 0.52; 95% CI, 0.37-0.71). Among 54 younger (aged 10-13 years) patients who were not eligible to start GAH at their first encounter, GnRHa use was associated with a longer median time to starting GAH, but age at the first TGD-related visit was not. CONCLUSIONS AND RELEVANCE: In this cohort study of TGD adolescents, GnRHa use was not associated with increased subsequent GAH use. These findings suggest that clinicians can offer the benefits of GnRHa treatment without concern for increasing rates of future GAH use.

Annotation: A cohort study examining the risk of GAH use in TGNB adolescents who used GnRHa.

Olson-Kennedy J, Chan Y-M, Garofalo R, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. *JMIR research protocols*. 2019;8(7):e14434. doi:10.2196/14434 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31290407

Abstract: BACKGROUND: Transgender children and adolescents (ie, those who experience incongruence between assigned sex at birth and internal gender identity) are poorly understood and an understudied population in the United States. Since 2008, medical care for transgender youth has generally followed guidelines developed by professional consensus, given the paucity of empirical research, particularly in the US setting., OBJECTIVE: The objective of this research was to provide evidence-based data to inform clinical care for transgender youth. The study aims (1) to evaluate the impact of gonadotropin-releasing hormone agonists administered for puberty suppression on mental health, psychological well-being, and metabolic and physiologic parameters including bone health in a cohort of children and adolescents (Tanner stages 2-4) with gender dysphoria, comparing baseline and follow-up assessments, and (2) to determine the impact of gender-affirming hormones (eg, estradiol and testosterone) administered for phenotypic gender transition on mental health, psychological well-being, and metabolic and physiologic parameters in a cohort of adolescents with gender dysphoria, comparing baseline and follow-up assessments., METHODS: The study uses a longitudinal observational design to examine the outcomes of existing medical treatment protocols for gender dysphoria in two distinct cohorts: youth initiating puberty suppression and youth pursuing a phenotypic gender transition. Data on routine anthropometric and physiologic parameters are collected through chart abstraction, questionnaires, and research interviews in the 24-month study period. Audio computer-assisted self-interview and individual interview survey instruments are used to collect demographic, mental health, psychosocial, and behavioral data from parents and youth in the

blocker cohort and only from youth in the gender-affirming hormone cohort at baseline and 6, 12, 18, and 24 months., RESULTS: Participant recruitment commenced in July 2016, and enrollment was completed in September 2018. A total of 90 participants were enrolled in the blocker cohort and 301 participants were enrolled in the gender-affirming hormone cohort. Findings based on baseline data are expected to be submitted for publication in 2019., CONCLUSIONS: This longitudinal, observational study is collecting critical data on the existing models of care for transgender youth that have been used in clinical settings for close to a decade, although with limited empirical research to support them. This research is a direct response to the Institute of Medicine report calling for such studies as well as the needs of clinicians and patients. Results from this study have the potential to significantly impact the medical and mental health services provided to transgender youth by making available rigorous scientific evidence on the impact and safety of early treatment based on the sexual development stage. Ultimately, we aim to understand if early medical intervention reduces the health disparities well known to disproportionately affect transgender individuals across their lifespan., INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): PRR1-10.2196/14434.

Annotation: Examines growth and bone density in TGNB adolescents starting puberty suppression and TGNB adolescents starting CSHT

Quain KM, Kyweluk MA, Sajwani A, et al. Timing and Delivery of Fertility Preservation Information to Transgender Adolescents, Young Adults, and Their Parents. *J Adolesc Health*. 2021;68(3):619-622. doi:10.1016/j.jadohealth.2020.06.044 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32826153

Abstract: PURPOSE: This study aimed to examine transgender adolescents and young adults' (AYA) and their parents' preferences regarding fertility preservation (FP) information provision and discussion timing. METHODS: Data were derived from two separate studies: an online survey and semistructured qualitative interviews. Survey data were analyzed using descriptive statistics and interview data using conventional content analysis. RESULTS: Survey participants (AYA: 88% and parents: 93%) preferred gender clinic physicians provide FP information, and nearly one-third endorsed mental health professionals (AYA: 28% and parents: 26%) or fertility specialists (AYA: 23% and parents: 30%). Interview participants' FP discussion timing preferences ranged from the initial clinic visit, follow-up visits, before medical intervention, to mentioning FP early but deferring in-depth discussion to follow-up visits. CONCLUSIONS: Gender clinic physicians, mental health professionals, and fertility specialists should be prepared to discuss FP with transgender AYA and their parents. Opinions varied regarding when to provide FP information; therefore, discussion timing may need to be individualized.

Annotation: A qualitative, descriptive study examining timing and delivery of fertility preservation information provided to TGNB youths and their parents

Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. *J Clin Endocrinol Metab*. 2022;107(9):e3937-e3943. doi:10.1210/clinem/dgac251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35452119

Abstract: INTRODUCTION: Concerns about future regret and treatment discontinuation have led to restricted access to gender-affirming medical treatment for transgender and gender-diverse (TGD) minors in some jurisdictions. However, these concerns are merely speculative because few studies have examined gender-affirming hormone continuation rates among TGD individuals. METHODS: We performed a secondary analysis of 2009 to 2018 medical and pharmacy records from the US Military Healthcare System. We identified TGD patients who were children and spouses of active-duty, retired, or deceased military members using International Classification of Diseases-9/10 codes. We assessed initiation and continuation of gender-affirming hormones using pharmacy records. Kaplan-Meier and Cox proportional hazard analyses estimated continuation rates. RESULTS: The study sample included 627 transmasculine and 325 transfeminine individuals with an average age of 19.2 +/- 5.3 years. The 4-year gender-affirming hormone continuation rate was 70.2% (95% CI, 63.9-76.5). Transfeminine individuals had a higher continuation rate than transmasculine individuals 81.0% (72.0%-90.0%) vs 64.4% (56.0%-72.8%). People who started hormones as minors had higher continuation rate than people who started as adults 74.4% (66.0%-82.8%) vs 64.4% (56.0%-72.8%). Continuation was not associated with household income or family member type. In Cox regression, both transmasculine gender identity (hazard ratio, 2.40; 95% CI, 1.50-3.86) and starting hormones as an adult (hazard ratio, 1.69; 95% CI, 1.14-2.52) were independently associated with increased discontinuation rates. DISCUSSION: Our results suggest that >70% of TGD individuals who start gender-affirming hormones will continue use beyond 4 years, with higher continuation rates in transfeminine individuals. Patients who start hormones, with their parents' assistance, before age 18 years have higher continuation rates than adults.

Annotation: A cohort study examining adherence and persistence outcomes between transmasculine and transfeminine TGNB individuals.

Rogers C, Webberley M, Mateescu R, El Rakhawy Y, Daly-Gourdialsing A, Webberley H. A retrospective study of positive and negative determinants of gamete storage in transgender and gender-diverse patients. *International journal of transgender health*. 2021;22(1-2):167-178. doi:10.1080/26895269.2020.1848693 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040686/pdf/WIJT_22_1848693.pdf

Abstract: Background: GenderGP is a novel, online telemedicine service for transgender and gender-diverse individuals. As part of the service, people are offered fertility counseling in regard to gamete storage. Aims: This study aims to formally categorize the reasons that transgender and gender-diverse people do and not store gametes prior to hormonal treatments. We hope to use this data and subsequent research to inform healthcare policy, improve the healthcare experience for transgender and gender-diverse people, and inform legislation for permanent change in UK healthcare. Methods: Data sets (electronic medical records) from June 2015 - April 2020 were derived from the GenderGP patient database. All patients starting treatment with GenderGP and undergoing routine fertility counseling were included in the study. Results: Of 3667 patients aged 10-85, 2722 (74.2%) were aged 18-45. 151 (5.4%) patients stored gametes. 678 (18.5%) patients wanted to store: 268 (39.5%) could not afford gamete storage, 84 (12.4%) had no local services, 307 (45.3%) did not want to delay hormone treatment. 2085 patients did not want to undertake gamete storage, 480 (23.0%) hoped to adopt, 1605 (77.1%) did not want children. All ages showed similar patterns. Discussion: Financial barriers mean many transgender and gender-diverse people cannot access fertility healthcare. Many participants suffered low self-esteem and struggled to envisage an accepting healthcare system, making them less likely to seek advice. Many patients favored adoption over

gamete storage. Younger patients (<18) often had very definite views on gamete storage. Many older patients without children would consider gamete storage and adoption, once their transition is complete. Copyright © 2020 Taylor & Francis Group, LLC.

Annotation: A database, cohort study examining predictors of gamete storage in TGNB patients from the UK, including adolescents at the time of the study

Rozga M, Linsenmeyer W, Cantwell Wood J, Darst V, Gradwell EK. Hormone therapy, health outcomes and the role of nutrition in transgender individuals: A scoping review. *Clin Nutr ESPEN*. 2020;40:42-56. doi:10.1016/j.clnesp.2020.08.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33183572

Abstract: OBJECTIVE: The objective of this scoping review is to describe the extent, range, and nature of available literature examining nutrition-related intermediate and long-term health outcomes in individuals who are transgender. Specific sub-topics examined include 1) dietary intake, 2) nutrition-related health disparities, 3) validity and reliability of nutrition assessment methods, 4) the effects of nutrition interventions/exposures, and 5) hormone therapy. METHODS: A literature search was conducted using MEDLINE, Embase, PsycINFO, CINAHL, Web of Science, and other databases for peer-reviewed articles published from January 1999 until December 5, 2019 to identify studies addressing the research objective and meeting eligibility criteria. Conference abstracts and registered trials published or registered in the five years prior to the search were also included. Findings were reported in a study characteristics table, a bubble chart and heat maps. RESULTS: The search of the databases identified 5403 studies, including full peer-reviewed studies, systematic reviews, conference abstracts and registered trials. Following title/abstract screening, 189 studies were included in the narrative analysis. Ten studies reported dietary intake in transgender individuals, 64 studies reported nutrition-related health disparities in transgender compared to cisgender individuals, one study examined validity and reliability of nutrition assessment methods, two studies reported nutrition interventions, and 127 studies reported on the intermediate and health effects of hormone therapy. CONCLUSION: Individuals who are transgender have unique nutrition needs, which may vary according to the stage and type of gender-affirmative therapy that they are undergoing. There is scant research examining effective nutrition therapy methods for nutrition professionals working with transgender individuals. More research is needed in order to inform evidence-based clinical practice guidelines for nutrition practitioners working with transgender individuals.

Annotation: A systematic review examining nutrition-related outcomes in TGNB children, adolescents, and adults.

Russell I, Pearson B, Masic U. A Longitudinal Study of Features Associated with Autism Spectrum in Clinic Referred, Gender Diverse Adolescents Accessing Puberty Suppression Treatment. *J Autism Dev Disord*. 2021;51(6):2068-2076. doi:10.1007/s10803-020-04698-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32936414

Abstract: Literature has documented inflated rates of features associated with autism spectrum (AS) in clinic referred, gender diverse young people. This study examined scores on the Social Responsiveness Scale, Second Edition (SRS-2) over time in a group of clinic referred, gender diverse adolescents accessing gonadotropin-releasing hormone analogues (GnRHa) to supress puberty. Primary caregivers of 95 adolescents presenting to the Gender Identity Development

Service (GIDS) completed the SRS-2 prior to receiving endocrine input (mean age: 13.6 +/- SEM: 0.11) and after approximately one year of accessing GnRHa (mean age: 14.6 +/- SEM: 0.13). No significant differences in SRS-2 scores over time and between birth assigned sex were found. No interactions between time and birth assigned sex were established for SRS-2 subscales or total scores.

Annotation: A London-based pre-post descriptive study examining autism-related characteristics before and after 1 year of GnRH analogue therapy in TGNB adolescents with autism. Only natal sexes were reported: 38 AMAB and 57 AFAB.

Schwartz BI, Bear B, Kazak AE. Menstrual Management Choices in Transgender and Gender Diverse Adolescents. *J Adolesc Health*. 2023;72(2):207-213. doi:10.1016/j.jadohealth.2022.09.023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36443161

Abstract: PURPOSE: Transgender and gender diverse patients who are assigned female at birth may request menstrual management to alleviate an increased dysphoria due to menses. The objective of this study is to describe the initiation and use over time of menstrual management methods (MMMs) in transgender and gender diverse adolescents. METHODS: A retrospective chart review was conducted of patients in a multidisciplinary pediatric gender program from March 2015 to December 2020 who were assigned female at birth, identified as transgender or gender diverse, and had achieved menarche. A descriptive statistical analysis was performed. RESULTS: Of 133 patients, 119 (90%) identified as transgender male, 11 (8%) as gender nonbinary, and 3 (2%) as another gender identity. Mean age was 15 (standard deviation 1.6) years. Only 12 (9%) patients had ever been sexually active. During the study period, 48 (36%) used gender-affirming testosterone. At the initial visit, 114 (86%) patients were not using an MMM. Of 80 patients who initiated a new MMM, 3 (4%) chose continuous oral contraceptive pills, 65 (83%) used norethindrone acetate (NETA), and 9 (11%) planned levonorgestrel intrauterine device (IUD) insertion. At 1 year, 56 patients were using NETA and 20 had an IUD in place. DISCUSSION: This study provides data on MMM choice in transgender and gender diverse adolescents using these methods almost exclusively for menstrual management and not contraception. Although few patients were using an MMM at baseline, most opted to start a method when given the opportunity. The most common methods were NETA or an levonorgestrel IUD.

Annotation: Examines menstrual suppression outcomes in transmasculine and gender-diverse adolescents receiving various menstrual management treatments in a gender specialty clinic

Schwartz BI, Bear B, Short VL, Kazak AE. Outcomes of Menstrual Management Use in Transgender and Gender-Diverse Adolescents. *Obstet Gynecol*. 2023;141(4):748-755. doi:10.1097/AOG.0000000000005123 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36897186

Abstract: OBJECTIVE: To describe and compare the outcomes of various menstrual-management methods, including method choice, continuation, bleeding patterns, amenorrhea rates, effect on moods and dysphoria, and side effects, in transgender and gender-diverse adolescents. METHODS: This was a retrospective chart review of all patients seen in a multidisciplinary pediatric gender program from March 2015 to December 2020 who were assigned female at birth, had achieved menarche, and used a menstrual-management method during the study period. Data were abstracted on patient demographics and menstrual-management method

continuation, bleeding patterns, side effects, and satisfaction at 3 months (T1) and 1 year (T2). Outcomes were compared between method subgroups. RESULTS: Among the 101 included patients, 90% chose either oral norethindrone acetate or a 52-mg levonorgestrel (LNG) intrauterine device (IUD). There were no differences in continuation rates for these methods at either follow-up time. Almost all patients had improved bleeding at T2 (96% for norethindrone acetate and 100% for IUD users), with no difference between subgroups. Amenorrhea rates were 84% for norethindrone acetate and 67% for IUD at T1 and 97% and 89%, respectively, at T2, with no differences at either point. The majority of patients had improved pain, menstrually related moods, and menstrually related dysphoria at both follow-up points. There were no differences in side effects between subgroups. There were no differences in method satisfaction between the groups at T2. CONCLUSION: Most patients chose norethindrone acetate or an LNG IUD for menstrual management. Continuation, amenorrhea, and improved bleeding, pain, and menstrually related moods and dysphoria were high for all patients, indicating that menstrual management is a viable intervention for gender-diverse patients who experience increased dysphoria related to menses.

Annotation: Examines menstrual suppression outcomes in transmasculine and gender-diverse adolescents receiving various progestins in a gender specialty clinic

Schwartz BI, Effron A, Bear B, et al. Experiences with Menses in Transgender and Gender Nonbinary Adolescents. *J Pediatr Adolesc Gynecol*. 2022;35(4):450-456. doi:10.1016/j.jpag.2022.01.015 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(22)00037-7/fulltext

Abstract: STUDY OBJECTIVE: To describe menstrual history, associated dysphoria, and desire for menstrual management in transgender male and gender diverse adolescents who were assigned female at birth DESIGN: Retrospective chart review SETTING: Tertiary care children's hospital PARTICIPANTS: All patients seen in a multidisciplinary pediatric gender program from March 2015 through December 2020 who were assigned female at birth, identified as transgender male or gender nonbinary, and had achieved menarche INTERVENTION: None MAIN OUTCOME MEASURES: Patient demographics, menstrual history, interest in and prior experiences with menstrual management, parental support, and concerns about menstrual management RESULTS: Of the 129 included patients, 116 (90%) identified as transgender male and 13 (10%) as gender nonbinary, with an average age of 15 (SD 1.6) years. Almost all (93%) patients reported menstrual-related dysphoria. Most (88%) were interested in menstrual suppression. The most common reasons for desiring suppression were achievement of amenorrhea (97%) and improvement of menstrual-related dysphoria (63%)., CONCLUSIONS: Most gender diverse patients assigned female at birth reported dysphoria associated with menses and desired menstrual suppression. This information can encourage physicians to raise this topic and offer menstrual management for gender diverse patients who experience distress related to menses, especially for those who are not ready for or do not desire gender-affirming hormonal treatment. Future research is needed to better understand patients' experiences with menses and to determine the optimal menstrual management methods. This could be an important intervention to improve outcomes for this vulnerable population.

Annotation: Compares menstrual history and menstrual management methods between transgender males and nonbinary patients

Shaffer LR, McCormack E, Sawicki GS, Keller A, Jain R. Understanding the Intersection between Gender Transition and Health Outcomes in Cystic Fibrosis. *Ann Am Thorac Soc*. 2022;19(3):504-506. doi:10.1513/AnnalsATS.202105-535RL Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34469707

Abstract: None

Annotation: A research letter summarizing findings from a research study examining 1-second FEV values in TGNB adolescents with CF from a national sample of centers

Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. *Front Psychiatry*. 2021;12:632784. doi:10.3389/fpsyt.2021.632784 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33854450

Abstract: This study reports follow-up data on the largest sample to date of boys clinic-referred for gender dysphoria (n = 139) with regard to gender identity and sexual orientation. In childhood, the boys were assessed at a mean age of 7.49 years (range, 3.33-12.99) at a mean year of 1989 and followed-up at a mean age of 20.58 years (range, 13.07-39.15) at a mean year of 2002. In childhood, 88 (63.3%) of the boys met the DSM-III, III-R, or IV criteria for gender identity disorder; the remaining 51 (36.7%) boys were subthreshold for the criteria. At follow-up, gender identity/dysphoria was assessed via multiple methods and the participants were classified as either persisters or desisters. Sexual orientation was ascertained for both fantasy and behavior and then dichotomized as either biphilic/androphilic or gynephilic. Of the 139 participants, 17 (12.2%) were classified as persisters and the remaining 122 (87.8%) were classified as desisters. Data on sexual orientation in fantasy were available for 129 participants: 82 (63.6%) were classified as biphilic/androphilic, 43 (33.3%) were classified as gynephilic, and 4 (3.1%) reported no sexual fantasies. For sexual orientation in behavior, data were available for 108 participants: 51 (47.2%) were classified as biphilic/androphilic, 29 (26.9%) were classified as gynephilic, and 28 (25.9%) reported no sexual behaviors. Multinomial logistic regression examined predictors of outcome for the biphilic/androphilic persisters and the gynephilic desisters, with the biphilic/androphilic desisters as the reference group. Compared to the reference group, the biphilic/androphilic persisters tended to be older at the time of the assessment in childhood, were from a lower social class background, and, on a dimensional composite of sex-typed behavior in childhood were more gender-variant. The biphilic/androphilic desisters were more gender-variant compared to the gynephilic desisters. Boys clinic-referred for gender identity concerns in childhood had a high rate of desistance and a high rate of a biphilic/androphilic sexual orientation. The implications of the data for current models of care for the treatment of gender dysphoria in children are discussed.

Annotation: A cohort study examining changes in gender identity over time among TGNB children who presented for treatment at a pediatric gender identity clinic during childhood. Only natal gender was reported: 139 AMAB.

Strang JF, Powers MD, Knauss M, et al. "They Thought It Was an Obsession": Trajectories and Perspectives of Autistic Transgender and Gender-Diverse Adolescents. *J Autism Dev Disord*. 2018;48(12):4039-4055. doi:10.1007/s10803-018-3723-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30140984

Abstract: Despite research exploring autism in gender-diverse adolescents, no studies have elicited these individuals' perspectives. In-depth interviews with 22 well-characterized autistic

gender-diverse adolescents revealed critical themes, including: recollections of pre-pubertal gender nonconformity; vivid experiences of gender dysphoria; a fear of social gender expression due to perceived animosity toward transgender people; and specific challenges that result from the interplay of gender diversity and neurodiversity. During the ~ 22 month study social gender affirmation increased in six participants and gender dysphoria attenuated in four participants. Given the ethical imperative to understand and prioritize the voiced perspectives and needs of autistic gender minority adolescents as well as the discovery of shared themes and experiences in this population, results should inform clinical research approaches and priorities.

Annotation: A qualitative examination of trajectories and perspectives of children diagnosed with both autism and gender dysphoria

Tankersley AP, Grafsky EL, Dike J, Jones RT. Risk and Resilience Factors for Mental Health among Transgender and Gender Nonconforming (TGNC) Youth: A Systematic Review. *Clin Child Fam Psychol Rev*. 2021;24(2):183-206. doi:10.1007/s10567-021-00344-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33594611

Abstract: In recent years, there has been a proliferation of research regarding transgender and gender nonconforming (TGNC) people. The stigma and legal discriminations that this population faces have obvious and documented repercussions for mental health. In 2015, the American Psychological Association (APA) published Guidelines for Psychological Practice with TGNC People. The APA noted that due to the nuances of working with TGNC youth and the dearth of related literature, the guidelines focus primarily on TGNC adults. To date, there has not been a systematic review of risk and resilience factors for mental health among TGNC children, adolescents, and young adults under the age of 25. Forty-four peer-reviewed articles met inclusion criteria for this systematic review, and were evaluated for their methodological rigor and their findings. Common risk factors for negative mental health variables included physical and verbal abuse, exposure to discrimination, social isolation, poor peer relations, low self-esteem, weight dissatisfaction, and age. Across studies, older children and adolescents tended to report higher rates of psychological distress. Resilience-promoting factors for mental health were also documented, including parent connectedness, social support, school safety and belonging, and the ability to use one's chosen name. By synthesizing the existing literature using a resilience-focused and minority stress framework, the present review provides clinicians and researchers with a coherent evidence-base to better equip them to promote psychological adaptation and wellbeing among TGNC youth.

Annotation: A review of the risk and resilience factors of living as a TGNB youth.

van der Loos M, Hannema SE, Klink DT, den Heijer M, Wiepjes CM. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health*. 2022;6(12):869-875. doi:10.1016/S2352-4642(22)00254-1 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36273487

Abstract: BACKGROUND: In the Netherlands, treatment with puberty suppression is available to transgender adolescents younger than age 18 years. When gender dysphoria persists testosterone or oestradiol can be added as gender-affirming hormones in young people who go on to transition. We investigated the proportion of people who continued gender-affirming hormone treatment at follow-up after having started puberty suppression and gender-affirming

hormone treatment in adolescence. METHODS: In this cohort study, we used data from the Amsterdam Cohort of Gender dysphoria (ACOG), which included people who visited the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medisch Centrum, Netherlands, for gender dysphoria. People with disorders of sex development were not included in the ACOG. We included people who started medical treatment in adolescence with a gonadotropin-releasing hormone agonist (GnRHa) to suppress puberty before the age of 18 years and used GnRHa for a minimum duration of 3 months before addition of gender-affirming hormones. We linked this data to a nationwide prescription registry supplied by Statistics Netherlands (Centraal Bureau voor de Statistiek) to check for a prescription for gender-affirming hormones at follow-up. The main outcome of this study was a prescription for gender-affirming hormones at the end of data collection (Dec 31, 2018). Data were analysed using Cox regression to identify possible determinants associated with a higher risk of stopping gender-affirming hormone treatment. FINDINGS: 720 people were included, of whom 220 (31%) were assigned male at birth and 500 (69%) were assigned female at birth. At the start of GnRHa treatment, the median age was 14.1 (IQR 13.0-16.3) years for people assigned male at birth and 16.0 (14.1-16.9) years for people assigned female at birth. Median age at end of data collection was 20.2 (17.9-24.8) years for people assigned male at birth and 19.2 (17.8-22.0) years for those assigned female at birth. 704 (98%) people who had started gender-affirming medical treatment in adolescence continued to use gender-affirming hormones at follow-up. Age at first visit, year of first visit, age and puberty stage at start of GnRHa treatment, age at start of gender-affirming hormone treatment, year of start of gender-affirming hormone treatment, and gonadectomy were not associated with discontinuing gender-affirming hormones. INTERPRETATION: Most participants who started gender-affirming hormones in adolescence continued this treatment into adulthood. The continuation of treatment is reassuring considering the worries that people who started treatment in adolescence might discontinue gender-affirming treatment. FUNDING: None.

Annotation: A cohort study comparing baseline characteristics and continuation rates between transgender males and transgender females, with and without treatment.

Van Der Miesen AI, Hurley H, De Vries AL. Gender dysphoria and autism spectrum disorder: A narrative review. *Int Rev Psychiatry*. 2016;28(1):70-80. doi:10.3109/09540261.2015.1111199 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26753812

Abstract: The current literature shows growing evidence of a link between gender dysphoria (GD) and autism spectrum disorder (ASD). This study reviews the available clinical and empirical data. A systematic search of the literature was conducted using the following databases: PubMed, Web of Science, PsycINFO and Scopus; utilizing different combinations of the following search terms: autism, autism spectrum disorder (ASD), Asperger's disorder (AD), co-morbidity, gender dysphoria (GD), gender identity disorder (GID), transgenderism and transsexualism. In total, 25 articles and reports were selected and discussed. Information was grouped by found co-occurrence rates, underlying hypotheses and implications for diagnosis and treatment. GD and ASD were found to co-occur frequently - sometimes characterized by atypical presentation of GD, which makes a correct diagnosis and determination of treatment options for GD difficult. Despite these challenges there are several case reports describing gender affirming treatment of co-occurring GD in adolescents and adults with ASD. Various underlying hypotheses for the link between GD and ASD were suggested, but almost all of them lack evidence.

Annotation: Examining the links between autism and gender dysphoria

Wagner S, Panagiotakopoulos L, Nash R, et al. Progression of Gender Dysphoria in Children and Adolescents: A Longitudinal Study. *Pediatrics*. 2021;148(1)doi:10.1542/peds.2020-027722 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34099504

Abstract: BACKGROUND AND OBJECTIVES: The progression of gender-expansive behavior to gender dysphoria and to gender-affirming hormonal treatment (GAHT) in children and adolescents is poorly understood. METHODS: A cohort of 958 gender-diverse (GD) children and adolescents who did not have a gender dysphoria-related diagnosis (GDRD) or GAHT at index were identified. Rates of first GDRD and first GAHT prescription were compared across demographic groups. RESULTS: Overall, 29% of participants received a GDRD and 25% were prescribed GAHT during the average follow-up of 3.5 years (maximum 9 years). Compared with youth assigned male sex at birth, those assigned female sex at birth were more likely to receive a diagnosis and initiate GAHT with hazard ratio (95% confidence interval) estimates of 1.3 (1.0-1.7), and 2.5 (1.8-3.3), respectively. A progression to diagnosis was more common among those aged >/=15 years at initial presentation compared with those aged 10 to 14 years and those aged 3 to 9 years (37% vs 28% vs 16%, respectively). By using the youngest group as a reference, the adjusted hazard ratios (95% confidence interval) for a GDRD were 2.0 (1.3-3.0) for age 10 to 14 years and 2.7 (1.8-3.9) for age >/=15 years. Racial and ethnic minorities were less likely to receive a diagnosis or be prescribed GAHT. CONCLUSIONS: This study characterized the progression of GD behavior in children and adolescents. Less than one-third of GD youth receive an eventual GDRD, and approximately one-quarter receive GAHT. Female sex at birth, older age of initial GD presentation to medical care, and non-Hispanic white race and ethnicity increased the likelihood of receiving diagnosis and treatment.

Annotation: Cohort study examining predictors of GD diagnosis and of CSHT initiation in gender-diverse children. Only natal sex reported (N = 531 AMAB and N = 527 AFAB).

Wright T, Candy B, King M. Conversion therapies and access to transition-related healthcare in transgender people: a narrative systematic review. *BMJ Open*. 2018;8(12):e022425. doi:10.1136/bmjopen-2018-022425 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30580262

Abstract: OBJECTIVES: Conversion is a term for treatments that seek to suppress or change a person's sexual orientation or gender. Our review focuses on transgender and gender-diverse (TGD) people. Our aims were to (1) describe the frequency, nature and structure of conversion practices; (2) document difficulties in accessing transition-related healthcare and (3) evaluate the mental health consequences of such practices and access barriers. METHOD: Systematic review and narrative synthesis using the Critical Appraisals Skills Programme and Joanne Briggs Institute critical appraisal tools. Data sources include Embase, MEDLINE, PsychINFO, PsychARTICLES and Web of Science between 1990 and June 2017. PARTICIPANTS: Studies were included that (1) document use of conversion therapies or access barriers to transition-related healthcare; and/or (2) describe how such therapeutic practices and access barriers have been applied and/or (3) evaluate the mental health impacts of such therapies and difficulties accessing transition-related healthcare. Two reviewers screened papers for eligibility. Data were then grouped according to the objectives. Narratives and themes were presented per study. RESULTS: Seven studies met inclusion criteria. Four reports were on 'realignment', involving case studies or case series. Two involved psychoanalysis, one self-exposure therapy and one open-ended play psychotherapy. All four studies concerning 'realignment' were of poor methodological quality. The other three studies explored access barriers from the view point of

TGD youth, their parents and healthcare providers. All papers reported access barriers, such as inability to access puberty-delaying medications. The papers concerning barriers to access were of good methodological quality. CONCLUSION: We found limited published evidence on use, nature, structure and/or health consequences of conversion therapies and access barriers to transition in TGD people. However, reports of restriction to access may indicate a more widespread problem. Research is needed into TGD people's experiences of conversion therapy and access barriers to transition-related healthcare TRIAL REGISTRATION NUMBER: CRD42017062149.

Annotation: A systematic review examining conversion therapy and access to transition care in TGNB people.

Eligible "Systematic" Reviews Lacking Adequate Reporting of Searches or Results (Bibliography Only)

Alegria CA. Gender nonconforming and transgender children/youth: Family, community, and implications for practice. *J Am Assoc Nurse Pract*. 2016;28(10):521-527. doi:10.1002/2327-6924.12363 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27031444

Abstract: PURPOSE: The aim of this article is to provide foundational knowledge on gender nonconforming/transgender children/youth. With this knowledge, providers' confidence and ability to address the needs of patients/families can increase. DATA SOURCES: Academic Search Premier, Cinahl, PubMed, World Professional Association for Transgender Health. CONCLUSIONS: The number of gender nonconforming/transgender children/youth presenting to healthcare providers is increasing. The situation presents a myriad of challenges to families. The identity trajectory of gender nonconforming children is variable, and watchful waiting while providing support to the child and family is advised. If gender dysphoria persists as puberty approaches, treatment with puberty blockers is recommended. This provides youth time to further explore their identity, while alleviating the distress of developing unwanted secondary natal sex characteristics. For these individuals, cross-sex hormones may be started at age 16. IMPLICATIONS FOR PRACTICE: The complexities of providing care to gender nonconforming children/youth and their families are best met through an interdisciplinary approach. Consultation with and/or referral to specialists knowledgeable about transgender health care is advised. Beyond a basic understanding of gender nonconformance, of primary importance to patients/families is being heard and supported by their providers. Establishing a safe and welcome environment is paramount. Resources are provided.

Annotation: A systematic review examining prevalence, trajectory, family and social networks, treatments, and implications for clinical practice in TGNB children and adolescents.

Biggs M. Gender Dysphoria and Psychological Functioning in Adolescents Treated with GnRHa: Comparing Dutch and English Prospective Studies. *Arch Sex Behav*. 2020;49(7):2231-2236. doi:10.1007/s10508-020-01764-1 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32594279

Abstract: None

Annotation: A systematic review examining mental health in Dutch and English TGNB youth.

Bonifacio JH, Maser C, Stadelman K, Palmert M. Management of gender dysphoria in adolescents in primary care. *CMAJ*. 2019;191(3):E69-E75. doi:10.1503/cmaj.180672 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30665976

Abstract: Adolescents with gender dysphoria present in a variety of health care settings, including primary care. Gender dysphoria is the distress experienced by an individual when their gender identity and their gender assigned at birth are discordant. Many tertiary pediatric centres across Canada and the Unites States have opened gender clinics for adolescents with gender dysphoria.1 However, high demand often exceeds the capacity of these clinics, and many youth are prevented from accessing such centres for a variety of reasons (e.g., lack of parental or physician support, geographical distance). Primary care providers are well placed to provide critical support for youth with gender dysphoria and their caregivers and families. However, primary care providers often lack exposure to trans health issues in training, and may lack experience in managing gender dysphoria in youth. A recent Canadian national survey found that less than 50% of transgender youth felt comfortable discussing their trans-related health care needs with their family doctor.2 We provide an overview of the management of gender dysphoria in postpubertal adolescents, including practical advice on approaches to social and medical transitioning, aimed at supporting primary care practitioners in supporting youth with gender dysphoria in their practices. We use the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria when referring to gender dysphoria. Because definitions and approaches to care have changed over the past 2 decades, we focus mainly on recent research that reflects the current diagnostic criteria, studies that apply contemporary assessment and measurement strategies, and findings that are applicable across multiple clinical settings. Our approach to gathering evidence used in this review is presented in Box 1. Box 2 defines commonly used terms.

Annotation: How to manage gender dysphoria in adolescents in a primary care setting

Byne W, Bradley SJ, Coleman E, et al. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav*. 2012;41(4):759-796. doi:10.1007/s10508-012-9975-x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22736225

Abstract: Both the diagnosis and treatment of Gender Identity Disorder (GID) are controversial. Although linked, they are separate issues and the DSM does not evaluate treatments. The Board of Trustees (BOT) of the American Psychiatric Association (APA), therefore, formed a Task Force charged to perform a critical review of the literature on the treatment of GID at different ages, to assess the quality of evidence pertaining to treatment, and to prepare a report that included an opinion as to whether or not sufficient credible literature exists for development of treatment recommendations by the APA. The literature on treatment of gender dysphoria in individuals with disorders of sex development was also assessed. The completed report was accepted by the BOT on September 11, 2011. The quality of evidence pertaining to most aspects of treatment in all subgroups was determined to be low; however, areas of broad clinical consensus were identified and were deemed sufficient to support recommendations for treatment in all subgroups. With subjective improvement as the primary outcome measure, current evidence was judged sufficient to support recommendations for adults in the form of an evidence-based APA Practice Guideline with gaps in the empirical data supplemented by clinical consensus. The report recommends that the APA take steps beyond drafting treatment recommendations. These include issuing position statements to clarify the APA's position

regarding the medical necessity of treatments for GID, the ethical bounds of treatments of gender variant minors, and the rights of persons of any age who are gender variant, transgender or transsexual.

Annotation: A systematic review conducted to support development of a guideline for the treatment of gender dysphoria from the American Psychiatric Association (APA).

Chou K, Johnson B. Working with Transgender Adolescents: Essential Guidelines and Applications. *Adolesc Psychiatry*. 2022;12(3):159-173. doi:10.2174/2210676611666210831161929 Accessed September 15, 2023. Available at https://www.eurekaselect.com/article/117582

Abstract: Background: There has been a rise in the numbers of adolescents identifying as transgender and seeking medical treatment for gender dysphoria. While gender clinics are developing across the country, not all transgender adolescents have access to these centers. There is, therefore, an increased need for other clinicians to be aware of interventions and guidelines to help transgender youth and their families. Objective: The aim of this article is to provide an overview of current literature and guidelines for treating transgender adolescents with gender dysphoria. Methods: Using keywords “gender”, “gender dysphoria”, “transgender”, “trans*”, “adolescent trans*”, the authors searched PubMed to gather current literature on treating transgender adolescents. Additionally, sources from primary transgender resources online were obtained, including current endocrine and psychological guidelines. Results: This article discusses important gender concepts that are relevant to treating all transgender individuals. It describes models of engagement with transgender adolescents seeking treatment, including assenting and consenting to medical intervention. Finally, we discuss the assessment of transgender adolescents’ needs and present an overview of the various guidelines outlining both non-medical and medical interventions targeted to treat gender dysphoria in this population. Conclusion: Knowledge of treating adolescents with gender dysphoria is imperative as gender dysphoria presents more commonly in practice. Multidisciplinary collaboration is required to provide comprehensive treatment to this population. Guidelines from professional organizations such as the World Professional Association for Transgender Health and the Endocrine Society provide instructions for clinical practice while the evidence base in this field continues to expand.

Annotation: Principles for working with gender dysphoric adolescents with psychiatric comorbidities

Conard LE. Supporting and caring for transgender and gender nonconforming youth in the urology practice. *J Pediatr Urol*. 2017;13(3):300-304. doi:10.1016/j.jpurol.2017.02.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28645619

Abstract: INTRODUCTION: Gender identity is a person's internal sense of gender, which may be different than the sex they were assigned at birth. Pediatric urologists are starting to see more transgender and gender non-conforming (TGN) youth and need to be able to provide culturally competent and appropriate care for these patients and their caregivers. This review will discuss common transgender terminology, specific health concerns and treatment options. METHODS AND MATERIALS: A systematic literature review was performed on Medline((R)), PubMed((R)), and Google Scholar for key words transgender, gender dysphoria and gender identity disorder. Original research articles and relevant reviews were examined as well as transgender treatment guidelines from several organizations. These studies and expert opinion are summarized in this

review. RESULTS: In this rapidly growing area of medicine, there is very little literature and few evidence-based studies. Treatment guidelines are based on small studies and expert opinion. CONCLUSION: Transgender and gender nonconforming youth are at high risk for mental health concerns and other health disparities based on their gender identity. Pediatric urologists can create a safe and welcoming environment for these patients and their caregivers to discuss these matters. Providers who are able to provide competent care for TGN youth can improve outcomes for this group.

Annotation: A systematic review examining etiology, presentation, common comorbidities, treatments, and surgeries for GD in TGNB children and adolescents.

Connolly MD, Zervos MJ, Barone CJ, 2nd, Johnson CC, Joseph CL. The Mental Health of Transgender Youth: Advances in Understanding. *J Adolesc Health*. 2016;59(5):489-495. doi:10.1016/j.jadohealth.2016.06.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27544457

Abstract: This review provides an update on the growing body of research related to the mental health of transgender youth that has emerged since the 2011 publication of the Institute of Medicine report on the health of lesbian, gay, bisexual, and transgender people. The databases PubMed and Ovid Medline were searched for studies that were published from January 2011 to March 2016 in English. The following search terms were used: transgender, gender nonconforming, gender minority, gender queer, and gender dysphoria. Age limits included the terms youth, child, children, teenager*, and adolescen*. The combined search produced 654 articles of potential relevance. The resulting abstracts went through a tiered elimination system, and the remaining 15 articles, which presented quantitative data related to the prevalence of transgender youth and their mental health, were included in the present review. In addition to providing new estimates of the number of young people who identify as transgender (.17%-1.3%), studies since 2011 have shown that transgender youth have higher rates of depression, suicidality and self-harm, and eating disorders when compared with their peers. Gender-affirming medical therapy and supported social transition in childhood have been shown to correlate with improved psychological functioning for gender-variant children and adolescents. Recent research has demonstrated increased rates of psychiatric morbidity among transgender youth compared to their peers. Future work is needed to understand those youth who identify as gender nonbinary, improve methods to capture and understand diverse gender identities and related health disparities, and delineate the social determinants of such disparities.

Annotation: A systematic review examining mental health outcomes in TGNB youth.

Davidge-Pitts C, Clarke BL. Transgender bone health. *Maturitas*. 2019;127:35-42. doi:10.1016/j.maturitas.2019.05.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31351518

Abstract: Gonadal sex steroids play a pivotal role in bone health. Medical and surgical therapies for gender dysphoria in both adolescents and adults can lead to skeletal changes. This review evaluates the literature on transgender bone health, and how the data can be translated into clinical practice.

Annotation: A systematic review examining bone health associated with therapies in patients with gender dysphoria.

Fuss J, Auer MK, Briken P. Gender dysphoria in children and adolescents: a review of recent research. *Curr Opin Psychiatry*. 2015;28(6):430-434. doi:10.1097/YCO.0000000000000203 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26382161

Abstract: PURPOSE OF REVIEW: With the advent of medical treatments such as puberty suppression and cross-sex hormones in gender dysphoric minors, there has been a debate around questions of gender identity and brain development. This review aimed to identify recent empirical studies that addressed this controversial topic. RECENT FINDINGS: Epidemiological data from several countries indicate that gender dysphoria in children and adolescents is far more common than initially anticipated. This is in line with the currently observed steady increase in referrals to gender clinics. Minors with gender dysphoria are a vulnerable population as they may face a high psychopathological burden. Recently published data on the long-term outcome of puberty suppression and subsequent hormonal and surgical treatment indicate that young people with gender dysphoria may benefit substantially with regard to psychosocial outcomes. Brain development studied by neuroimaging methods seems not to be disturbed by puberty suppression. SUMMARY: The first reports about long-term outcome in adolescents having undergone puberty suppression have shown promising results. However, in a substantial part of gender dysphoric minors, puberty suppression is not indicated so far because of psychiatric comorbidity and long-term follow-up data from these patients are still scarce.

Annotation: A systematic review examining epidemiology, comorbidity, and puberty suppression in TGNB children and adolescents.

Kameg BN, Nativio DG. Gender dysphoria in youth: An overview for primary care providers. *J Am Assoc Nurse Pract*. 2018;30(9):493-498. doi:10.1097/JXX.0000000000000068 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30095668

Abstract: BACKGROUND AND PURPOSE: Primary care providers who encounter children are often the first line of contact for individuals with gender dysphoria, which occurs when sex assigned at birth is incongruent with one's true, expressed sexual identity. Because those with untreated gender dysphoria are at risk of a variety of negative outcomes, including mood symptomatology, suicidality, substance use disorders, and other psychosocial risk factors, it is critical that health care providers are adept in the provision of holistic, patient-centered care. The purpose of this report is to provide an updated review of the current evidence from the literature pertaining to the identification, treatment, and coordination of care among children with gender dysphoria within the primary care setting or medical home. METHODS: Using PubMed and CINAHL, a literature review spanning from 2012 to the present was conducted using the following key words: gender dysphoria, transgender health, LGBT health, and hormone therapy. Reference lists of identified articles were also explored for relevance. CONCLUSIONS: Treatment may include a social transition, hormone antagonist therapy, or the administration of cross-sex hormone therapy, with a medical home needed to facilitate coordination of care. Best practice guidelines vary across pediatric and developmental groups and include both reversible and nonreversible modalities. Screening for negative psychosocial sequelae must be completed to include mood symptomatology, suicidality, substance use disorders, and risky sexual behavior, so that appropriate screening, identification, and treatment interventions can be implemented. IMPLICATIONS FOR PRACTICE: The primary care medical home must act as a foundation for the identification of gender dysphoria and/or associated comorbidities and must treat, when able, or refer, when indicated. In addition, because of structural barriers and

stigmatization, public policy often fails the transgender community and can exacerbate the aforementioned psychosocial comorbidities faced by the transgender youth community. Health care providers, particularly nurse practitioners, are in a unique position to expand on the face-to-face care provided to the community and engage in advocacy efforts to dismantle structural barriers impeding transgender individuals and communities while also providing primary health care, anticipatory guidance, and care coordination.

Annotation: A systematic review examining prevalence, treatment considerations, risk factors, and comorbidities among TGNB children and adolescents.

Karalexi MA, Georgakis MK, Dimitriou NG, et al. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2020;119:104721. doi:10.1016/j.psyneuen.2020.104721 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32512250

Abstract: BACKGROUND: Previous studies have examined whether steroid hormone treatment in transgender individuals may affect cognitive function; yet, their limited power does not allow firm conclusions to be drawn. We leveraged data from to-date literature aiming to explore the effect of gender-affirming hormone administration on cognitive function in transgender individuals. METHODS: A search strategy of MEDLINE was developed (through June 1, 2019) using the key terms transgender, hormone therapy and cognitive function. Eligible were (i) cohort studies examining the longitudinal effect of hormone therapy on cognition, and (ii) cross-sectional studies comparing the cognitive function between treated and non-treated individuals. Standardized mean differences (Hedges' g) were pooled using random-effects models. Study quality was evaluated using the Newcastle-Ottawa Scale. OUTCOMES: Ten studies (seven cohort and three cross-sectional) were eligible representing 234 birth-assigned males (aM) and 150 birth-assigned females (aF). The synthesis of cohort studies (n = 5) for visuospatial ability following hormone treatment showed a statistically significant enhancement among aF (g = 0.55, 95% confidence intervals [CI]: 0.29, 0.82) and an improvement with a trend towards statistical significance among aM (g = 0.28, 95%CI: -0.01, 0.58). By contrast, no adverse effects of hormone administration were shown. No heterogeneity was evident in most meta-analyses. INTERPRETATION: Current evidence does not support an adverse impact of hormone therapy on cognitive function, whereas a statistically significant enhancing effect on visuospatial ability was shown in aF. New longitudinal studies with longer follow-up should explore the long-term effects of hormone therapy, especially the effects on younger individuals, where there is greater scarcity of data.

Annotation: An analysis of studies investigating cognitive function in adolescents who are treated for gender dysphoria

Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. *Nat Rev Endocrinol*. 2011;7(8):466-472. doi:10.1038/nrendo.2011.78 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21587245

Abstract: The use of gonadotropin-releasing hormone analogs (GnRHa) to suppress puberty in adolescents with gender dysphoria is a fairly new intervention in the field of gender identity disorders or transsexualism. GnRHa are used to give adolescents time to make balanced decisions on any further treatment steps, and to obtain improved results in the physical appearance of those who opt to continue with sex reassignment. The effects of GnRHa are

reversible. However, concerns have been raised about the risk of making the wrong treatment decisions, as gender identity could fluctuate during adolescence, adolescents in general might have poor decision-making abilities, and there are potential adverse effects on health and on psychological and psychosexual functioning. Proponents of puberty suppression emphasize the beneficial effects of GnRHa on the adolescents' mental health, quality of life and of having a physical appearance that makes it possible for the patients to live unobtrusively in their desired gender role. In this Review, we discuss the evidence pertaining to the debate on the effects of GnRHa treatment. From the studies that have been published thus far, it seems that the benefits outweigh the risks. However, more systematic research in this area is needed to determine the safety of this approach.

Annotation: A systematic review focused on developing a protocol for puberty suppression, based on the Dutch experience.

Leibowitz S, de Vries ALC. Gender dysphoria in adolescence. *International review of psychiatry (Abingdon, England)*. 2016;28(1):21-35. doi:10.3109/09540261.2015.1124844 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26828376

Abstract: Adolescents presenting with gender-related concerns are increasingly seeking support from providers from a variety of disciplines within health care settings across the world. For those treating young people who meet the criteria for the DSM 5 diagnosis of gender dysphoria (GD), complex decisions in clinical care are common. Defining best practice with this population with respect to interventions that span mental health, physical, and surgical domains can be challenging, given a relative dearth of empirical data available; yet practice guidelines have emerged from different professional organizations which can aid with this. For this review paper, a broad literature search was performed to identify relevant studies pertaining to the care of adolescents with GD. In addition, an overview of trends in clinical practice, including shifts in conceptualization of how clinicians and patients define care that is considered affirming when working with this population, is described. This paper explores the characteristics of referral patterns to specialized clinics, provides a brief overview of gender identity development in adolescence, and then describes the phenomenology of known aetiological factors and co-occurring psychiatric issues in adolescents with GD. Additionally, clinical management considerations that detail assessment aims and common treatment interventions across disciplines will be explored.

Annotation: A systematic review of gender dysphoria diagnostic criteria

Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2017;5(10):816-826. doi:10.1016/S2213-8587(17)30099-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28546095

Abstract: The World Professional Association for Transgender Health's standards of care recommend suspending puberty, preferably with the use of gonadotropin-releasing hormone agonists, in certain gender non-conforming minors (aged under 18 years) who have undergone a psychiatric assessment and have reached at least Tanner stage II of puberty. This approach seeks to lessen the discordance between assigned natal sex and gender identity by temporarily halting the development of secondary sexual characteristics, essentially widening the temporal window for gender clarification. Despite promising preliminary evidence on the clinical utility of

this approach, there is a dearth of research to inform evidence-based practice. In view of these challenges, we review the available empirical evidence on the cognitive, physical, and surgical implications of puberty suppression in gender-incongruent children and adolescents. We also explore the historical underpinnings and clinical impetus for suspending puberty in this population, and propose key research priorities.

Annotation: A systematic review examining puberty suppression in TGNB children and adolescents.

Mason KA, Schoelwer MJ, Rogol AD. Androgens During Infancy, Childhood, and Adolescence: Physiology and Use in Clinical Practice. *Endocr Rev*. 2020;41(3):421-456. doi:10.1210/endrev/bnaa003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32115641

Abstract: We provide an in-depth review of the role of androgens in male maturation and development, from the fetal stage through adolescence into emerging adulthood, and discuss the treatment of disorders of androgen production throughout these time periods. Testosterone, the primary androgen produced by males, has both anabolic and androgenic effects. Androgen exposure induces virilization and anabolic body composition changes during fetal development, influences growth and virilization during infancy, and stimulates development of secondary sexual characteristics, growth acceleration, bone mass accrual, and alterations of body composition during puberty. Disorders of androgen production may be subdivided into hypo- or hypergonadotropic hypogonadism. Hypogonadotropic hypogonadism may be either congenital or acquired (resulting from cranial radiation, trauma, or less common causes). Hypergonadotropic hypogonadism occurs in males with Klinefelter syndrome and may occur in response to pelvic radiation, certain chemotherapeutic agents, and less common causes. These disorders all require testosterone replacement therapy during pubertal maturation and many require lifelong replacement. Androgen (or gonadotropin) therapy is clearly beneficial in those with persistent hypogonadism and self-limited delayed puberty and is now widely used in transgender male adolescents. With more widespread use and newer formulations approved for adults, data from long-term randomized placebo-controlled trials are needed to enable pediatricians to identify the optimal age of initiation, route of administration, and dosing frequency to address the unique needs of their patients.

Annotation: A systematic review examining the use of androgens during infancy, childhood, and adolescents.

Roden RC. Reversible interventions for menstrual management in adolescents and young adults with gender incongruence. *Ther Adv Reprod Health*. 2023;17:26334941231158251. doi:10.1177/26334941231158251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36938373

Abstract: The newly released World Professional Association for Transgender Health Standards of Care, 8th Edition specify that adolescents should be offered menstrual suppression as part of their treatment plans to suppress menses and alleviate dysphoria, provide contraception, or improve irregular bleeding on testosterone therapy. This is a review of current evidence-based options for reversible interventions for menstrual suppression in adolescents with gender dysphoria or incongruence. Shared decision-making should be used by the clinician at all times, and the clinician should be intentional in prioritizing the patient's stated needs and desires when offering interventions. No method should be withheld due to the experience of gender

incongruence alone. Contraceptive options offering menstrual suppression include depot-medroxyprogesterone acetate, levonorgestrel intrauterine systems, progestin-only contraceptive pills, and combined hormonal contraceptives. Non-contraceptive options include norethindrone acetate, oral medroxyprogesterone acetate, gonadotropin-releasing hormone analogues/agonists, and danazol. Certain patients may also benefit from non-pharmacologic interventions, such as specialty menstrual underwear. PLAIN LANGUAGE SUMMARY: Using medicine to stop Menstrual periods in teens with gender incongruence Summary: Newly released recommendations for the care of teens and young adults with gender dysphoria or incongruence specifically recommend using medications to get rid of menstrual periods if desired or medically necessary. Patients may ask for this to help improve dysphoria, as a feature they want in birth control, or simply because they do not want to have periods. Because temporarily getting rid of periods is something that doctors can do for any patient old enough to have periods, patients with gender dysphoria should also be able to have their periods temporarily stopped using medications if requested. Doctors should ensure that they always help the patient make a decision that is right for them instead of prescribing what they think is right without considering the patient's input. Options for temporarily getting rid of periods can include birth control, such as oral contraceptive pills, patches, or rings; intrauterine devices; or shots, and it can also be done with things that are not birth control, such a progesterone pills or puberty blockers. Finally, some patients may only need improved period hygiene with period underwear to feel better in their bodies.

Annotation: A systematic review examining menstrual outcomes associated with menstrual suppression treatments and testosterone in adolescents and young adults with gender dysphoria.

Rodriguez-Wallberg K, Obedin-Maliver J, Taylor B, Van Mello N, Tilleman K, Nahata L. Reproductive health in transgender and gender diverse individuals: A narrative review to guide clinical care and international guidelines. *Int J Transgend Health*. 2023;24(1):7-25. doi:10.1080/26895269.2022.2035883 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36713139

Abstract: BACKGROUND: Hormonal treatments and surgical interventions practiced with the aim to affirm gender identity in transgender and gender diverse patients may impact their future reproductive ability, family building, and family planning options. Whereas it is recommended by international guidelines to discuss the potential risks of infertility and to present fertility preservation (FP) options to transgender individuals and their families prior to initiating any of these treatments, many barriers still remain. Further, transgender and gender diverse individuals often experience barriers to accessing contraception, abortion, pre-conception care, and comprehensive perinatal care. AIMS: In this review we summarize the current literature on reproductive healthcare issues reported in transgender people including fertility issues, fertility preservation (FP), contraception, pregnancy and lactation and perinatal health. METHODS: A narrative literature search of major databases (Pubmed, Medline, PsycInfo, Google Scholar, Web of Science) was conducted. Given the paucity and heterogeneity of studies, summative review tactics were not available. The literature was critically reviewed by international experts in the field with focus on the impact of gender-affirming medical interventions on future fertility, current FP options and reproductive health issues in transgender people. RESULTS: The current literature supports that transgender and gender diverse individuals may wish to have genetically related children in the future, rendering the issue of FP relevant to this patient group. The cryopreservation of mature gametes is an

efficacious option for FP for post-pubertal adolescents and adults. It is recommended to discuss these options at time of planning for gender-affirming hormonal therapy (GAHT) or engaging with other gender-affirming procedures that can limit future fertility. Discontinuation of GAHT may allow individuals to undergo FP later, but data are limited and there is the concern of symptoms and consequences of stopping GAHT. For pre-pubertal and early pubertal children, FP options are limited to the cryopreservation of gonadal tissue. At present the tissue can become functional only after re-transplantation, which might be undesirable by transgender individuals in the future. Preconception counseling, prenatal surveillance, perinatal support, contraceptive, and pregnancy termination related healthcare need to be meaningfully adapted for this patient population, and many knowledge gaps remain. DISCUSSION: Specialized FP reproductive healthcare for transgender and gender diverse individuals is in early evolution. Research should be conducted to examine effects of medical interventions on fertility, timing of FP, gamete preservation and outcome of the fertility treatments. Strategies to inform and educate transgender and gender diverse patients can lead to optimization of reproductive care and counseling and decision making of FP for this population.

Annotation: A narrative review of fertility management when counseling TGNB patients

Wilhelm S, Kelsberg G, Safranek S. How does gender-affirming hormone therapy affect QOL in transgender patients? *The Journal of family practice*. 2022;71(10):442-444. doi:10.12788/jfp.0521 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L640249400&from=export

Abstract: There are modest effects on depression but not anxiety. Gender-affirming hormone therapy (GAHT) is associated with modest improvements in standardized scores for quality of life (QOL) and depression in adult male-to-female and female-to-male transgender people and modest improvements in depression scores in transgender adolescents, but the effect on anxiety is uncertain (strength of recommendation [SOR]: B, based on a preponderance of low-quality prospective cohort studies with inconsistent results). GAHT is associated with reduced gender dysphoria and decreased suicidality (SOR: B, based on a prospective cohort study). However, there is insufficient evidence to determine any effect on suicide completion. No studies associated GAHT with worsened QOL, depression, or anxiety scores.

Annotation: The impact of GAHT on quality of life for TGNB youth

Likely Eligible Studies Published in Other Languages but with English Abstracts (Bibliography Only)

Condat A, Bekhaled F, Mendes N, Lagrange C, Mathivon L, Cohen D. Gender dysphoria in children and adolescents: French history and clinical observations. *Neuropsychiatr Enfance Adolesc*. 2016;64(1):7-15. doi:10.1016/j.neurenf.2015.06.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L605213392&from=export

Abstract: Background: While specialized consultations in the clinical evaluation and management of sexual identity disorders in children and adolescents have developed since the 1970s abroad, access to information and specialized care is not yet well established in France. Gender dysphoria is a rare disorder and in the context of a lack of specialized center, every French child psychiatrist has met about 2 to 4 cases during his career. Also, in the absence of in-depth clinical experience or integrated thinking, many French child psychiatrists or psychologists

have tried to formulate own views and ideas from isolated observations, in a context where the clinical issues raised by these complex cases are crossed by societal debates about gender, sex, procreation and human rights. We recently created a consultation specialized in sexual identity in a Parisian university hospital to provide children and adolescents questioning their sexual identity, with or without disorder of sex development, and their families a diagnostic evaluation, information and if necessary treatment. Methods: We reviewed available medical information, proposed care and international recommendations. In addition, we also reviewed the history of the interests in gender dysphoria in France. Finally, we report four clinical observations that meet all DSM-criteria of gender dysphoria and appeared paradigmatic of the diversity of issues and clinical expressions. Results: The review of both the international and the French literatures confirms that the debates, passions and issues are similar across culture and context despite specific local variations that may explain why French child psychiatry appeared reluctant to follow international changes until recently. The four cases that included 2 boys and two girls aged 17, 16 (= 2) and 10 years, all asking for a change of sex, show (1) the clinical diversity in terms of main expression (school refusal and anxiety, suicidal behaviors, anorexia), age of onset, and medical context (with or without disorder of sex development); and (2) the relevance of a multidisciplinary clinical approach taking into account the genetic, hormonal, psychological, developmental, family and social dimensions. Conclusion: Besides the validity of gender dysphoria as a clinical category, the diversity of the issues and clinical expression promotes a dimensional approach of the cases. Many clinical and research questions need to be addressed in the future: should we propose subgroups based on age of onset or comorbidities? What are the consequences of hormonal suppression on child development and adolescence both in terms of somatic and psychological milestones? Does social transition in child and adolescent favour latter transsexual choices in adulthood? What is the right balance between hormonal treatment and psychological therapies?

Annotation: A French case series reporting on 2 AMAB and 2 AFAB with gender dysphoria

Fernandez M, Guerra P, Martin E, Martinez N, Alvarez-Diz JA, Grupo G. [Health care for adolescents with gender dysphoria]. *Rev Esp Salud Publica*. 2018;92Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29493565

Abstract: OBJECTIVE: Dysphoria gender treatment in adolescents is recent. Studies of adolescents treated with analogs are reduced. To ensure the quality of care and safety of the child, follow-up studies are necessary. The aim of the present research was to describe the characteristics of the process of medical and psychological attention in adolescents with the DG in the Gender Identity Treatment Unit of Asturias in the period 2007-2015. METHODS: The sample included 20 minors attended in the Gender Identity Treatment Unit of Asturias in the period 2007-2015. The clinical history was made to collect the variables. It was made descriptive analysis. RESULTS: 10% of adolescents abandoned in the process of psychological counseling, 80% began to be valued by endocrinology and 10% continued exclusively in psychological consultations. Of the medical treated adolescents, 13.3% were treated with analogues and 86.7% received cross-hormonal treatment (THC) directly. The most prevalent secondary effects were dermatological problems (40%), followed by mastodynia without galactorrhea (26.7%) and hot flashes (20%). 20% performed gender confirmation surgeries. CONCLUSIONS: The profile of the adolescent treated in the unit of Asturias is a subject that begins hormonal treatment after psychological accompaniment and endocrinological evaluation. The minor has adverse effects after treatment. Once the hormonal treatment has been established, they do not abandon the process.

Annotation: A survey of TGNB youth on their treatment decisions after they presented complaints of gender dysphoria. In Spanish.

Fernandez Rodriguez M, Guerra Mora P, Martin Sanchez E, Grupo G. [Characteristics of Adolescents with Gender Dysphoria Referred to the Gender Identity Treatment Unit]. *Rev Esp Salud Publica*. 2017;91Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28141788

Abstract: OBJECTIVE: The demand for treatment among people with gender dys-phoria has increased during the last years. The aim of the present research was to carry out an analysis of the demand of the teenagers that requested consultation at the UTIGPA (Gender Identity Treatment Unit of Principality of Asturias) as they presented complains of gender dysphoria. METHODS: The sample included 20 minors that were treated between March 2007 and December 2015. The clinical history was made to collect informa-tion. It was made descriptive analysis and the reason sex/gender was used. RESULTS: The 20 teenagers represented the 14,6% of the whole sample (of 137 demands). The age average was 15,20 years (SD=1,473) and the range of years was between 12-17. The reason sex/gender was 1/1 (10 into the man to woman group and 10 into the woman to man group). At the arrival at the Treatment Unit, 100% of the individuals lived with their nuclear or extended family and in the 60% of the cases, their parents were separated. 70% of the cases were referred from mental health services. 10% hadn t got any past medical history and 35% had never received any prescription for a psychopharmacological treatment. 95% hadn't done any hormonal self-treatment. 100% defined themselves as heterosexual. 25% requested exclusively for psychological interventions and 75% asked for medical treatments. CONCLUSIONS: The profile of the minor was a teenager of approximately 15 years old that was referred from mental health services. Contrary to the fin-dings of other national and international researches, the rate sex/gender was equated in our research. The minor had got a past medical history and their prio-rity request was for medical treatments, both hormonal and surgical therapies.

Annotation: A survey of TGNB youth who requested consultation as they presented complaints of gender dysphoria. In Spanish.

Korte A, Beier KM, Wermuth I, Bosinski HAG. The treatment of gender dysphoria (gender identity disorders) in childhood and adolescence open-outcome psychotherapeutic support or early setting of therapy course with the introduction of hormonal therapy? *Padiatrische Praxis*. 2017;88(1):67-87. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L617597046&from=export

Abstract: Child and adolescent psychiatrists experience more and more patients who are uncertain or dissatisfied in regard to their birth sex; some wish to join the opposite sex. Within the framework of the recently revised DSM, DSM-5(2013), this article discusses the diagnostic classification gender dysphoria (GD), in particular the question of the persistence of GD and the therapeutic implications. It reviews at length the different approaches for treatment, especially the pros and cons of early hormonal therapy. The study is based on a selective Medline literature search, national and international guidelines, and the results of a debate among experts in multiple relevant disciplines. Strong evidence indicates that only a minority of children with GD manifest an irreversible transsexualism in adulthood. This indicates the use of age-differentiated therapy with an open outcome, a treatment approach which in the case of younger children primarily aims at strengthening the sense of concordance with their birth sex and which in principle uses developmental tasks beyond the gender identity issue for all age

groups, and takes possible comorbid psychiatric disorders into account, for adolescents with transsexualism in statu nascendi a real-life test under psychotherapeutical supervision is indicated. The treatment with developmental- and bodyaltering hormones should be initiated only after the juvenile's somato- and psychosexual development has been completed. The article also debates the medical ethics involved here.

Annotation: A review of the applications of the gender dysphoria diagnostic criteria.

Martinez S, Mazoyer AV. Impacts of the sexual reassignment on the parenthood. *Ann Med Psychol (Paris)*. 2017;175(9):797-802. doi:10.1016/j.amp.2017.09.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618996605&from=export

Abstract: Nous avons cherché à comprendre le vécu parental après une réassignation sexuelle (male to female) d'un sujet. Après avoir exposé les différents travaux cliniques consacrés à la transidentité (ou transsexualisme) et défini la parentalité, nous avons analysé les données cliniques issues d'un entretien clinique de recherche et d'une passation d'une épreuve projective, le TAT, étayée par une méthodologie innovante développée par des projectivistes (Lintanff et Verdon, 2014). Nous avons rencontré une femme, Mme L., qui a été père par trois fois et qui a décidé de changer de sexe après des événements traumatiques et somatiques et une longue période de travestisme. Mme L. a peu évoqué son propre vécu de père, si ce n'est que la réassignation sexuelle a occasionné une rupture des liens avec ses enfants de leur plein gré. Elle a surtout évoqué son histoire de vie et son vécu d'enfant, d'adolescent et d'adulte confronté à la transidentité et les aménagements qu'elle a pu mettre en œuvre pour soulager une identité de genre non conforme à l'identité biologique. Le TAT a pu souligner la précarité identificatoire, rendant complexe le rapport aux polarités : masculine, féminine, paternelle, maternelle. La réassignation sexuelle vers le sexe féminin n'a pas occasionné une meilleure qualité des identifications féminines et maternelles. Nous soulignons la valeur heuristique des épreuves projectives dans la clinique de la transidentité. Objectives We tried to understand the parental real-life experience after a hormonal and surgical sex reassignment (male to female). Patients and methods After exposed research on transidentity and defined the parenthood, we analyzed the clinical data from interviewing and projective test: TAT. Our research is based on the French interpretation of this test, and on the show both the BM and the GF cards (Lintanff and Verdon, 2014). We met a woman, Mrs L., who was a father by three times and who decided to change sex after traumatic and somatic events and long period of transvestitism. Results The reassignment caused a loss of contacts with his children. Mrs L. (now) little evoked his life story, except his suffering when child, he repudiates his body's sex, which he oppose to his gender. We analyse (TAT) wavering of female and maternal identifications even after reassignment. Conclusion Projective tests provide a particularly heuristic solution for understanding the weaknesses and psychic resources of subjects having changed gender.

Annotation: A TGNB parent of 3 children reviews her youth and decision to transition. In French.

Mendes N, Lagrange C, Condat A. Gender dysphoria in children and adolescents: Literature review. *Neuropsychiatr Enfance Adolesc*. 2016;64(4):240-254. doi:10.1016/j.neurenf.2016.04.003 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L610761157&from=export

Abstract: Background Today in France, specialised consultations for gender dysphoria in children and adolescents are just being developed although specialised teams already address this public abroad since decades. Their experience inspired the medical care in a remarkable way. Methods To illustrate the present state of research in child and adolescents with gender dysphoria, we first made a review of Zucker and al. publication (2013). We then compiled further researches available on the subject (post 2013) as well as precursor works on transsexualism or gender concept in general. We also took into consideration the most recent publications available in scientific journals and the most relevant clinical trials. Results This research allows us to highlight the evolution of diagnostic criteria, prevalence data, comorbidity and associated psychopathologies, biological factors, and available treatments. We also discuss psychodynamics observations and more generic issues based on available data. Conclusion The recurrence of anxious and depressive signs and suicide risk in the studied population demonstrate the need to consider gender dysphoria when providing medical and psychological care to these children and adolescents. The recommended treatments also need to consider possible comorbidity and the frequent related difficulties (such as social ostracism, anxiety, etc.). Currently, there is an urgent need to develop specialised centres and platforms in France to allow clinical practitioners to share their knowledge and researches results.

Annotation: A review of gender dysphoria in adolescents and children

Meyenburg B. [Gender dysphoria in adolescents: difficulties in treatment]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):510-522. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296511

Abstract: In many children and adolescents with gender dysphoria only minor or no psychopathology is found. 43% of patients seen in the Frankfurt University Gender Identity Clinic for children and adolescents suffer from major psychopathology. To demonstrate difficulties in treatment of these patients courses of treatment in four such patients are presented. In two natal females major psychopathology made decision for reassignment very difficult. Two natal males were in addition not able to follow recommended treatment steps, in these patients diagnostic doubts arose.

Annotation: Reviews treatment course for TGNB youth in a gender identity clinic. In German.

Meyenburg B, Korte A, Moller B, Romer G, Deutsche Gesellschaft fur Kinder- und Jugendpsychiatrie PuP. [Gender identity disorders in childhood and adolescence (F64)]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):542-552. Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296513

Annotation: Reviews treatment course for TGNB youth in a gender identity clinic. In German.

Meyenburg B, Kroger A, Neugebauer R. [Gender dysphoria in children and adolescents - treatment guidelines and follow-up study]. *Z Kinder Jugendpsychiatr Psychother*. 2015;43(1):47-55. doi:10.1024/1422-4917/a000332 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25536896

Abstract: Treatment guidelines for transidentity in children and adolescents are presently under discussion. We present an overview of the various treatment modalities. Further, follow-up data on children and adolescents referred for gender-identity problems are presented. Of the 84 patients seen for the first time more than 3 years before follow-up, 37 mailed in the completed

questionnaires. In addition, 33 patients agreed to answer some short follow-up questions. We assessed steps of treatment, gender role, psychopathology, and psychotherapy. We compared differences in psychopathology in patients with vs. without gender role change and in patients with intense vs. less intense psychotherapy. A total of 22 patients had completely changed gender role, and some had started hormonal treatment und sex reassignment surgery. Most patients were satisfied with the treatment results. All patients showed less psychopathology on follow-up, independent of role change or intensity of psychotherapy. In general, the patients reported little psychopathology. Our follow-up results support the present treatment approach. In patients with little psychopathology, low-frequency supportive treatment appears sufficient to obtain safe judgement on hormonal of surgical treatment.

Annotation: Survey of prior GD pediatric patients after 3 years, who did or did not transition. In German.

Pamfile D, Soldati L, Brovelli S, et al. [Role of the psychiatrist-psychotherapist in the assessment and treatment of gender dysphoria]. *Rev Med Suisse*. 2020;16(709):1877-1880. Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33026731

Abstract: This article is the result of the joint work of psychiatrists-psychotherapists working with patients with gender dysphoria (children, adolescents and adults) in Lausanne and Geneva university hospitals. It emphasizes the importance of their clinical interventions when hormone therapy and sex reassignment surgery are requested.

Annotation: Practice guidelines for the mental health specialist for gender dysphoric adolescents

Pauli D, Günthard M, Schenker T, et al. The Zurich Specialist Clinic for Adolescent with Gender Dysphoria - Preliminary Follow-up Results. *Prax Kinderpsychol Kinderpsychiatr*. 2020;69(6):570-589. doi:10.13109/prkk.2020.69.6.570 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L633037474&from=export

Abstract: The Zurich Specialist Clinic for Adolescent with Gender Dysphoria - Preliminary Follow-up Results The specialist clinic for children and adolescents with gender dysphoria (GD) of the Psychiatric University Hospital of Zurich shows an increasing number of referrals since its foundation in 2009. Since 2014 we started an observational study including adolescents aged 13 years and older. At the time of the first appointment (T0) N = 77 participants completed a battery of questionnaires assessing demographic factors, general psychopathology, quality of life as well as gender identity, social transitioning and GD treatment modalities. Few of the adolescents were socially transitioned and had hormone therapy but 77.9 % wished to get hormone therapy. Follow up assessment T1 was performed after at least one year of treatment in our specialist clinic. 51 adolescents completed an online follow-up examination including the same questionnaires and baseline parameters as well as a scale measuring treatment satisfaction. At T0, 77.3 % of the adolescents scored in the clinical range of the Youth Self Report (YSR) total score, which did not decrease significantly until T1 in our preliminary follow up sample. Puberty blocking before T0 correlated negatively with the YSR score, indicating less psychopathology in treated patients. Preliminary longitudinal analysis suggests that social transitioning influences quality of life (Kidscreen subscale autonomy and parental relationship). At T1, 52 % of the adolescents were socially transitioned in all contexts and 70 % received

gender affirming hormonal treatment. Gender identity changed between T0 and T1 in about 18 % of the cases. Treatment satisfaction in most cases was high.

Annotation: A pre-post follow up study of adolescents presenting with GD at a gender specialty clinic. In German.

Pierce S, Mazziotta A, Möller-Kallista B. Experiences of Children with Gender Dysphoria/Gender Incongruence and their Parents with the Health Care System in Germany. *Prax Kinderpsychol Kinderpsychiatr*. 2022;71(7):597-619. doi:10.13109/prkk.2022.71.7.597 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L639549895&from=export

Abstract: The aim of the study is to describe experiences within the health care system of children and adolescents with gender dysphoria/gender incongruence (GD/GI) as well as their parents in Germany.The findings are intended to improve health care of children and adolescents with GD/GI and their families and have been incorporated into the development of the new S3 Guidelines "Gender Incongruence and Gender Dysphoria in Childhood and Adolescence: Diagnosis and Treatment". A total of 78 people, 35 children, adolescents, and young adults (6- 21 years) with GD/GI as well as 33mothers and 10 fathers, were interviewed. Seventeen semistructured individual interviews and five focus groups were conducted. Many of the participants reported waiting times of several months or years as well as inadequately trained doctors and therapists. A trans*identity, especially amongst smaller children and their parents, was often dismissed by health care providers, as a temporary phenomenon or an imagination of the child or the parents. Trans*ident children, adolescents and young adults as well as their parents were rarely perceived as experts in their own right. Recommendations for an affirmative care of trans* children and adolescents are formulated.

Annotation: A qualitative, interview survey of TGNB youths and their parents. In German

Poirier F, Condat A, Laufer L, Rosenblum O, Cohen D. Non-binary gender and transgender youth: A literature review. *Neuropsychiatr Enfance Adolesc*. 2019;67(5-6):268-285. doi:10.1016/j.neurenf.2018.08.004 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2001164253&from=export

Abstract: Background: Recently international scientific literature has been increasingly interested in situations where gender identity is unconventional – neither male nor female, part-time male part-time female, male and female. Binary transgender identity and gender dysphoria are now well recognized. However, this is not the case for non-binary gender identities. Objective: In the current report, we aim at reviewing the literature on non-binary gender and genderqueer identities in order to appreciate the interest of this recognition in medicine and its understanding by the health professionals. Methods: The article is based on a literature review on non-binary gender and genderqueer identities and on the accompaniment of binary and non-binary transgender youth. The results are presented within different themes. Results: Research shows that non-binary/genderqueer people tend to be young, urban, have a higher level of education, and to remain often as students or unemployed. If non-binary trans people are mostly teenagers and young adults between the ages of 14 and 25, it is not simply a question of considering non-binary gender identity as an adolescent process, or even simply a recent societal phenomenon. Indeed, the issues that are facing these adolescents and young

people are very specific, starting with marginalization and precariousness. According to previous studies, psychic difficulties (including self-aggressive gestures, suicidal thoughts and behaviors, eating disorders, anxiety and depression) are more or less equal or superior to those of binary transgender people. It is necessary to consider the different methodological biases, or the cultural and geographical context of a study. The rate of indecision is particularly high among non-binary youth, but access to care is more complicated when they are ready to make a change. Then, the physical transformations desired will vary, depending on the needs, but frequently only the cross-sex hormones and/or top surgery are needed. In that way, non-binary gender youth tend to have a better relationship with their own bodies than binary transgender youth. Conclusion: The scientific literature is increasingly trying to raise the question of the inclusivity of all genres in national surveys and in the accompaniment of people. A better understanding of these questions will allow better support of young people questioning their gender in a binary or non-binary perspective.

Annotation: A review of the literature concerning TGNB youth.

Rebetez N. [I want an accepting society]. *Krankenpfl Soins Infirm*. 2014;107(11):56-57. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25438414

Abstract: None

Annotation: A TGNB youth discusses her transition. In French.

Rutzen KM, Nieder TO, Schreier H, Moller B. [Clinical treatment of children and adolescents with gender dysphoria from international experts' point of view]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):449-464. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296508

Abstract: The clinical treatment of children and adolescents with gender dysphoria is still a controversial issue. The aim of this study was to get an overview of the knowledge and experience of international experts and to highlight shared views as well as differences in theoretical convictions and treatment approaches. Half-structured, guide-line based interviews were carried out with international experts in the field. The interviews were analyzed using qualitative content analysis (Mayring, 2010).

Annotation: The clinical treatment of children and adolescents with gender dysphoria

Strittmatter E, Holtmann M. [Gender identities in transition]. *Z Kinder Jugendpsychiatr Psychother*. 2020;48(2):93-102. doi:10.1024/1422-4917/a000724 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32162593

Abstract: Gender identities in transition Abstract. In recent years, the healthcare system has been confronted with an increasing number of children and adolescents with gender nonconformity, gender incongruence, and gender dysphoria. Medical professionals are still debating how to interpret this phenomenon and how best to meet the healthcare needs of this diverse group of young people. Meanwhile, the transgender and gender nonconforming youths themselves face enormous challenges in finding appropriate support and treatment in the mental healthcare system. This article reviews the available epidemiological data, the paradigm shift in the social, legal, and medical systems, the developments in diagnostic classifications (DSM-5, ICD-11) as well as important aspects of the AWMF S3 guideline for adults with gender

incongruence and gender dysphoria. In addition, it describes the complexity of working with transgender, gender nonconforming, and gender-questioning youth in the context of the current discourse and the underlying ethical dilemmas. In conclusion, this article outlines the challenges facing child and adolescent psychiatry and psychotherapy in this complex environment.

Annotation: A review of the diagnosis and treatment of gender dysphoria

Repeat Publications of Included Studies (Bibliography Only)

de Vries ALC. Autism Spectrum Disorders in Gender Dysphoric Children and Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:51-62:chap 4. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. *Gender Dysphoria in Adolescents*. PhD Thesis. Vrije Universiteit Amsterdam; 2010. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Psychiatric Comorbidity in Gender Dysphoric Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:63-76:chap 5. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Puberty Suppression in Adolescents with Gender Identity Disorder: A Prospective Follow-up Study. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:77-90:chap 6. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *Endocr Pract*. 2017;23(12):1437. doi:10.4158/1934-2403-23.12.1437 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29320642

Annotation: A guideline for treating gender dysphoria

Korte A, Beier KM, Wermuth I, Bosinski HAG. The treatment of gender dysphoria (gender identity disorders) in childhood and adolescence open-outcome psychotherapeutic support or early setting of therapy course with the introduction of hormonal therapy? *Gynakologische Praxis*. 2018;43(2):303-323. Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L617597046&from=export

Abstract: Child and adolescent psychiatrists experience more and more patients who are uncertain or dissatisfied in regard to their birth sex; some wish to join the opposite sex. Within the framework of the recently revised DSM, DSM-5(2013), this article discusses the diagnostic classification gender dysphoria (GD), in particular the question of the persistence of GD and the therapeutic implications. It reviews at length the different approaches for treatment, especially the pros and cons of early hormonal therapy. The study is based on a selective Medline literature search, national and international guidelines, and the results of a debate among experts in multiple relevant disciplines. Strong evidence indicates that only a minority of

children with GD manifest an irreversible transsexualism in adulthood. This indicates the use of age-differentiated therapy with an open outcome, a treatment approach which in the case of younger children primarily aims at strengthening the sense of concordance with their birth sex and which in principle uses developmental tasks beyond the gender identity issue for all age groups, and takes possible comorbid psychiatric disorders into account, for adolescents with transsexualism in statu nascendi a real-life test under psychotherapeutical supervision is indicated. The treatment with developmental- and bodyaltering hormones should be initiated only after the juvenile's somato- and psychosexual development has been completed. The article also debates the medical ethics involved here.

Annotation: Gender development in children and implications for gender dysphoria

Commentaries on or Corrections of Included Studies (Bibliography Only)

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. CORRIGENDUM FOR "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline". *J Clin Endocrinol Metab*. 2018;103(7):2758-2759. doi:10.1210/jc.2018-01268 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29905821

Abstract: In the Summary of Recommendations, 1.0 Evaluation of youth and adults, Recommendation 1.1 on page 3870 and in Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence on page 3877, the Recommendation was originally: 1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the persons understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement).

Annotation: A correction to a guideline for treating gender dysphoria

Hewitt JK, Paul C, Newman LK. Author Reply to Conway, et al. regarding “Hormone treatment of gender identity disorder in a cohort of children and adolescents”. *Med J Aust*. 2012;197(5):274. doi:10.5694/mja12.10911 Accessed June 16, 2023. Available at https://pubmed.ncbi.nlm.nih.gov/22938117/

Annotation: Author’s reply to comment on prior article, “Hormone treatment of gender identity disorder in a cohort of children and adolescents”

APPENDIX I.G: CHARACTERISTICS OF INCLUDED RELEVANT CLINICAL STUDIES

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Multistate/national studies			
National internet survey, n ≥ 3235 TGNB youths			
Green (2022)[111] Observational cross-sectional study Nationwide, cross-sectional, survey study comparing demographic and mental health characteristics between adolescents and young adults who self-reported receiving GAHT versus not, including TGNB adolescents ages 13-17 years recruited from an unspecified number of US states via ads on social media	All subjects: 5,753 TNGB patients: 5,753 **TGNB youths: 3,235** Transmasculine: 2,547 Transfeminine: 702 OGD: 2,504	Relevant outcomes • Mental health Study period: 10/2020–12/2020 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
National internet survey, n ≥ 156 TGNB youths			
Chen (2018)[455] Observational study A survey study examining attitudes about fertility among TGNB adolescents who were participants in a larger study about sexual health and HIV prevention	All subjects: 156 TNGB patients: 156 **TGNB youths: 156** Transmasculine: 57 Transfeminine: 9 OGD: 90	Relevant outcomes • Attitudes towards fertility Study period: 9/2016–10/2016 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
US Youth Risk Behavior Survey, n ≥ 3494 TGNB youths			
Turban (2020)[121] Observational cross-sectional study A cross-sectional survey study including cisgender and transgender adolescent respondents from 2017 and 2019, including an examination of the association between self-reported GnRH analog use and suicide ideation in TGNB adolescents	All subjects: 20,619 TNGB patients: 3,494 **TGNB youths: 3,494** Transmasculine: 1,213 Transfeminine: 1,385 OGD: 896 Cisgender peers/others: 17,125	Relevant outcomes • Mental health • Self-harm Study period: 8/2015–9/2015 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Turban (2022)[122] Observational cross-sectional study A cross-sectional study of 2015 Youth Behavioral Risk Survey respondents including transgender adults who started treatment in early adolescence, late adolescence, or adulthood; examines the risk of mental health problems associated with the age of treatment initiation.	All subjects: 27,715 TNGB patients: 27,715 **TGNB youths: 481**	Relevant outcomes • Mental health • Psychosocial metrics Study period: 8/2015–9/2015 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) • Risk of bias details in Appendix I.I
Children's Hospital Association's Pediatric Health and Information System,[a] n ≥ 264 TGNB youths			
Lopez (2018)[456]	All subjects: 1,506 TNGB patients: 264	Relevant outcomes	Bibliography only (Appendix I.F)

[a] *Includes up to 43 institutions.*

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
Descriptive study Examines off-label use of GnRH analogs among pediatric patients with GD or developmental sex disorders. Neither affirmed genders nor birth-assigned sexes were reported.	**TGNB youths:** Cisgender peers/others:	**264** 1,242	• FDA-approved indications and off-label uses Study period: 2013–2016 Follow-up duration: N/A	Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Lopez (2018)[435] Descriptive study Examines use of GnRH analogs in pediatric patients, including TGNB children and cis children with CPP. Authors did not report affirmed gender ratios, only natal sex (N = 52 AMAB, N = 39 AFAB, and 1 whose natal sex was unknown).	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD: Cisgender peers/others:	2,332 92 **92** N/R N/R N/R 2,240	Relevant outcomes • Utilization of histrelin acetate implants Study period: 2004–2016 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Military Healthcare Data Repository, n = 952 TGNB youths				
Roberts (2022)[457] Observational study A US, multi-state cohort study examining treatment continuation in N = 952 transmasculine vs transfeminine TGNB dependents of US military personnel	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	952 952 **952** 627 325	Relevant outcomes • Initiation and continuation of GAH Study period: 2009–2018 Follow-up duration: 4.4 years	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Nos (2022)[173] Observational study Cohort study examining the risk of CSHT use in TGNB adolescents who used GnRH analogs and had the TRICARE benefit. Only natal sexes reported (N = 122 AMAB and N = 312 AFAB).	All subjects: TNGB patients: **TGNB youths:**	434 434 **434**	Relevant outcomes • Likelihood of initiation of GAH Study period: 10/2009–4/2018 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Cystic Fibrosis care centers surveyed, N = 30 TGNB youths				
Shaffer (2022)[458] Longitudinal, pre-post descriptive study A research letter summarizing findings from a research study examining 1-second FEV values in TGNB adolescents with CF from a national sample of centers	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	30 30 **30** 13 11 6	Relevant outcomes • 1-second FEV values Study period: 12/2019–2/2020 Follow-up duration: 24 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Trans Youth Project in 23 states and Canada, N = 317 TGNB youths				
Durwood (2017)[109] Observational cross-sectional study	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	310 116 **116** 48	Relevant outcomes • Mental health Study period: 3/2015–2/2016	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I.I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
Cross-sectional study comparing mental health and self-worth outcomes between TGNB treatment groups and between TGNB adolescents versus controls (ie, siblings and community controls).	Transfeminine: Cisgender peers/others:	68 194	Follow-up duration: N/A	
Olson (2022)[175] Descriptive study A nationwide survey study examining gender identities 5 years after initial presentation	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	317 317 **317** 109 208	Relevant outcomes Study period: 7/2013–12/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
A dataset from PEDSnet (a pediatric learning health system network), comprising data from 7 PEDSnet participating institutions , N = 4172 TGNB youths				
Valentine (2022)[98] Observational cohort and cross-sectional study Cross-sectional, database study comparing cardiometabolic parameters between TGNB adolescents and controls, as well as between TGNB adolescents receiving different treatments. Only natal sexes reported (N = 2766 AFAB and N = 1407 AMAB).	All subjects: TNGB patients: **TGNB youths:** Cisgender peers/others:	20,625 4,172 **4,172** 16,648	Relevant outcomes • Cardiometabolic parameters Study period: 2009–2019 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I.I
Trans Youth Care Study [redacted] Hospitals),[b] n ≥ 391 TGNB youths				
Olson-Kennedy (2019)[162] Longitudinal, pre-post descriptive study Examines growth and bone density in TGNB adolescents starting puberty suppression and TGNB adolescents starting CSHT	All subjects: TNGB patients: **TGNB youths:**	481 391 **391**	Relevant outcomes • Mental health • Physiologic/Metabolic parameters • Bone health Study period: 7/2016–9/2018 Follow-up duration: 24 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Lee (2020)[85] Observational cohort study Examines changes in bone between TGNB patients treated with GnRH analogs. Authors did not specify affirmed gender identities other than to specify 58 as binary and 5 nonbinary. They also specified natal sexes (N = 33 AMAB and N = 30 AFAB)	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	63 63 **63** N/R N/R 5	Relevant outcomes • BMD Z-scores Study period: N/R Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Nahata (2020)[459] Descriptive study[a]	All subjects: TNGB patients: **TGNB youths:**	44 44 **44**	Relevant outcomes • Sexual attitudes and behaviors • Attitudes towards fertility Study period: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[b] *Sites include* [redacted]

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Examines gender identity, sexual orientation, contraception counseling, and attitudes towards fertility among TGNB adolescents seen in 4 gender clinics across 3 states		Follow-up duration: N/A	
Chen (2021)[104] Observational cross-sectional study Cross-sectional study examining psychosocial outcomes in TGNB youth initiating treatment with GnRH analogs or CSHT.	All subjects: 95 TNGB patients: 95 **TGNB youths: 95** Transmasculine: 41 Transfeminine: 45 OGD: 9	Relevant outcomes • Psychosocial Study period: 7/2016–9/2018 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Millington (2021)[89] Descriptive, longitudinal pre-post study A research letter examining growth, body composition, and cholesterol changes in TGNB adolescents receiving CSHT. Only natal sex reported (N = 83 AMAB and N = 186 AFAB).	All subjects: 269 TNGB patients: 269 **TGNB youths: 269**	Relevant outcomes • Cholesterol changes • Body changes/Growth Study period: 7/2016–9/2018 • Follow-up duration: 12 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Millington (2022)[90] Descriptive, longitudinal pre-post study Examines changes in kidney function measures in TGNB adolescents receiving GAHT.	All subjects: 286 TNGB patients: 286 **TGNB youths: 286** Transmasculine: 181 Transfeminine: 87 OGD: 18	Relevant outcomes • Kidney function metrics Study period: N/R Follow-up duration: 24 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers), and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Schulmeister (2022)[95] Observational cohort study Multi-state cohort study comparing height velocity (ie, growth) in TGNB patients who initiated GnRH analogs for puberty suppression at the various Tanner stages.	All subjects: 55 TNGB patients: 55 **TGNB youths: 55** Transmasculine: 28 Transfeminine: 24 OGD: 3	Relevant outcomes • Growth • Height velocity Study period: 7/2016–9/2018 Follow-up duration: 14 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I.I
Chen (2023)[75] Descriptive, longitudinal pre-post study Examines mental health and psychosocial outcomes in TGNB adolescents after 2 years of CSHT. Also compares mental health outcomes between early- and late-treated adolescents.	All subjects: 315 TNGB patients: 315 **TGNB youths: 315** Transmasculine: 190 Transfeminine: 106 OGD: 19	Relevant outcomes • Mental health • Psychosocial functioning Study period: 7/2016–6/2019 • Follow-up duration: 24 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Conn (2023)[105] Observational cross-sectional study	All subjects: 315 TNGB patients: 315 **TGNB youths: 315** Transmasculine: 190	Relevant outcomes • Mental health	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Examines risk factors for mental health outcomes in TGNB adolescents from the Trans Youth Care Study.	Transfeminine: OGD	106 19	• Gender Minority Stress and Resilience Measure for Adolescents (GMSR-A) Study period: 7/2016–9/2018 Follow-up duration: N/R	
[redacted] *which links medical records at multiple health care sites throughout* [redacted], *n = 22 TGNB youths*				
James (2020)[460] Observational study Examines changes in gender identity between AFAB and AMAB TGNB patients, including adolescents. Outcomes of interest were not reported separately for adolescents.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	80 80 **22** 29 32 19	Relevant outcomes • Health risk factors • Mental health risk factors • Gender identity Study period: 1974–2015 • Follow-up duration: Median 40.5 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
[redacted][c] *n = 116 TGNB youths*				
Jarin (2017)[136] Longitudinal, pre-post descriptive study Examines cardiovascular and metabolic changes associated with CSHT in adolescents with gender dysphoria	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	116 116 **116** 72 44	Relevant outcomes • Cardiovascular risk factors • Metabolic parameters Study period: 2008–2014 Follow-up duration: Max of 35 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
STRONG cohort, n = 958 TGNB youths				
Wagner (2021)[461] Observational study Cohort study examining predictors of GD diagnosis and of CSHT initiation in gender-diverse children. Only natal sex reported (N = 531 AMAB and N = 527 AFAB).	All subjects: TNGB patients: **TGNB youths:**	958 958 **958**	Relevant outcomes • Predictors of GD diagnosis • Predictors of CSHT Study period: 1/2006–12/2014 Follow-up duration: Mean 3.5 years	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[c] *Sites include the* [redacted].

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
[redacted] *n = 36 TGNB youths*			
Stevens (2015)[462] Observational study Examines insurance barriers to treatment access among TGNB children seen in 2 University-based pediatric clinics	All subjects: 36 TNGB patients: 36 **TGNB youths: 36**	Relevant outcomes • Insurance coverage patterns Study period: 2010–2015 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Unspecified or inconclusive locations in the US			
Either [redacted][a] *, n ≥ 1 TGNB youth*			
Penney (2022)[463] Case report[a] A 17 year-old transgender male diagnosed with VTE who went on to receive testosterone therapy	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • VTE events after testosterone Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
A regional, referral-based adolescent specialty clinic that cares for dependent children of active duty, activated selected reserve, and retired military service members, n ≥ 53 TGNB youth			
Van Donge (2019)[464] Observational study A cross-sectional study examining mental health outcomes in TGNB adolescent dependents of active-duty or retired US military personnel	All subjects: 53 TNGB patients: 53 **TGNB youths: 53**	Relevant outcomes • Mental health outcomes • Psychosocial outcomes • Healthcare utilization Study period: 7/2014–7/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) • Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Arizona [redacted]			
[redacted] *clinic, n ≥ 13 TGNB youths*			
Parks (2020)[465] Descriptive study Examines menstrual outcomes in adolescents who received levonorgestrel IUDs, including transgender male patients	All subjects: 260 TNGB patients: 13 **TGNB youths: 13** Transmasculine: 13	Relevant outcomes • Menstruation patterns Study period: 2012–2018 Follow-up duration: N/R	• Bibliography only (Appendix I.F) • Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
California [redacted]			
[redacted] *n ≥ 66 TGNB youths*			
Khazal (2014)[466] Case report	All subjects: 1 TNGB patients: 1	Relevant outcomes • Blood and marrow transplantation • Psychosocial	Bibliography only (Appendix I.F)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
A transgender adolescent with chronic myelogenous leukemia (CML)	**TGNB youths:** Transfeminine:	**1** 1	Study period: N/A Follow-up duration: 18 months	Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Olson-Kennedy (2018)[143] Descriptive, longitudinal pre-post study Examines the amount of chest dysphoria in transmasculine youth who had had chest reconstruction surgery compared with those who had not undergone this surgery.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	59 59 **59** 34 25	Relevant outcomes • Body changes • Testosterone utilization Study period: 6/2016–12/2016 Follow-up duration: N/A	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Olson-Kennedy (2021)[93] Observational cohort study Cohort study comparing puberty suppression outcomes in TGNB subjects receiving two forms of histrelin (Vantas vs Supprelin LA), and examining changes in the same outcomes within-TGNB groups	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	66 66 **66** 32 34	Relevant outcomes • Body change prevention Study period: N/R Follow-up duration: 12 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
[redacted] *n = 14 TGNB youths*				
Krishna (2021)[467] Descriptive study Examines on characteristics and temporal trends in use of histrelin implants in pediatric patients, including patients with GD	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Cisgender peers/others:	73 14 **14** 14 59	Relevant outcomes • Success of utilization • Adverse events Study period: 2008–2020 Follow-up duration: 37 months	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
California [redacted]				
[redacted] *n = 417 TGNB youths*				
Handler (2019)[468] Descriptive study Examines trends in TGNB referrals and requests for cross-sex hormones, puberty blockers, and surgery	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	417 417 **417** 257 102 58	Relevant outcomes • Referral and request trends Study period: 2/2015–6/2018 Follow-up duration: Median > 2 years	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints Descriptive studies that did not measure outcomes at multiple time-points were excluded from data extraction due to time constraints.

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
California [redacted]			
[redacted] *n = 106 TGNB youths*			
Avila (2019)[101] Observational cross-sectional study Cross-sectional study comparing eating disorder outcome scores (see **Appendix I.H**) between treated and untreated TGNB subjects	All subjects: 106 TNGB patients: 106 **TGNB youths: 106** Transmasculine: 64 Transfeminine: 30 OGD: 12	Relevant outcomes • Eating disorder metrics • Body satisfaction Study period: 1/2018–1/2019 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
California [redacted]			
[redacted] *n = 119 TGNB youths*			
Laurenzano (2021)[84] Descriptive, longitudinal pre-post study Examines endogenous hormone levels, menstrual outcomes, and body changes in transmasculine and gender-diverse adolescents treated with subcutaneous testosterone	All subjects: 119 TNGB patients: 119 **TGNB youths: 119** Transmasculine: 110 OGD: 9	Relevant outcomes • Body and hormone changes Study period: 8/2012–2/2020 Follow-up duration: Up to 5.5 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
California [redacted]			
[redacted] *urology department, n = 1 TGNB youth*			
Adeleye (2023)[469] Case report Examines treatment course and outcomes in a transgender female adolescent with spermatogenesis during hypothalamic suppression and low testosterone	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Semen cryopreservation; fertility Study period: N/R Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
California [redacted]			
[redacted] *n = 60 TGNB youths*			
Ni (2023)[470] Longitudinal, pre-post descriptive study Examining endogenous hormone levels associated with implantable GnRH analog therapy in TGNB adolescents. Only natal sex reported (N = 63 AFAB and N = 40 AMAB).	All subjects: 103 TNGB patients: 103 **TGNB youths: 60**	Relevant outcomes • Utility of biochemical monitoring Study period: 1/2018–3/2021 Follow-up duration: Median 135 days	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Colorado [redacted]			
[redacted] *n = 35 TGNB youths*			
Nokoff (2020)[131] Observational cohort study Cohort study comparing insulin and body composition outcomes between TGNB patients on estradiol or testosterone and cisgender peers	All subjects: 143 TNGB patients: 35 **TGNB youths: 35** Transmasculine: 21 Transfeminine: 14 Cisgender peers/others: 108	Relevant outcomes • Insulin sensitivity • Body composition Study period: 2016–2018 Follow-up duration: N/A	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I.I
Nokoff (2021)[134] Observational study Study comparing insulin sensitivity and glycemic control outcomes between TGNB youths on GnRH analogs and cisgender peers	All subjects: 48 TNGB patients: 17 **TGNB youths: 17** Transmasculine: 9 Transfeminine: 8 Cisgender peers/others: 31	Relevant outcomes • Insulin sensitivity/glycemic control • Body composition Study period: 2016–2019 Follow-up duration: N/A	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I.I
Roy (2023)[146]ClinicalTrials.gov Longitudinal, pre-post descriptive study A research letter reporting findings from a Colorado-based, longitudinal, pre-post study of transgender boys receiving testosterone therapy.	All subjects: 15 TNGB patients: 15 **TGNB youths: 15** Transmasculine: 15	Relevant outcomes • Metabolic changes Study period: 6/2018–8/2019 Follow-up duration: 12 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
[redacted] *n = 220 TGNB youths*			
Alaniz (2023)[471] Longitudinal, pre-post descriptive study Examines time to menstrual suppression in transmasculine and gender expansive youths receiving GAHT, including testosterone	All subjects: 220 TNGB patients: 220 **TGNB youths: 220** Transmasculine: 212 OGD: 8	Relevant outcomes • Time to menstrual suppression Study period: 1/2013–1/2019 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Connecticut [redacted][a]			
[redacted][a] *n = 8 TGNB youths*			
Sayeem (2021)[472] Case series[a] Describes pain and functionality outcomes in TGNB youths with gender dysphoria presenting in a pain clinic	All subjects: 8 TNGB patients: 8 **TGNB youths: 8** Transmasculine: 6 Transfeminine: 2	Relevant outcomes • Pain and functionality Study period: 1/2017–9/2019 Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
				No ethics review, IRB, or consent for research was described
Connecticut [redacted]				
[redacted], *n = 23 TGNB youths*				
Morrison (2020)[473] Descriptive study Cross-sectional survey results about fertility preference in transgender children seen at a university-affiliated clinic.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	23 23 **23** 15 6 2	Relevant outcomes • Fertility preferences Study period: 8/2016–8/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Delaware [redacted]				
[redacted] *n ≥ 133 TGNB youths*				
Schwartz (2022)[474] Observational, cross-sectional study Compares menstrual history and menstrual management methods between transgender males and nonbinary patients	All subjects: TNGB patients: **TGNB youths:** Transmasculine: OGD:	129 129 **129** 116 13	Relevant outcomes • Menstruation, menstrual dysphoria Study period: 3/2015–12/2020 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Schwartz (2023)[475] Longitudinal, pre-post descriptive study Examines menstrual suppression outcomes in transmasculine and gender-diverse adolescents receiving various progestins in a gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transmasculine: OGD:	101 101 **101** 90 11	Relevant outcomes • Menstrual suppression Study period: 3/2015–12/2020 Follow-up duration: 18 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Schwartz (2023)[476] Longitudinal, pre-post descriptive study Examines menstrual suppression outcomes in transmasculine and gender-diverse adolescents receiving various menstrual management treatments in a gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transmasculine: OGD:	133 133 **133** 119 14	Relevant outcomes • Menstrual management methods Study period: 3/2015–12/2020 Follow-up duration: 18 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Georgia [redacted]				
[redacted] *n = 60 TGNB youths*				
Chu (2023)[477] Descriptive study	All subjects: TNGB patients:	60 60	Relevant outcomes • Acne • Predictors of acne	Bibliography only (Appendix I.F)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Examines acne outcomes in transmasculine adolescents receiving testosterone in a pediatric endocrinology clinic	**TGNB youths:** Transmasculine:	**60** 60	Study period: 1/2016–12/2018 Follow-up duration: 24 months	Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Illinois [redacted]				
[redacted] *n ≥ 105 TGNB youths*				
Chen (2017)[478] Descriptive study Examines fertility consultation outcomes in TGNB adolescents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	105 105 **105** 77 28	Relevant outcomes • Fertility preservation utilization Study period: 7/2013–7/2016 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Chen (2018)[479] Case series[a] Examines fertility preservation outcomes in transmasculine youths undergoing oocyte cryopreservation	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	5 5 **3** 5	Relevant outcomes • Fertility preservation Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Kyweluk (2018)[480] Descriptive study A qualitative, descriptive interview study examining ethical considerations related to fertility preservation in TGNB youth and their parents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	18 18 **7** 5 2	Relevant outcomes • Opinions on medical care • Opinions on fertility preservation Study period: 12/2016–8/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Jensen (2019)[60] Observational study[a] Cohort study comparing demographic characteristics, adverse effects, and estrogen/testosterone dosages between transgender patients receiving GnRH analogs versus not	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	83 83 **83** 61 22	Relevant outcomes • GnRH analog efficacy • CSHT doses Study period: 3/2016–1/2018 Follow-up duration: Median 24 or 29 months on or off GnRH analogs, respectively	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Harris (2020)[481] Descriptive study A qualitative, descriptive interview study examining ethical considerations related to fertility preservation in TGNB youth and their parents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	54 35 **35** 24 10	Relevant outcomes • Ethical views of fertility preservation Study period: 12/2016–5/2017	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
	OGD: Parents:	1 19	Follow-up duration: N/A	
Indiana [redacted]				
[redacted], *n = 13 TGNB youths*				
Neyman (2019)[64] Longitudinal, pre-post descriptive study Clinical and laboratory characteristics of transfeminine patients treated with the antiandrogen bicalutamide as an androgen blocker after insurance denials of claims for GnRH analogs	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	13 13 **13** 13	Relevant outcomes • Clinical and lab characteristics • Body changes Study period: N/R Follow-up duration: 29 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Iowa [redacted]				
[redacted] *n = 1 TGNB youth*				
Daniolos (2013)[482] Case report Case report of the clinical findings in one transgender male adolescent	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Mental health Study period: N/R Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Massachusetts [redacted]				
[redacted] *n ≥ 1124 TGNB youths*				
Razzak (2012)[483] Descriptive study A research letter describing the experience of a pediatric gender specialty clinic, and the Tanner stages of children presenting for care. Investigators did not report the affirmed gender of their patients, only natal sex (N = 43 AMAB and N = 54 AFAB).	All subjects: TNGB patients: **TGNB youths:**	97 97 **97**	Relevant outcomes • Mental health • Gender-specific characteristics Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints No ethics review, IRB, or consent for research was described
Spack (2012)[484] Descriptive study	All subjects: TNGB patients: **TGNB youths:**	97 97 **97**	Relevant outcomes • Gender history • Mental health Study period: 1/1998–2/2010	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Reports on characteristics, baseline mental health status, and treatment trajectory of patients with gender dysphoria, including percentages starting CSHT in a pediatric gender specialty clinic. Affirmed genders were not reported, only natal sex (N = 43 AMAB and N = 54 AFAB).		Follow-up duration: N/R	
Shumer (2015)[485] Case report[a] Ethics of assent to treatment in a transgender female patient.	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Ethics of assent • Decision-making Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Millington (2019)[88] Observational cohort study Cohort study examining the risk of hyperkalemia associated with spironolactone in transfeminine or nonbinary adolescents in a pediatric gender specialty clinic	All subjects: 85 TNGB patients: 85 **TGNB youths: 85** Transfeminine: 82 OGD: 3	Relevant outcomes • Risk of hyperkalemia Study period: 2007–2017 Follow-up duration: 7 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Shim (2020)[486] Descriptive study Examining treatment trajectories, risk factors, and endometriosis in transgender males with dysmenorrhea	All subjects: 35 TNGB patients: 35 **TGNB youths: 35** Transmasculine: 35	Relevant outcomes • Risk factors for dysmenorrhea • Menstrual changes after treatment Study period: 1/2000–3/2020 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Grimstad (2021)[81] Observational cohort study Cohort study comparing menstrual suppression outcomes in transgender boys in different GnRH analog and hormone treatment groups. Also makes case-control-type comparisons examining risk factors for breakthrough bleeding in transgender males.	All subjects: 232 TNGB patients: 232 **TGNB youths: 232** Transmasculine: 232	Relevant outcomes • Menstrual suppression • Breakthrough bleeding Study period: 2010–2020 Follow-up duration: N/R	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Grimstad (2021)[487] Case report Hirsutism in a nonbinary, masculine AFAB adolescent	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** OGD: 1	Relevant outcomes • Hirsutism • Response to modified Ferriman-Gallwey (mFG) diagram Study period: N/A Follow-up duration: 12 weeks	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Maru (2021)[128]	All subjects: 1124 TNGB patients: 1124	Relevant outcomes • Risk factors for T1DM	Details of data extraction available in Appendix I.J (TGNB vs TGNB)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
Observational case-control study A case-control study examining risk factors for T1DM, including age at presentation, and hormone therapy.	**TGNB youths:** Transmasculine: Transfeminine: OGD:	**1124** 671 355 98	• Stress Study period: 1/2007–12/2018 Follow-up duration: 12 months	Risk of bias details in Appendix I.I
Millington (2021)[488] Case report A transgender male adolescent on CSHT with a serous borderline ovarian tumor	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Tumor treatment in TGNB population • Cancer risk Study period: N/A Follow-up duration: 6 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Garborcauskas (2022)[489] Observational study Cohort study examining predictors of fertility beliefs and attitudes in testosterone-treated TGNB adolescents ages 15-17 years	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	195 195 **195** 195	Relevant outcomes • Predictors of family planning beliefs and desires Study period: 1/2010–12/2019 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Garborcauskas (2023)[490] Descriptive study Examines characteristics and counseling topics in TGNB adolescents seeking testosterone CSHT	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	195 195 **195** 195	Relevant outcomes • Sexual, gender, and reproductive counseling Study period: 1/2010–12/2019 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Hranilovich (2023)[491] Observational study Cumulative case-control study comparing risks of headache in TGNB patients receiving testosterone/estrogen versus not in a pediatric gender specialty hospital	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	763 763 **763** 490 273	Relevant outcomes • Prevalence of headache with and without CSHT Study period: 2007–2017 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
[redacted] *n ≥ 3 TGNB youths*				
Insogna (2020)[492] Case series Describes fertility-preservation outcomes in transgender males presenting for a fertility consultation. Authors did not report gender identities for most subjects, but all subjects were AFAB.	All subjects: TNGB patients: **TGNB youths:**	27 27 **3+**	Relevant outcomes • Fertility preservation Study period: 1/2016–2/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
[redacted] *n = 1 TGNB youth*			
Turban (2018)[178] Case report A transfeminine child's clinical presentation and treatment with histrelin for puberty suppression at age 15 and estrogen CSHT at age 16	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Body and hormonal changes Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Massachusetts [redacted]			
[redacted] *n = 1 TGNB youth*			
Fan (2020)[493] Case report Venous thromboembolism (VTE) in a transgender male adolescent on testosterone CSHT	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • Risks of VTE Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Michigan [redacted]			
[redacted] *n = 30 TGNB youth*			
Warwick (2022)[494] Descriptive study[a] Qualitative study examining sexual health and education outcomes in transgender adolescents	All subjects: 30 TNGB patients: 30 **TGNB youths: 30** Transmasculine: 18 Transfeminine: 12	Relevant outcomes • Sexual behaviors and education Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Minnesota [redacted]			
[redacted] *n = 2 TGNB youth*			
Parikh (2021)[495] Case series Transgender females undergoing sperm cryopreservation	All subjects: 2 TNGB patients: 2 **TGNB youths: 2** Transfeminine: 2	Relevant outcomes • Sperm cryopreservation Study period: N/A Follow-up duration: N/A	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
			No ethics review, IRB, or consent for research was described
Missouri [redacted]			
[redacted] *n ≥ 47 TGNB youths*			
Allen (2019)[56] Descriptive, longitudinal pre-post study Examines mental health and suicidality outcomes among TGNB adolescents who received GnRH analogs followed by CSHT vs CSHT only	All subjects: 47 TNGB patients: 47 **TGNB youths: 47**	Relevant outcomes • Mental health Study period: 2015–2018 Follow-up duration: Mean of 349 days	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Missouri [redacted]			
[redacted] *n ≥ 67 TGNB youths*			
Lin (2020)[496] Case report A 17-year-old, testosterone-treated transgender male presenting with androgen-receptor positive hepatocellular carcinoma	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • Disease progression Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Komorowski (2021)[497] Observational study Cohort study examining fertility-related outcomes in TGNB adolescents seen in a pediatric endocrinology specialty clinic	All subjects: 67 TNGB patients: 67 **TGNB youths: 67** Transmasculine: 45 Transfeminine: 22	Relevant outcomes • Fertility counselling, referral, and utilization Study period: 1/2012–1/2017 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Martin (2021)[498] Case report Successful oocyte cryopreservation in a transgender male adolescent	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • Fertility preservation Study period: 12/2019–8/2020 Follow-up duration: 8 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
New York [redacted]			
[redacted][a], *n = 2 TGNB youths*			
Salvatore (2022)[499] Case report[a] Anorexia nervosa in transgender females who were ages < 18 years when they first sought treatment, but who were seen for eating disorders in a tertiary care center	All subjects: 2 TNGB patients: 2 **TGNB youths: 2** Transfeminine: 2	Relevant outcomes • Eating disorder outcomes Study period: N/A Follow-up duration: 5 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
New York [redacted]			
[redacted] *n = 1 TGNB youth*			
Bentsianov (2018)[500] Case report[a] A trio of case reports on use of hormones and copper IUDs in transgender young men, including one that was age 17 upon presentation	All subjects: 3 TNGB patients: 3 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • IUD outcomes • Hormonal outcomes Study period: N/A Follow-up duration: up to 24 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *n = 1 TGNB youth*			
Maxwell (2017)[501] Case series A New York-based case series reporting on pregnancy outcomes in 3 transgender men (1 adolescent) who underwent fertility preservation	All subjects: 3 TNGB patients: 3 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Fertility/Pregnancy outcomes Study period: N/A Follow-up duration: 9 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
New York [redacted]			
[redacted] *n = 139 TGNB youths*			
O'Bryan (2018)[174] Descriptive study Examines characteristics (including medication use) in a cohort of TGNB adolescents	All subjects: 139 TNGB patients: 139 **TGNB youths: 139** Transmasculine: 90 Transfeminine: 40 OGD: 9	Relevant outcomes • General health parameters • Quality of life Study period: N/R Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Wolf-Gould (2018)[502] Case report[a]	All subjects: 1 TNGB patients: 1	Relevant outcomes • Risks of BRCA-1 mutation	Bibliography only (Appendix I.F)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Reports on one US-based, transfeminine youth with a BRCA-1 mutation	**TGNB youths:** Transfeminine:	**1** 1	Study period: N/A Follow-up duration: N/R	Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
New York [redacted]				
[redacted], *n = 1 TGNB youth*				
Lee (2022)[503] Case report[a] Acne fulminans in a transgender boy receiving testosterone CSHT	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Acne fulminans Study period: N/A Follow-up duration: 12 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
New York [redacted]				
[redacted], *n = 50 TGNB youth*				
Achille (2020)[55] Observational cohort study Examines the effect of hormonal treatments on mental health outcomes in TGNB adolescents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	50 50 **50** 33 17	Relevant outcomes • Mental health Study period: 12/2013–12/2018 Follow-up duration: 12 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I
Ohio [redacted]				
[redacted], *n ≥ 611 TGNB youths*				
Daley (2019)[504] Descriptive study A qualitative study of pediatric transmasculine patients and their parents, focusing on decision-making around the initiation of GAHT	All subjects: TNGB patients: **TGNB youths:** Transmasculine Parents:	30 17 **17** 17 13	Relevant outcomes • GAHT decision-making Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Kanj (2019)[505] Descriptive study Examines oral contraceptive use in transgender males	All subjects: TNGB patients: **TGNB youths:** Transmasculine	231 231 **231** 231	Relevant outcomes • Menstrual management • Pregnancy prevention Study period: 7/2013–9/2016 Follow-up duration: > 6 months for 60% of subjects	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Mullins (2021)[91] Observational cohort study A cohort study examining thrombosis risk factors and outcomes in TGNB adolescents initiating CSHT	All subjects: 611 TNGB patients: 611 **TGNB youths: 611** Transmasculine: 416 Transfeminine: 176 OGD: 19	Relevant outcomes • Thrombosis risk factors • Thrombosis Study period: 7/2013–3/2019 Follow-up duration: Median 554 days for estrogen, 577 days testosterone	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Nasomyont (2022)[506] Descriptive, longitudinal pre-post study Examines changes in bone marrow adipose tissue among TGNB youths undergoing puberty suppression. Also an observational study comparing findings to controls not undergoing puberty suppression. Only natal sexes were reported (N = 4 AMAB and N = 2 AFAB).	All subjects: 9 TNGB patients: 6 **TGNB youths: 6** Cisgender peers/others: 3	Relevant outcomes • Bone marrow adipose tissue • BMD Study period: N/R Follow-up duration: 12 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Ohio [redacted]			
[redacted], n ≥ 79 TGNB youths			
Nahata (2017)[115] Observational cross-sectional study[a] A cross-sectional study examining mental health and psychosocial outcomes between transgender males and transgender females	All subjects: 79 TNGB patients: 79 **TGNB youths: 79** Transmasculine: 51 Transfeminine: 28	Relevant outcomes • Mental health conditions • Psychosocial metrics Study period: 2014–2016 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Akgül (2019)[507] Observational study Cohort study examining menstrual suppression in transmasculine versus cisgender adolescents	All subjects: 50 TNGB patients: 30 **TGNB youths: 30** Transmasculine: 30 Cisgender peers/others: 20	Relevant outcomes • Menstrual suppression Study period: 6/2014–1/2018 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Grannis (2021)[110] Observational cross-sectional study[a] Compares depression and anxiety severity in treated vs untreated transgender boys	All subjects: 42 TNGB patients: 42 **TGNB youths: 42** Transmasculine: 42	Relevant outcomes • Mental health Study period: 12/2018–3/2020 Follow-up duration: 12 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Valentine (2021)[97] Observational cohort study[a]	All subjects: 124 TNGB patients: 42 **TGNB youths: 42**	Relevant outcomes • Cardiometabolic parameters	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I.I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Cohort study examining cardiometabolic parameters in transgender adolescents receiving testosterone versus cisgender females. The study also compares outcomes between transgender treatment groups.	Transmasculine Cisgender peers/others:	42 82	Study period: 2014–2018 Follow-up duration: Max of 25.7 months	
Morningstar (2023)[114] Observational cross-sectional study[a] Cross-sectional study comparing neural responses to peer and caregiver voices between CSHT-treated or untreated transgender boys.	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	44 44 **44** 44	Relevant outcomes • Hormonal/Neural response to known voices • fMRI results Study period: N/R Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Olsavsky (2023)[116] Observational cross-sectional study[a] A cross-sectional study examining associations between treatments and mental health outcomes among TGNB adolescents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	75 75 **75** 41 28 6	Relevant outcomes • Mental health conditions Study period: 12/2018–3/2020 and 3/2021–2/2022 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I.I
Oklahoma [redacted]				
[redacted] *n = 1 TGNB youth*				
Eisenberg (2019)[508] Case report A transgender male adolescent treated in the rural setting	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Quality of GD medical and mental health care Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Oklahoma [redacted]				
[redacted][a], *n = 118 TGNB youth*				
Lawlis (2017)[509] Observational study[a] A cross-sectional study comparing attitudes about GD drug treatments between TGNB youths and their parents	All subjects: TNGB patients: **TGNB youths:** Parents:	221 118 **118** 103	Relevant outcomes • Frequency and types of health and social concerns Study period: N/R Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Silverstein (2020)[510] Case report[a] A transmasculine adolescent with gender dysphoria and comorbid trichotillomania, depression, and anxiety	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Trichotillomania outcomes • Mental health outcomes Study period: N/A • Follow-up duration: 16 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Oregon [redacted]				
[redacted] *n = 80 TGNB youths*				
Cantu (2020)[74] Descriptive, longitudinal pre-post study Examines changes in anxiety and depression in treated and untreated TGNB youths	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	80 80 **80** 58 15 7	Relevant outcomes • Mental health Study period: 9/2017–6/2019 Follow-up duration: Mean of 20.4 weeks	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Pennsylvania [redacted]				
[redacted] *n ≥ 64*				
Boris (2019)[511] Case series Transgender adolescents presenting with complicated POTS and undergoing hormonal treatment	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	3 3 **3** 3	Relevant outcomes • POTS characteristics on hormonal treatment Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Persky (2020)[512] Descriptive study Survey of characteristics, attitudes, and beliefs about fertility and GAHT in TGNB youth and their parents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD: Parents:	110 64 **64** 37 23 4 46	Relevant outcomes • Fertility attitudes Study period: 4/2017–12/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Quain (2021)[513] Descriptive study	All subjects: TNGB patients: **TGNB youths:** Parents:	141 82 **64** 59	Relevant outcomes • Timing and delivery of fertility information	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
A qualitative, descriptive study examining timing and delivery of fertility preservation information provided to TGNB youths and their parents		Study period: N/R Follow-up duration: N/A	
Hobson (2022)[514] Descriptive study A qualitative study examining patient and parent preferences in TGNB patients with implantable GnRH analogs for puberty suppression. Investigators did not report affirmed gender identities; only natal sex reported (N = 15 AMAB and N = 21 AFAB).	All subjects: 36 TNGB patients: 36 **TGNB youths: 36** Parents: 36	Relevant outcomes • Parent and patient preferences for implantable GnRH analogs Study period: 2/2019–5/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Pennsylvania [redacted]			
[redacted] *n ≥ 7 TGNB youths*			
Stanley (2018)[515] Case report A 17-year-old transgender male presenting with venous thromboembolism	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • VTE events Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Barnard (2019)[163] Case series Reports fertility-preservation outcomes in TGNB patients, including 2 who were < 18 years of age at the fertility preservation consult, 4 who were < 18 at the time of their initial GD consultation, and 7 who were < 18 at the time of GD onset.	All subjects: 10 TNGB patients: 10 **TGNB youths: 7** Transfeminine: 10	Relevant outcomes • Fertility preservation Study period: 1/2015–9/2018 Follow-up duration: 4 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Rhode Island [redacted]			
[redacted], *n = 5 TGNB youths*			
Donaldson (2018)[516] Case series Eating disorders, suicidality, and self-harm behaviors in TGNB cases	All subjects: 5 TNGB patients: 5 **TGNB youths: 5** Transmasculine: 3 Transfeminine: 1 OGD: 1	Relevant outcomes • Eating disorders • Self-harm/Suicidality Study period: 1/2012–1/2017 Follow-up duration: Up to 5 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** Study period	**Disposition in this review**
Texas (Statewide)			
[redacted], *n ≥ 192 TGNB youths*			
Abu-Ghname (2021)[517] Descriptive study Examines GD-related utilization in a cohort of TGNB adolescents seen in a state-managed Medicaid program. Affirmed genders were not reported, only natal sexes (N = 70 AMAB and N = 122 AFAB).	All subjects: 192 TNGB patients: 192 **TGNB youths: 192**	Relevant outcomes • Healthcare utilization for GD Study period: 2013–2018 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Texas [redacted]			
[redacted] *n ≥ 148 TGNB youths*			
Lopez (2016)[518] Case report An adolescent presenting with gender dysphoria	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Mental Health Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Kuper (2020)[141] Longitudinal, pre-post descriptive study Examines changes in body dissatisfaction and mental health (anxiety/depression) among TGNB adolescents receiving puberty suppression and/or CSHT	All subjects: 148 TNGB patients: 148 **TGNB youths: 148** Transmasculine: 90 Transfeminine: 54 OGD: 3	Relevant outcomes • Mental health Study period: 8/2017–3/2018 Follow-up duration: 12 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Dilday (2022)[519] Observational study Cross-sectional study comparing sperm quality outcomes between transgender females vs cisgender males with cancer receiving gonadotoxic therapy	All subjects: 45 TNGB patients: 18 **TGNB youths: 18** Transfeminine: 18 Cisgender peers/others: 27	Relevant outcomes • Sperm quality Study period: 3/2015–3/2020 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Marwa (2022)[87] Observational cohort study Cohort study examining differences in bone density in TGNB patients based on natal sex (N = 46 AMAB and N = 73 AFAB).	All subjects: 119 TNGB patients: 119 **TGNB youths: 119**	Relevant outcomes • Bone mineral density Study period: 6/2014–6/2019 Follow-up duration: N/R	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
[redacted] *n = 30 TGNB youths*				
Mejia-Otero (2021)[520] Observational study Cohort study comparing puberty suppression outcomes in TGNB youth versus youth with CPP	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: Cisgender peers/others:	60 30 **30** 13 17 30	Relevant outcomes • Blood hormonal metrics Study period: 1/2014–6/2018 Follow-up duration: 9 months	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Texas [redacted]				
[redacted][a], *n ≥ 1 TGNB youth*				
Day (2019)[521] Case report[a] A transgender boy presents to an academic emergency department with mental health crisis after detransitioning	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Mental health Study period: N/A Follow-up duration: N/A	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Washington [redacted]				
[redacted] *n ≥ 104 TGNB youths*				
Barthel (2020)[522] Case report A transgender female adolescent cancer survivor with hypogonadism in a pediatric gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	1 1 **1** 1	Relevant outcomes • Hypogonadism • Complications of GD treatment due to comorbidities Study period: N/A Follow-up duration: 10 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Kerman (2021)[523] Descriptive study A qualitative survey study examining fertility attitudes among TGNB children seen in a pediatric gender clinic	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	23 23 **23** 9 10 4	Relevant outcomes • Attitudes towards family and fertility Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Pham (2021)[524] Case series A trio of clinical cases of autistic, transgender, pediatric patients with eating disorders	All subjects: TNGB patients: **TGNB youths:**	3 3 **3**	Relevant outcomes • Eating disorders • Characteristics of presentation	Bibliography only (Appendix I.F)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted]*; CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
	Transmasculine: Transfeminine:	1 2	Study period: 1/2018–1/2019 Follow-up duration: > 2 years	Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Tordoff (2022)[96] Observational cohort study Cohort study examining mental health outcomes (depression/anxiety) in TGNB adolescents and young adults receiving puberty blockers, cross-sex hormones, or both	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	104 104 **104** 63 27 14	Relevant outcomes • Mental health Study period: 8/2017–11/2021 Follow-up duration: 12 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Eitel (2023)[80] Observational cohort study Cohort study comparing hormone levels and puberty suppression outcomes between transgender youths receiving Lupron vs Eligard. Only natal sex was reported (N = 16 AFAB and N = 32 AMAB).	All subjects: TNGB patients: **TGNB youths:**	55 55 **55**	Relevant outcomes • Hormone levels • Puberty suppression Study period: 7/1/2014–Unknown Follow-up duration: > 15 months	Appendix I.J: Observational Study Data Extraction Tables
[redacted]				
[redacted] *n ≥ 68*				
Strang (2018)[525] Descriptive study A qualitative comparison of attitudes about fertility preservation between autistic and allistic TGNB youths	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD: Parents:	51 25 **25** 14 10 1 26	Relevant outcomes • Fertility preservation attitudes Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Strang (2018)[526] Descriptive study[a] A qualitative examination of trajectories and perspectives of children diagnosed with both autism and gender dysphoria	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	22 22 **22** 6 14 2	Relevant outcomes • Critical themes/preoccupations for autistic GD patients Study period: N/R Follow-up duration: 22 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Cohen (2023)[167] Observational study	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	68 68 **68** N/R	Relevant outcomes • Predictors of GD treatment discontinuation Study period: 2010–2021	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.1. Characteristics of N = 118 relevant clinical studies conducted in pediatric TGNB populations in the US, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** Study period	**Disposition in this review**
A case-control study examining potential predictors of GD treatment discontinuation in TGNB adolescents in a gender services program. Only natal sex (29 AMAB and 39 AFAB) and transbinary/nonbinary were reported.	Transfeminine: OGD:	N/R 15	Follow-up duration: Up to 15 years	

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: US, United States; TGNB, transgender, nonbinary, or otherwise gender-diverse; GAHT, gender-affirming hormone therapy; OGD, other gender-diverse; GnRH, gonadotropin releasing hormone; AMAB, assigned male at birth; AFAB, assigned female at birth; GD, gender dysphoria; CPP, central precocious puberty; TRICARE, healthcare payer for US military personnel and their families; CSHT, cross-sex hormone therapy; FEV, forced expiratory volume; CF, cystic fibrosis; PEDSnet, a Clinical Research Network in, the National Patient-Centered Clinical Research Network; DC, District of Columbia; STRONG cohort, Study of Transition, Outcomes, and Gender from [redacted] *CML, chronic myelogenous leukemia; LA, long-acting; IRB, investigational review board; DM, diabetes mellitus; VTE, venous thromboembolism; POTS, postural orthostatic tachycardic syndrome; GENECIS, Children's Health GENder, Education and Care Interdisciplinary Support program*

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
[redacted]			
[redacted] *n ≥ 1766 TGNB youths*			
Wiepjes (2018)[67] Descriptive study First describes [redacted] cohort, adults, adolescents, and children with a GD/TGNB diagnosis and at least one [redacted] visit. Examines temporal trends in diagnosis, treatment, and surgical interventions, as well as reporting on the proportions of subjects who reported regret after gonadectomy	All subjects: 6,793 TNGB patients: 6,793 **TGNB youths: 1,360** Transmasculine: 2,361 Transfeminine: 4,432	Relevant outcomes • GD diagnosis, treatment, and surgical interventions • Regrets Study period: 1972–2015 Follow-up duration: Median of 6.4 years	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
van der Loos (2021)[69] Observational study Reports on bone changes over time in TGNB adolescents seen in a gender specialty clinic. Reports the size of the [redacted] as 8210 patients in 2018, up from 6793 patients in 2015.	All subjects: 322 TNGB patients: 322 **TGNB youths: 322** Transmasculine: 216 Transfeminine: 106	Relevant outcomes • Changes in bone geometry • Subperiosteal width (SPW) • Endocortical diameter (ED) Study period: 1972–2018 Follow-up duration: censored at 12/31/2018	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Boogers (2022)[66] Observational cohort and descriptive, longitudinal pre-post study A cohort study comparing dosages, growth, bone age, IGF-1 levels, and more outcomes among transgender females with different hormone treatments and dosages from a gender specialty clinic	All subjects: 161 TNGB patients: 161 **TGNB youths: 161** Transfeminine: 161	Relevant outcomes • Dosages • Metabolic and growth parameters Study period: 1972–2018 Follow-up duration: "Until adult height was reached"	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
van der Loos (2022)[68] Observational study Cohort study comparing baseline characteristics and continuation rates between transgender males and transgender females in subjects, with and without treatment, from a gender specialty clinic. Only natal sexes were reported: 220 AMAB and 500 AFAB	All subjects: 720 TNGB patients: 720 **TGNB youths: 720**	Relevant outcomes • GAH continuation/discontinuation Study period: 1972–2018 Follow-up duration: censored at 12/31/2018	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
van der Loos (2023)[70] Descriptive study Examines characteristics, treatment trajectories, and temporal trends in TGNB adolescents over 20 years of applying the Dutch protocol in [redacted] clinic. Authors did not specify affirmed gender identities, only natal sex: N = 689 AMAB and N = 1077 AFAB. Reports the size of the [redacted] as 8831 patients in 2018, up from 8210 in previous publication.	All subjects: 1,766 TNGB patients: 1,766 **TGNB youths: 1,766**	Relevant outcomes • Trajectories of adolescents treated with Dutch protocol Study period: 1972–2018 Follow-up duration: censored at 12/31/2018	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Willemsen (2023)[127] Descriptive, longitudinal pre-post study A longitudinal, pre-post descriptive study examining height and weight outcomes in TGNB adolescent boys who initiated GnRH analogs before age 16 years.	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	146 146 **146** 146	Relevant outcomes • Growth, bone age, adult height • Differences among height, predicted height, parental height Study period: 1972–2018 Follow-up duration: censored at 12/31/2018	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Non[redacted] studies *Although these studies do not affiliate with the formal[redacted] as described above, their patient populations, including all TGNB youths, should be counted as nesting in the[redacted] population above. They are counted by study below, but they do not contribute further to the total patients at this[redacted] location.*				
de Vries (2010)[527] Descriptive study Examines the prevalence of autism and autism traits in TGNB children and adolescents. Only natal sex reported: 115 AMAB and 89 AFAB	All subjects: TNGB patients: **TGNB youths:**	204 204 **204**	Relevant outcomes • Autism, autistic traits Study period: 4/2004–10/2007 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
de Vries (2010)[528] Thesis with various study designs, by chapter A PhD thesis comprising studies of gender dysphoria in adolescents.	All subjects: TNGB patients: **TGNB youths:**	Variable Variable **Variable**	Relevant outcomes • Psychological functioning • Treatment outcomes Study period: before 2010 Follow-up duration: Variable	Bibliography only (Appendix I.F) Concurrent/dual publications occur when one study is published in two different publications. Second publications were noted in the bibliography but not extracted.
de Vries (2010)[529] Thesis, Chapter 4 Descriptive study A survey study of children and adolescents referred to a gender identity clinic who received diagnoses of GD and ASD. Only natal sexes were reported: 70 AMAB children, 45 AMAB adolescents, 38 AFAB children, and 51 AFAB adolescents.	All subjects: TNGB patients: **TGNB youths:**	204 204 **182**	Relevant outcomes • Incidence of autism spectrum disorder Study period: 4/2004–10/2007 Follow-up duration: N/A	Bibliography only (Appendix I.F) Concurrent/dual publications occur when one study is published in two different publications. Second publications were noted in the bibliography but not extracted.
de Vries (2010)[530] Thesis, Chapter 5 Observational study A survey study examining psychiatric comorbidity in TGNB adolescents, according to their parents. Only natal sexes were reported for TGNB subjects: 53 AMAB and 52 AFAB.	All subjects: TNGB patients: **TGNB youths:** Parents:	105 105 **105** 105	Relevant outcomes • Psychiatric comorbidities Study period: 4/2002–12/2009 Follow-up duration: N/A	Bibliography only (Appendix I.F) Concurrent/dual publications occur when one study is published in two different publications. Second publications were noted in the bibliography but not extracted.
de Vries (2010)[531] Thesis, Chapter 6 Longitudinal, pre-post descriptive study Compares psychological functioning and gender dysphoria before and after puberty suppression in gender dysphoric adolescents who progress to CSHT. Only natal sexes reported: 33 AMAB and 37 AFAB	All subjects: TNGB patients: **TGNB youths:**	70 70 **70**	Relevant outcomes • Psychological functioning • GD severity Study period: 2000–2008	Bibliography only (Appendix I.F) Concurrent/dual publications occur when one study is published in two different publications. Second

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** **Study period**	**Disposition in this review**
			Follow-up duration: Mean of 1.9 years	publications were noted in the bibliography but not extracted.
de Vries (2010)[78] Thesis, Chapter 7 Descriptive, longitudinal pre-post study Assessed long-term outcome of adolescents with a gender identity disorder (GID), from initial intake at gender identity clinic until post-treatment at least 1 year after gender reassignment surgery.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	27 27 **27** 11 16	Relevant outcomes • Psychological functioning • Psychosocial functioning • GD severity Study period: Follow-up duration: Mean of 7.4 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Cohen-Kettenis (2011[168]) Case report Reports on 22-year outcomes in an adolescent who received puberty suppression	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	1 1 **1** 1	Relevant outcomes • Regret/Satisfaction • Metabolic and endocrine parameters Study period: N/A Follow-up duration: 22 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
de Vries (2011)[106] Observational cross-sectional study A cross-sectional study examining mental health diagnoses among AFAB vs AMAB TGNB adolescents, and between treated vs untreated TGNB patients	All subjects: TNGB patients: **TGNB youths:**	105 105 **105**	Relevant outcomes • Mental Health Study period: 4/2002–12/2009 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
de Vries (2011)[57] Observational cohort study Examines mental health outcomes in TGNB patients treated with GnRH analogs. Only natal sex reported: 33 AMAB and 37 AFAB	All subjects: TNGB patients: **TGNB youths:**	70 70 **70**	Relevant outcomes • Mental health Study period: 2000–2008 Follow-up duration: mean of 3 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Steensma (2011)[532] Descriptive study A interview-based, qualitatively-analyzed descriptive study of desisting or persisting Dutch TGNB adolescents	All subjects: TNGB patients: **TGNB youths:**	25 25 **25**	Relevant outcomes • GD treatment desistance/persistence • Factors influencing desistance/ persistence Study period: 1/2000–1/2007 Follow-up duration: 7-8 years	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
de Vries (2014)[79] Observational cohort study A cohort study examining psychosocial functioning after GnRH analogs for puberty suppression, CSHT, and surgery among TGNB adolescents. Also reports within-group comparisons vs baseline of psychosocial functioning (pre-post descriptive)	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	55 55 **55** 33 22	Relevant outcomes • Psychosocial functioning • Mental health Study period: 2000–2012 Follow-up duration: Mean of 7.1 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
Burke (2015)[133] Observational cross-sectional study A cohort study examining effects of testosterone on fMRI outcomes in TGNB youth vs age- and sex-matched cisgender controls seen in a specialty gender clinic. Only natal sex of TGNB youth was reported: 17 AFAB and 19 AMAB	All subjects: 75 TNGB patients: 36 **TGNB youths: 36** Cisgender peers/others: 39	Relevant outcomes • Hypothalamic activation • fMRI outcomes Study period: N/R Follow-up duration: N/R	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I
Klink (2015)[140] Longitudinal, pre-post descriptive study Examines patient characteristics and bone outcomes over time in GnRH analog- and CSHT-treated adolescents in a gender specialty clinic	All subjects: 34 TNGB patients: 34 **TGNB youths: 34** Transmasculine: 19 Transfeminine: 15	Relevant outcomes • Bone mineral density Study period: 6/1998–8/2012 Follow-up duration: Median of 6.9 years	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Staphorsius (2015)[119] Observational cross-sectional study Cross-sectional study of the impact of GAHT on executive function in TGNB adolescents	All subjects: 41 TNGB patients: 40 **TGNB youths: 40** Transmasculine: 22 Transfeminine: 18 Cisgender peers/others 45	Relevant outcomes • Executive functioning on tasks • Region-of-interest analysis Study period: N/R Follow-up duration: N/R	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I
Burke (2016)[130] Observational cohort study A cohort study examining effects of testosterone on fMRI outcomes in TGNB adolescents vs age- and sex-matched controls	All subjects: 62 TNGB patients: 21 **TGNB youths: 21** Transmasculine: 21 Cisgender peers/others: 41	Relevant outcomes • fMRI outcomes • gender-typical mental rotation task Study period: N/R Follow-up duration: 10 months	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I
Schagen (2016)[148] Longitudinal, pre-post descriptive study Examines growth, body composition, and endogenous hormone levels in TGNB adolescents who received GnRH analogs for 1 year in a gender specialty clinic	All subjects: 116 TNGB patients: 116 **TGNB youths: 116** Transmasculine: 67 Transfeminine: 49	Relevant outcomes • Body changes • Hormone levels Study period: 1988–2009 Follow-up duration: 24 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Hannema (2017)[59] Longitudinal, pre-post descriptive study Examines changes in endogenous hormone levels, anthropometric measures, bone, blood pressure measures among transgender girls treated with estradiol seen in a gender specialty clinic	All subjects: 28 TNGB patients: 28 **TGNB youths: 28** Transfeminine: 28	Relevant outcomes • Hormone levels • Body changes • Bone changes • Blood biomarkers Study period: 1998–2006 Follow-up duration: 3 years	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	Participants		Relevant outcomes Study period	Disposition in this review
Vlot (2017)[99] Longitudinal, pre-post descriptive study Examines bone changes over time with puberty suppression and CSHT in TGNB adolescents in a gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	70 70 **70** 42 28	Relevant outcomes • Bone turnover markers Study period: N/R Follow-up duration: 24 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Klaver (2018)[454] Descriptive, longitudinal pre-post study Examines body composition changes over time in transgender patients who received unspecified GnRH analogs and CSHT	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	192 192 **192** 121 71	Relevant outcomes • Body composition Study period: 1998–2015 Follow-up duration: Mean of 7 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Schagen (2018)[147] Descriptive, longitudinal pre-post study Examines changes in endogenous hormones during puberty suppression and CSHT in adolescents with GD	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	127 127 **127** 73 54	Relevant outcomes • Adrenal androgen levels Study period: 1998–2009 Follow-up duration: 4 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Arnoldussen (2020)[100] Observational cross-sectional study A cohort study examining the association between birth-assigned sex and psychosocial functioning in TGNB adolescents, including 404 AFAB and 668 AMAB youths.	All subjects: TNGB patients: **TGNB youths:**	1072 1072 **1072**	Relevant outcomes • Psychosocial functioning • Demographic, diagnostic, treatment characteristics Study period: 2000–2016 Follow-up duration: Time-trend analysis with reference year of 2016	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Beking (2020)[129] Experimental study Examines the effects of testosterone on amygdala lateralization between transgender boys seen and cisgender boys/girls	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Cisgender peers/others:	62 21 **21** 21 41	Relevant outcomes • Brain development • fMRI outcomes Study period: N/R Follow-up duration: 12 months	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Burke (2020)[533] Observational study A cross-sectional study examining the effect of GnRH analogs and sex hormones on click-evoked otoacoustic emissions in TGNB adolescents. Also compares TGNB adolescents to cisgender peers.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: Cisgender peers/others:	186 105 **105** 62 43 81	Relevant outcomes • Sex differences in click-evoked otoacoustic emissions (CEOAEs) Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Klaver (2020)[139] Longitudinal, pre-post descriptive study	All subjects: TNGB patients: **TGNB youths:**	192 192 **192**	Relevant outcomes • Cardiovascular risk factors • Body composition	Details of data extraction available in Appendix I.L (pre-post comparisons)

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	**Participants**		**Relevant outcomes** **Study period**	**Disposition in this review**
A pre-post descriptive study examining cardiovascular risk factors and body changes in TGNB subjects over time.	Transmasculine: Transfeminine:	121 71	Study period: 1998–2015 Follow-up duration: Mean of 7 years	Risk of bias details in Appendix I
Schagen (2020)[94] Observational cohort study[a] A cohort study comparing bone changes over time for TGNB subjects at different pubertal stages. Also a pre-post descriptive study examining changes over time in TGNB patients. The study was registered with the International Standard Randomized Controlled Trial Number register (ISRCTN 81574253).	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	121 121 **121** 70 51	Relevant outcomes • Bone changes Study period: 1998–2009 Follow-up duration: 36 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Van de Grift (2020)[123] Observational cross-sectional study Compares surgical outcomes between TGNB youths who received early versus late puberty suppression.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	300 300 **300** 184 116	Relevant outcomes • Surgery outcomes Study period: 2006–2013 Follow-up duration: Mean of 8 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Van der Miesen (2020)[124] Observational cross-sectional study A study comparing mental health outcomes in treated versus untreated TGNB adolescents; also compares mental health outcomes between TGNB adolescents and cisgender peers	All subjects: TNGB patients: **TGNB youths:** Cisgender peers/others:	1101 450 **450** 651	Relevant outcomes • Mental health Study period: 2012–2015 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers) Risk of bias details in Appendix I
Arnoldussen (2022)[71] Observational cohort study Examines changes in IQ and educational achievement after puberty suppression with GnRH analogs and CSHT in TGNB adolescents from a gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	72 72 **72** 45 27	Relevant outcomes • IQ • Educational level Study period: Before 2010 Follow-up duration: N/R	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Arnoldussen (2022)[135] Longitudinal, pre-post descriptive study Examines changes in psychosocial outcomes in TGNB adolescents before (while on hormonal treatments only) vs after gender-affirming surgery.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	70 70 **70** 49 21	Relevant outcomes • Psychosocial outcomes Study period: 2000–2013 Follow-up duration: Mean of 6 years	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
de Nie (2022)[534] Observational study A cohort study comparing potential for fertility preservation in transgender women, including adolescents, who initiated cross-sex hormones at different pubertal stages at a gender specialty clinic	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	214 214 **78** 78	Relevant outcomes • Fertility preservation • Histological parameters Study period: 2006–2018 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	Participants	Relevant outcomes Study period	Disposition in this review
[redacted] ***the Netherlands, n = 143***			
Vrouenraets (2016)[451] Descriptive study Examines perceptions and attitudes about gender in transgender youths	All subjects: 13 TNGB patients: 13 **TGNB youths: 13** Transmasculine: 8 Transfeminine: 5	Relevant outcomes • Perceptions and attitudes about gender Study period: 10/2013–8/2014 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Brik (2019)[535] Descriptive study Examines use of fertility preservation among transgender girls	All subjects: 35 TNGB patients: 35 **TGNB youths: 35** Transfeminine: 35	Relevant outcomes • Fertility preservation Study period: 6/2011–8/2017 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Stoffers (2019)[149] Longitudinal, pre-post descriptive study Examines body changes, growth, cardiovascular risk factors, and metabolic outcomes in testosterone-treated adolescents with GD	All subjects: 62 TNGB patients: 62 **TGNB youths: 62** Transmasculine: 62	Relevant outcomes • Body changes/growth • Metabolic biomarkers • Cardiovascular risk factors Study period: 11/2010–8/2018 Follow-up duration: 24 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Brik (2020)[164] Descriptive study Examines GnRH analog treatment trajectories in TGNB adolescents	All subjects: 143 TNGB patients: 143 **TGNB youths: 143** Transmasculine: 105 Transfeminine: 38	Relevant outcomes • Physical, neurocognitive, and psychosocial effects of GD treatment • Persistence/Desistence Study period: 11/2010–12/2017 Follow-up duration: 8.67 years	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Multisite: [redacted] ***N ≥ 36***			
Vrouenraets (2021)[126] Observational cross-sectional study A cross-sectional study examining medical competence and related outcomes in TGNB adolescents. Natal sexes reported only: 16 AMAB and 58 AFAB.	All subjects: 74 TNGB patients: 74 **TGNB youths: 74**	Relevant outcomes • Medical decision-making competence Study period: 2016–2017 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Vrouenraets (2022)[536] Descriptive study A qualitative interview/focus group study of TGNB adolescents who either continued or discontinued treatment, and their parents. TGNB natal sexes reported only: 5 AMAB and 9 AFAB.	All subjects: 26 TNGB patients: 14 **TGNB youths: 14** Parents: 12	Relevant outcomes • Treatment continuation/ discontinuation Study period: 1/2019–9/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.2. Characteristics of N = 43 relevant clinical studies conducted in pediatric TGNB populations in the Netherlands, chronologically by site

Author (Year) Study design Description	**Participants**	**Relevant outcomes** **Study period**	**Disposition in this review**
Vrouenraets (2022)[179] Descriptive study A qualitative study examining perceptions about the function of puberty suppression in TGNB adolescents who continued vs discontinued treatment, their parents, and clinicians. TGNB natal sexes reported only: 5 AMAB and 9 AFAB.	All subjects: 36 TNGB patients: 14 **TGNB youths: 14** Parents: 12 Healthcare providers: 10	Relevant outcomes • Perceptions and attitudes towards puberty suppression • Treatment continuation/ discontinuation Study period: 1/2019–9/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

[a] *Site unconfirmed; inferred from author affiliations.*

Table abbreviations: TGNB, transgender, nonbinary, or otherwise gender-diverse; AMAB, assigned male at birth; AFAB, assigned female at birth; GnRH, gonadotropin releasing-hormone; OGD, other gender-diverse; CSHT, cross-sex hormone therapy; fMRI, functional magnetic resonance imagery; GAHT, gender-affirming hormone therapy; GD, gender dysphoria

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
Multinational: Canada [redacted] and the Netherlands [redacted]				
[redacted] *Canada, n = 177* [redacted] *the Netherlands, n = 139*				
de Vries (2016)[107] Observational cross-sectional study A cross-sectional study examining mental health characteristics of TGNB patients who were referred (ie, for GnRH analog treatment) versus non-referred across 2 clinics. Only natal sexes were reported: 173 AMAB and 143 AFAB	All subjects: TNGB patients: **TGNB youths:**	316 316 **316**	Relevant outcomes • Behavioral, psychosocial, and emotional problems Study period: 1980–2010 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Multinational: Canada [redacted] UK [redacted], and the Netherlands [redacted]				
[redacted], *Canada, n = 260* [redacted] *the Netherlands, n = 266* [redacted] *London, UK, n = 2245*				
De Graaf (2022)[108] Observational cross-sectional study A cross-sectional study examining mental health characteristics of TGNB patients who were referred (ie, for GnRH analog treatment) versus non-referred across 3 clinics. Only natal sexes were reported: 937 AMAB and 1834 AFAB.	All subjects: TNGB patients: **TGNB youths:**	2771 2771 **2771**	Relevant outcomes • Mental health • Suicidality Study period: 1978–2017 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Australia				
[redacted] *South Australia, n = 10*				
Riggs (2020)[537] Descriptive study A qualitative, descriptive interview study that examined the views of TGNB adolescents and their parents about medical treatments.	All subjects: TNGB patients: **TGNB youths:** Transmasculine Transfeminine OGD: Parents:	20 10 **10** 5 4 1 10	Relevant outcomes • Views of GD treatments Study period: 5/2019–7/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
[redacted] *Victoria, n ≥ 39*				
Hewitt (2012)[538,539] Descriptive study plus commentary A descriptive study reporting on characteristics of pediatric TGNB cases and their treatments	All subjects: TNGB patients: **TGNB youths:**	39 39 **39**	Relevant outcomes • GD treatment experience Study period: 2003–2011 Follow-up duration: Max of 8.2 years	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints Commentaries or corrections of included studies did not have their data extracted due to time constraints
Pang (2020)[540]	All subjects: TNGB patients:	1 1	Relevant outcomes • Androgynous appearance	Bibliography only (Appendix I.F)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
Case report A case report describing outcomes in a nonbinary patient receiving long-term puberty suppression	**TGNB youths: 1** OGD: 1	• Mental health • Health risks Study period: N/A Follow-up duration: N/R	Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Pang (2021)[541] Case report A case report of minoxidil use to promote facial hair growth in a transgender male adolescent	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine 1	Relevant outcomes • Facial hair growth Study period: N/A Follow-up duration: 2 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
O'Connell (2022)[542] Case report A pair of case reports, including one transfeminine and one transmasculine adolescent	All subjects: 2 TNGB patients: 2 **TGNB youths: 2** Transmasculine: 1 Transfeminine: 1	Relevant outcomes • Modulating GD treatment towards patient goals Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
[redacted] *Victoria, n ≥ 359*			
Tollit (2023)[120] Observational cross-sectional study An cross-sectional study examining characteristics of AFAB vs AMAB TGNB adolescents, including mental health and psychosocial parameters. Natal genders were reported: 166 AMAB and 193 AFAB.	All subjects: 359 TNGB patients: 359 **TGNB youths: 359** Transmasculine: N/R Transfeminine: N/R OGD: 35 Cisgender peers/others: 4	Relevant outcomes • GD characteristics • Comorbidities • Mental health • Psychosocial functioning Study period: 2007–2016 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Belgium			
[redacted] *Ghent, n = 27*			
Tack (2017)[150] Longitudinal, pre-post descriptive A Belgian pre-post, descriptive study examining growth, cardiovascular risk factors, and metabolic changes in transgender female adolescents taking estrogen with an antiandrogen not available in the US (cyproterone)	All subjects: 27 TNGB patients: 27 **TGNB youths: 27** Transfeminine: 27	Relevant outcomes • Body and metabolic changes • Cardiovascular risk factors Study period: 2008–2016 Follow-up duration: 12 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Canada			
Multisite: [redacted] *n = 35*			
Pullen Sansfaçon (2019)[176] Descriptive study	All subjects: 70 TNGB patients: 35 **TGNB youths: 35**	Relevant outcomes • GD treatment decision-making	Bibliography only (Appendix I.F)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
A Canadian, multi-province, interview-based, qualitative, descriptive study examining the decision and initiation of GD treatment	Transmasculine: Transfeminine: Parents	22 14 35	• GD initiation Study period: 11/2017–8/2018 Follow-up duration: N/A	Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Multisite [redacted] Trans Youth Can!, n ≥ 174				
Bauer (2021)[102] Observational cross-sectional study A Canadian study comparing characteristics and mental health needs between TGNB groups.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	174 174 **174** 137 37	Relevant outcomes • Mental health Study period: 9/2017–6/2019 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Pullen Sansfaçon (2022)[543] Descriptive study A Canada-based, descriptive survey study (Trans Youth CAN!) examining stressors in TGNB adolescents who were referred for puberty suppression and/or hormones and their parents	All subjects: TNGB patients: **TGNB youths:** Parents:	319 160 **160** 159	Relevant outcomes • Psychosocial stressors Study period: 2017–2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
[redacted] *Alberta, n = 33*				
Waldner (2023)[544] Descriptive study A descriptive study examining QTc intervals of TGNB youths on leuprolide acetate	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	33 33 **33** 23 10	Relevant outcomes • Prolonged QTc intervals Study period: 7/2018–12/2019 Follow-up duration: N/R	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
[redacted] *British Columbia, n = 84*				
Khatchadourian (2014)[82] Observational cohort study A Canadian cohort study comparing demographic characteristics, adverse effects, GnRH analog/cross-sex hormone initiation, Tanner stages, and psychiatric comorbidities between MTF and FTM transgender youth.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	84 84 **84** 45 37 2	Relevant outcomes • Treatment regimens • Treatment response • Adverse effects Study period: 1/1998–12/2011 Follow-up duration: Mean of 2.3 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
[redacted] *British Columbia, n = 21*				
Clark (2020)[166] Descriptive study A Canadian descriptive study examining the hormone treatment decision-making process with TGNB adolescents and their parents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD: Parents:	36 21 **21** 8 8 5 15	Relevant outcomes • Treatment decision-making • Barriers to care Study period: 8/2016–2/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
[redacted] *British Columbia, n = 21*			
Clark (2021)[545] Descriptive study A qualitative descriptive study examining aspects of decision-making in TGNB youths	All subjects: 47 TNGB patients: 21 **TGNB youths: 21** Parents: 15 Healthcare providers: 11	Relevant outcomes • Treatment decision-making • Barriers to care Study period: N/R Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
[redacted], *Ontario, n = 1*			
Fung (2021)[546] Case report A [redacted]-based case report of a 17-year-old transgender boy experiencing gynecomastia during ongoing testosterone therapy, after having received puberty suppression	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transmasculine: 1	Relevant outcomes • Gynecomastia outcomes • Breast development Study period: N/A Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *Ontario, n = 172*			
Navabi (2021)[92] Observational cohort study A Canadian cohort study examining baseline and follow-up changes in bone mass, body composition, vitamin D, and pubertal suppression outcomes between transgender male vs female youths who received GnRH analogs. Also a pre-post descriptive study that looked at changes from baseline in each group.	All subjects: 172 TNGB patients: 172 **TGNB youths: 172** Transmasculine: 119 Transfeminine: 51 OGD: 2	Relevant outcomes • Body changes and composition • Pubertal suppression Study period: 1/2006–4/2017 Follow-up duration: 18 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
[redacted] *Ontario, n ≥ 139*			
Zucker (2010)[65] Observational cross-sectional study A cross-sectional study examining correlates of puberty suppressive treatment in treated vs untreated TGNB patients. Only natal sexes were reported: 54 AMAB and 55 AFAB.	All subjects: 109 TNGB patients: 109 **TGNB youths: 109**	Relevant outcomes • Mental and behavioral problems • Psychosexual outcomes Study period: 2000–2009 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Singh (2021)[177] Observational study A cohort study examining changes in gender identity over time among TGNB children who presented for treatment at a pediatric gender identity clinic during childhood. Only natal gender was reported: 139 AMAB.	All subjects: 139 TNGB patients: 139 **TGNB youths: 139**	Relevant outcomes • Cognitive functioning • Gender alignment • Sexual orientation Study period: 1975–2009 Follow-up duration: Mean of 13 years	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
[redacted], *Ontario, n ≥ 300*				
Chiniara (2018)[76] Observational cohort study A study examining mental health in TGNB youth	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	79 79 **79** 60 14 5	Relevant outcomes • Mental health Study period: 1/2014–6/2016 Follow-up duration: up to 30 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Chiniara (2019)[547] Observational study A cross-sectional study of TGNB adolescents and their parents examining fertility- and treatment-related questionnaire responses	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD: Parents:	152 79 **79** 60 14 5 73	Relevant outcomes • Fertility • GD treatment Study period: 10/2016–5/2017 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Sorbara (2020)[118] Observational cross-sectional study A cross-sectional study examining mental health problems in older- versus younger-presenting TGNB adolescents	All subjects: TNGB patients: **TGNB youths:**	300 300 **300**	Relevant outcomes • Mental health Study period: 10/2013–6/2016 and 8/2017 - 6/2018 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
[redacted], *Ontario, n = 1*				
Margolin (2020)[548] Case report A case of a transgender male adolescent with idiopathic intracranial hypertension	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Intracranial hypertension resolution Study period: N/A Follow-up duration: 2 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
[redacted], *Quebec, n = 1*				
Nayman (2021)[549] Case report A case report of intracranial hypertension in a 17-year-old transgender male	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Intracranial hypertension resolution Study period: N/A Follow-up duration: 10 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Finland				
[redacted], *n ≥ 124*				
Vehmas (2022)[125] Observational cross-sectional study	All subjects: TNGB patients:	124 124 **124**	Relevant outcomes	Details of data extraction available in Appendix I.J (TGNB vs TGNB)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
A cross-sectional study examining characteristics of pediatric TGNB patients presenting for treatment.	**TGNB youths:** Transmasculine: Transfeminine:	104 20	• Mental and physical comorbidities • Pubertal development • Psychosocial background Study period: 2011–2018 Follow-up duration: N/R	Risk of bias details in Appendix I
[redacted] *n = 52*				
Kaltiala (2020)[138] Longitudinal pre-post descriptive study A pre-post study examining psychosocial functioning in TGNB adolescents before and after 1-year of CSHT	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	52 52 **52** 41 11	Relevant outcomes • Psychosocial functioning Study period: 2011–2017 Follow-up duration: 1 year	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
France				
[redacted] *n = 4*				
Condat (2016)[550] Case series A French case series reporting on 2 AMAB and 2 AFAB with gender dysphoria. In French.	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	4 4 **4** 4	Relevant outcomes • Gender dysphoria characteristics Study period: N/A Follow-up duration: N/A	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *France, n = 1*				
Martinez (2017)[551] Case report A TGNB parent of 3 children reviews her youth and decision to transition. In French.	All subjects: TNGB patients: **TGNB youths:** Transfeminine:	1 1 **1** 1	Relevant outcomes • Unavailable Study period: N/A Follow-up duration: N/A	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Germany				
Multiple sites [redacted] *n = 82*				
Becker (2018)[103] Observational cross-sectional study A cross-sectional study examining the effect of hormones and GnRH analogs on body image outcomes in TNGB adolescents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	202 202 **82** 62 20	Relevant outcomes • Body image Study period: 9/2013–12/2015 Follow-up duration: N/A	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
[redacted] *n ≥ 22*				
Meyenburg (2014)[552] Case series Reviews treatment course for TGNB youth in a gender identity clinic. In German.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	4 4 **4** 2 2	Relevant outcomes • Unavailable Study period: N/A Follow-up duration: Unavailable	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Meyenburg (2015)[553] Guideline and Descriptive study Survey of prior GD pediatric patients after 3 years, who did or did not transition. In German.	All subjects: TNGB patients: **TGNB youths:**	70 22 **22**	Relevant outcomes • Gender identity outcomes • Psychosocial and mental health Study period: Unavailable Follow-up duration: 3 years	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted
[redacted] *n = 75*				
Becker-Hebly (2021)[72] Observational cohort study A cohort study examining the effect of unspecified GnRH analogs and cross-sex hormone therapy on psychosocial functioning in treated versus untreated TGNB youth. Also contains within-group longitudinal comparisons vs baseline (pre-post descriptive study).	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	75 75 **75** 64 11	Relevant outcomes • Psychosocial functioning Study period: 9/2013–6/2017 Follow-up duration: up to 48 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Nieder (2021)[172] Observational study A cohort study examining patient satisfaction with transition-related care (TRC) over time and with various treatments in adolescents and young adults with a mean age of 17.4 years. Only natal sexes reported: 61 AFAB and 14 AMAB.	All subjects: TNGB patients: **TGNB youths:**	75 75 **75**	Relevant outcomes • GD treatment/care Study period: 9/2013–6/2017 Follow-up duration: 48 months	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
[redacted] *n = 35*				
Pierce (2022)[554] Descriptive study A qualitative, interview survey of TGNB youths and their parents. In German	All subjects: TNGB patients: **TGNB youths:** Parents:	78 35 **35** 43	Relevant outcomes • Unavailable Study period: Unavailable Follow-up duration: Unavailable	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted
Italy				
Multisite: [redacted] *, n = 125*				
Mirabella (2022)[113] Observational cross-sectional study	All subjects: TNGB patients: **TGNB youths:**	125 125 **125**	Relevant outcomes • Gender identity expression	Details of data extraction available in Appendix I.J (TGNB vs TGNB)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
A study examining gender identity changes between AMAB vs AFAB TGNB subjects, and between trans binary vs nonbinary TGNB subjects. Only natal sexes reported: 40 AMAB and 85 AFAB.	Transmasculine: Transfeminine: OGD:	N/R N/R 32	Study period: 4/2019–6/2021 Follow-up duration: N/A	Risk of bias details in Appendix I
[redacted] *n = 2*				
Ristori (2019)[555] Case series A pair of case reports about the occurrence of anorexia nervosa in TGNB adolescents	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine:	2 2 **2** 1 1	Relevant outcomes • Eating disorder outcomes Study period: N/A Follow-up duration: 6 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Poland				
[redacted] *n = 166*				
Gawlik (2022)[556] Descriptive study A survey-based, descriptive study of Polish TGNB young adults with self-reported testosterone and GnRH analog treatment initiation before age 16, before age 18, and current use.	All subjects: TNGB patients: **TGNB youths:** Transmasculine: Transfeminine: OGD:	166 166 **166** 95 34 37	Relevant outcomes • GD treatments • Opinions on GD treatment Study period: 11/2020–12/2021 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Slovenia				
[redacted] *n = 1*				
Zupanič (2021)[557] Case report A case report of a transgender male adolescent with autism	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Mental health • GD treatment Study period: N/A Follow-up duration: 4.5 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Spain				
[redacted] *Spain, n = 1*				
Sanchez Lorenzo (2017)[558] Case report A Spanish clinical case report on the presentation, assessment, findings, and treatment of a 16-year-old transgender boy	All subjects: TNGB patients: **TGNB youths:** Transmasculine:	1 1 **1** 1	Relevant outcomes • Mental health • Body image Study period: N/A Follow-up duration: 2 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *Spain, n = 80*				
Martinez-Martin (2023)[86] Observational cohort study	All subjects: TNGB patients: **TGNB youths:**	302 302 **80**	Relevant outcomes • Blood pressure Study period: 3/2000–3/2020	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
A Spanish cohort study comparing blood pressure outcomes in young transgender patients receiving different hormone therapies, including treatment groups with mean ages < 18 years.		Follow-up duration: 5 years	
[redacted] *Spain, n ≥ 23*			
Campos-Munoz (2018)[559] Case series A pediatric case series reporting on transgender male adolescents presenting with acne (no IRB)	All subjects: 5 TNGB patients: 5 **TGNB youths: 5** Transmasculine: 5	Relevant outcomes • Acne outcomes Study period: 2016–2017 Follow-up duration: Up to 12 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described
Lopez de Lara (2020)[62] Descriptive study Examines psychosocial outcomes in TGNB patients who attend a pediatric endocrinology clinic before and after one-year of cross hormonal therapy (CHT). In Spanish.	All subjects: 53 TNGB patients: 23 **TGNB youths: 23** Cisgender peers/others: 30	Relevant outcomes • Treatment outcomes • Psychosocial outcomes Study period: 2018–2019 Follow-up duration: 1 year	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers), and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
[redacted] *Spain, n ≥ 20*			
Fernandez Rodriguez (2017)[560] Descriptive study A survey of TGNB youth who requested consultation as they presented complaints of gender dysphoria. In Spanish.	All subjects: 20 TNGB patients: 20 **TGNB youths: 20**	Relevant outcomes • Medical history • Mental health history Study period: 3/2007–12/2015 Follow-up duration: N/A	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted
Fernandez (2018)[561] Descriptive study A survey of TGNB youth on their treatment decisions after they presented complaints of gender dysphoria. In Spanish.	All subjects: 20 TNGB patients: 20 **TGNB youths: 20**	Relevant outcomes • GD treatment decisions • Adverse effects Study period: 3/2007–12/2015 Follow-up duration: Unavailable	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted
[redacted] *Spain, n = 1*			
Expösito-Campos (2022)[169] Case report Two case reports of Spanish transgender patients presenting for medical detransition, one of whom was an AMAB adolescent	All subjects: 2 TNGB patients: 2 **TGNB youths: 1**	Relevant outcomes • Reasons for detransition Study period: N/A Follow-up duration: 2 years	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
Switzerland			
[redacted] *Switzerland, n = 1*			
Rebetez (2014)[562]	All subjects: 1 TNGB patients: 1	Relevant outcomes	Bibliography only (Appendix I.F)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
Case report A TGNB youth discusses her transition. In French.	**TGNB youths: 1** Transfeminine 1	• Unavailable Study period: N/A Follow-up duration: N/A	Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *n = 51*			
Pauli (2020)[563] Descriptive study. In German. A pre-post follow up study of adolescents presenting with GD at a gender specialty clinic. In German.	All subjects: 51 TNGB patients: 51 **TGNB youths: 51**	Relevant outcomes • Mental health • GD severity • Treatment decisions Study period: 2014–onward Follow-up duration: at least 1 year	Bibliography only (Appendix I.F) Despite having abstracts in English that obviously met inclusion criteria, non-English language studies could not have their data extracted
United Kingdom (UK)			
Multisite [redacted] England, Wales, and Ireland, n ≥ 668			
Costa (2015)[77] Observational cohort study A [redacted]-based cohort study examining mental health changes in TGNB adolescents, including a comparison between transgender males vs transgender females treated with unspecified GnRH analogs according to the WPATH guideline. Only natal sexes were reported: 76 AMAB and 125 AFAB adolescents. They also looked at changes over time within groups.	All subjects: 201 TNGB patients: 201 **TGNB youths: 201**	Relevant outcomes • Mental health Study period: 2010–2014 Follow-up duration: 18 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB), Appendix I.K (TGNB vs cisgender peers), and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Carmichael (2021)[73] Descriptive, longitudinal pre-post study A [redacted]-based pre-post descriptive study examining short-term (ie, 1-3 years) bone and psychosocial outcomes in TGNB youths ages 12-15 years who received GnRH analog monotherapy. Only natal sexes were reported: 25 AMAB and 19 AFAB	All subjects: 44 TNGB patients: 44 **TGNB youths: 44**	Relevant outcomes • Bone outcomes • Psychosocial outcomes Study period: 6/2011–4/2014 Follow-up duration: 48 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Masic (2022)[170] Descriptive study A [redacted]-based descriptive study examining treatment trajectories in TGNB adolescents referred for treatment with GnRH analogs and cross-sex hormones. Only natal sexes were reported: N = 227 AMAB and N = 441 AFAB.	All subjects: 668 TNGB patients: 668 **TGNB youths: 668**	Relevant outcomes • GD treatment trajectories Study period: 1/2017–12/2019 Follow-up duration: 2017-onward	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Lavender (2023)[142] Longitudinal pre-post descriptive study	All subjects: 38 TNGB patients: 38 **TGNB youths: 38**	Relevant outcomes • Mental health Study period: 2014–10/2021	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
A[redacted] based, pre-post, descriptive study examining changes in mental health and suicidality for TGNB youths after initiating unspecified GnRH analogs and CSHT. Only natal sexes were reported: N = 28 AFAB and N = 10 AMAB.		Follow-up duration: 2 years	
Multisite: England, Northern Ireland, Scotland, and Wales, n ≥ 360			
Rogers (2021)[564] Observational study A database, cohort study examining predictors of gamete storage in TGNB patients from the UK, including adolescents at the time of the study	All subjects: 3667 TNGB patients: 3667 **TGNB youths: 360**	Relevant outcomes • Fertility preservation • Reasons for fertility decisions Study period: 6/2015–4/2020 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
Multisite: [redacted] *England, n = 980*			
Butler (2022)[165] Descriptive study A descriptive study examining gender identities of TGNB adolescents after discharge from 2 English children's hospitals for GD-related treatments. Only natal genders were reported: 329 AMAB and 651 AFAB adolescents < 18 years.	All subjects: 1089 TNGB patients: 1089 **TGNB youths: 980**	Relevant outcomes • Gender identity decisions post-discharge Study period: 2008–2021 Follow-up duration: up to age 18	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints
Indeterminate site: [redacted] *England, n = 95*			
Russell (2021)[565] Longitudinal pre-post descriptive study A[redacted]-based pre-post descriptive study examining autism-related characteristics before and after 1 year of GnRH analog therapy in TGNB adolescents with autism. Only natal sexes were reported: 38 AMAB and 57 AFAB.	All subjects: 97 TNGB patients: 97 **TGNB youths: 95**	Relevant outcomes • Social responsiveness scores (see **Appendix I.H**) Study period: N/R Follow-up duration: 1 year	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
[redacted] *England, n = 12*			
Churcher Clarke (2019)[566] Case series A case series reporting on TGNB patients seen in the[redacted]	All subjects: 12 TNGB patients: 12 **TGNB youths: 12** Transmasculine: 6 Transfeminine: 3 OGD: 3	Relevant outcomes • Desistance • Reasons for desistance Study period: 10/2015–4/2017 Follow-up duration: 18 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *England, n ≥ 36*			
Joseph (2019)[137] Longitudinal pre-post descriptive study A[redacted] based pre-post descriptive study examining bone outcomes in TGNB adolescents treated with GnRH analogs	All subjects: 31 TNGB patients: 31 **TGNB youths: 31** Transmasculine: 21 Transfeminine: 10	Relevant outcomes • Bone outcomes Study period: 2011–2016 Follow-up duration: 3 years	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Ghelani (2020)[58] Longitudinal pre-post descriptive study	All subjects: 36 TNGB patients: 36 **TGNB youths: 36**	Relevant outcomes • Body composition	Details of data extraction available in Appendix I.L (pre-post comparisons)

Return to TOC

Table I.G.3. Characteristics of N = 60 relevant clinical studies conducted in pediatric TGNB populations in Canada, Australia, the United Kingdom, and Europe, chronologically by site

Author (Year) Study design Description	Participants		Relevant Outcomes	Disposition in this Review
A[redacted] based study examining body composition changes in TGNB adolescents receiving triptorelin for puberty suppression	Transmasculine: Transfeminine:	25 11	Study period: 2013–2015 Follow-up duration: 12 months	Risk of bias details in Appendix I
[redacted] *Scotland, n ≥ 91*				
Gilani (2021)[567] Observational study A Scotland-based, cross-sectional, survey study examining sports participation and motivation levels in TGNB adolescents treated with GnRH analogs, including a subset who were treated with CSHT. Only natal sex was reported: N = 39 AFAB and N = 16 AMAB.	All subjects: TNGB patients: **TGNB youths:**	55 55 **55**	Relevant outcomes • Sports/Physical activity participation • Barriers to participation Study period: 6/2019–10/2019 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
McCallion (2021)[171] Descriptive study A Scotland-based descriptive study of characteristics of pediatric TGNB patients referred to a pediatric gender care clinic. Only natal sexes were reported: 59 AFAB and 32 AMAB.	All subjects: TNGB patients: **TGNB youths:**	91 91 **91**	Relevant outcomes • Endocrine medical care • Pubertal-early adulthood and treatment trajectory Study period: 2011–2019 Follow-up duration: 18 months	Bibliography only (Appendix I.F) Studies that did not make one of our three highest-priority comparisons did not have data extracted due to time constraints

Return to TOC

Table I.G.4. Characteristics of N = 9 relevant, English-language clinical studies conducted in other pediatric TGNB populations, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
Brazil			
[redacted] *Brazil, n = 1*			
Schneider (2017)[442] Case report Describes brain maturation, cognition, and voice pattern in a patient with GD receiving GnRH analog therapy for puberty suppression	All subjects: 1 TNGB patients: 1 **TGNB youths: 1** Transfeminine: 1	Relevant outcomes • Brain and cognition development • Vocal development Study period: N/A Follow-up duration: 28 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
7 municipalities in [redacted] *Brazil, n = 28*			
Maschião (2020)[568] Observational study A cross-sectional/case -control study examining risk factors for use of non-prescribed sex hormones in transgender females	All subjects: 616 TNGB patients: 616 **TGNB youths: 28** Transfeminine: 28	Relevant outcomes • Risk factors for non-prescribed GD treatment Study period: 2014–2015 Follow-up duration: N/A	Bibliography only (Appendix I.F) Studies that did not evaluate our high-priority outcomes did not have data extracted due to time constraints
[redacted] *Brazil, n = 15*			
Alvares (2022)[132] Observational cross-sectional study A cross-sectional study comparing cardiopulmonary capacity and muscle strength (ie, determinants of physical performance) in Brazilian transgender women versus cisgender men and women, none of whom were athletes	All subjects: 42 TNGB patients: 15 **TGNB youths: 15** Transfeminine: 15 Cisgender peers/others: 27	Relevant outcomes • Cardiopulmonary capacity • Muscle strength Study period: N/R Follow-up duration: N/A	Details of data extraction available in Appendix I.K (TGNB vs cisgender peers) and Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Israel			
[redacted] *Israel, n = 106*			
Segev-Becker (2020)[117] Observational cross-sectional study Examines mental health and behavioral outcomes in transgender boys vs girls	All subjects: 106 TNGB patients: 106 **TGNB youths: 106** Transmasculine: 59 Transfeminine: 47	Relevant outcomes • Mental health • Behavioral outcomes Study period: 3/2013–12/2018 Follow-up duration: Max of 5.1 years	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
Perl (2020)[144] Longitudinal, pre-post descriptive study Examines blood pressure outcomes in transgender males receiving puberty-suppressing GnRH analogs, followed by CSHT for 9 of them	All subjects: 15 TNGB patients: 15 **TGNB youths: 15** Transmasculine: 15	Relevant outcomes • Blood pressure Study period: 2013–2018 Follow-up duration: Mean of 7 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I

Return to TOC

Table I.G.4. Characteristics of N = 9 relevant, English-language clinical studies conducted in other pediatric TGNB populations, chronologically by site

Author (Year) Study design Description	Participants	Relevant Outcomes	Disposition in this Review
Perl (2021)[145] Longitudinal, pre-post descriptive study Examines blood pressure, weight, and hormone levels in transfeminine adolescents who received GnRH analogs for puberty suppression, 15 of whom went on to receive CSHT with estradiol	All subjects: 19 TNGB patients: 19 **TGNB youths: 19** Transfeminine: 19	Relevant outcomes • Blood pressure • Hormone biomarkers • Body weight Study period: 2/2013–12/2020 Follow-up duration: Max of 63 months	Details of data extraction available in Appendix I.L (pre-post comparisons) Risk of bias details in Appendix I
Turkey			
[redacted], *Turkey, n = 4*			
Akgül (2022)[569] Case series Reports on use of GnRH analogs for menstrual suppression in Turkish gender minority youth	All subjects: 4 TNGB patients: 4 **TGNB youths: 4** Transmasculine: 3 ONB: 1	Relevant outcomes • Menstrual suppression Study period: 9/2018–5/2020 Follow-up duration: N/R	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints
[redacted] *Turkey, n = 30*			
Karakilic Ozturan (2023)[112] Observational cross-sectional study Examines body changes and endogenous hormone levels in TGNB adolescents	All subjects: 30 TNGB patients: 30 **TGNB youths: 30** Transmasculine: 15 Transfeminine: 15	Relevant outcomes • Body changes • Hormone levels Study period: 2016–2022 Follow-up duration: Max of 45 months	Details of data extraction available in Appendix I.J (TGNB vs TGNB) Risk of bias details in Appendix I
[redacted] *Turkey, n = 2*			
Cesur (2022)[570] Case report A pair of case reports of Turkish, transgender adolescents with long-term follow-up	All subjects: 2 TNGB patients: 2 **TGNB youths: 2** Transmasculine: 1 Transfeminine: 1	Relevant outcomes • Gender identity trajectory • Response to puberty suppression Study period: N/A Follow-up duration: 35 months	Bibliography only (Appendix I.F) Case reports and series do not contain high-priority comparisons and therefore did not have data extracted, due to time constraints No ethics review, IRB, or consent for research was described

Return to TOC

APPENDIX I.H: MENTAL HEALTH ASESSMENT TOOLS USED IN INCLUDED CLINICAL STUDIES

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
ASR	Adult Self-report	The Adult Self-Report (ASR), a component of the ASEBA, is specifically designed to assess psychopathology in individuals aged 18 to 59. Ratings of problem items are summed to yield scores on eight statistically derived narrow-band syndrome scales (e.g., Anxious/Depressed), three broad-band scales (Internalizing, Externalizing, and Total Problems), six DSM-oriented scales, as well as a Friends and Spouse/Partner scale. The ASR is utilized for self-assessment.	Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003[455] Used by de Vries et al. 2014[79]
ASQ	Ask Question-Screening Questions	A questionnaire is used to assess suicidality.	Horowitz, L. M., Bridge, J. A., Teach, S. J., Ballard, E., Klima, J., Rosenstein, D. L., . . . Pao, M. (2012). Ask Suicide-Screening Questions (ASQ): A brief instrument for the pediatric emergency department. Archives of Pediatrics & Adolescent Medicine, 166, 1170–1176.[456] Used by Allen et al. 2019[56]
BDI-(Y)	Beck Depression Inventory-for youth	20-item questionnaire used to measure used to assess presence and severity of depressive symptoms in youth. Each item was rated on a 4- point scale. Scores were summed and compared to standardized cutoffs reflecting minimal, mild, moderate, or severe depression.	Beck JS, Beck AT, Jolly JB. Beck youth inventories, 2nd edition. San Antonio (TX): Pearson Assessments; 2005.[457] Used by Chen et al. 2021[104]
BDI-II	Beck Depression Inventory-II	21-item questionnaire used to measure depression. Each item was rated on a 4-point scale, summed and compared to standardized cutoffs reflecting minimal (0-13), mild (14-19), moderate (20-28), or severe depression symptoms (29-63).	Beck, et al. Manual for Beck Depression Inventory-II. 1996.[458] Used in Chen et al. 2023[75]
BES	Body Esteem Scale for Adolescents	22-item questionnaire with items that assess general perceptions about appearance (“I’m pretty happy with the way I look.”), weight (“I am satisfied with my weight.”), and how others view one’s body or appearance (“Young people my age like my looks.”). Each item was rated on a 4-point	Mendelson BK, Mendelson MJ, White DR. Body-esteem scale for adolescents and adults. Journal of Personality

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
		scale and summed, with higher scores indicating greater body esteem.	Assessment. 2001;76(1):90–106. [PubMed: 11206302][459] Used by Chen et al. 2021[104]
BIS	Body Image Scale	Tool is designed to assess body imaging or dissatisfaction. 30-item self-report measure assessing BIS or dissatisfaction. Thirty body features are listed, and satisfaction is rated on a 5-point Likert scale. A total score and three subscale scores for primary sexual characteristics, secondary sexual characteristics (both of which are affected by sex hormones), and "neutral" characteristics are calculated. Higher scores represent more body dissatisfaction	Lindgren and Pauly. A body image scale for evaluating transsexuals. *Arch Sex Behav.* 1975;4(6):639–656.[460] Used in Lavender et al. 2023[142], and Grannis et al. 2021[110]
CESD-R	Center for Epidemiologic Studies Depression Scale	20-item questionnaire with scores ranging from 0 to 60. Individual items are scored on a 4-level scale that ranges from 0 (for "Not at all or less than one day") to 3 (for "5-7 days" and/or "nearly every day for 2 weeks"). A total CESD-R score less than 16 implies no clinical depression.	Eaton, et al. Center for Epidemiologic Studies Depression Scale: Review and Revision (CESD and CESD-R). In: *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment: Instruments for Adults, Vol. 3*. 3rd ed. Lawrence Erlbaum Associates Publishers; 2004:363–77.[461] Haroz, et al. Psychometric evaluation of a self-report scale to measure adolescent depression: the CESDR-10 in two national adolescent samples in the United States. *J Affect Disord*. 2014;158:154-160.[462]
CBCL	Child Behavior Checklist	Tool is designed as a parent report as a general measure of psychological functioning. Part of ASEBA (www.aseba.org). 112-item caregiver-reported measures of psychological and behavioral functioning of young people. Generated scores reflect six DSM-V orientated categories: Depressive, Anxiety, Somatic, Attention Deficit/Hyperactivity, Oppositional Defiant, and Conduct problems. Internalizing	Crijnen, et al. Comparisons of problems reported by parents of children in 12 cultures: Total problems, externalizing, and internalizing. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1269–1277.[463]

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
		behaviors (such as depression and anxiety) and externalizing behaviors (such as aggression and conduct issues) are measured.	Achenbach System of Empirically Based Assessment (ASEBA). Updated 2022. Available at https://aseba.org/[455] Used in Lavender et al. 2023[142]
CGAS	Children's Global Assessment Tool	Used to assess adolescent's global functioning via clinician's reports. Designed to measure how children and adolescents' function in daily life and can be used to assess psychosocial/psychiatric outcomes, socio-cognitive competence, and changes due to interventions. It is divided into 10-point intervals from 10 to 100, with higher scores (above 80) indicating good global functioning.	Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983;40(11): 1228–1231[464] Used by de Vries et al. 2014[79]
CDI	Children's Depression Inventory	Children's depression inventory-The CDI consists of 27 items rated from 0-2; the clinical cutoff suggestive of depression is a sum of 20 or higher.	Figueras Masip A, Amador-Campos JA, Gómez-Benito J, del Barrio Gándara V. Psychometric properties of the Children's Depression Inventory in community and clinical sample. Span J Psychol 2010;13:990e9.[465] Used in Olsavsky et al. 2023[116] Kovacs, M., 1985. The children's depression inventory (CDI). Psychopharmacol. Bull. 21 (4), 995–998.[466] Used by Grannis et al. 2021[110]
C-SSRS	Columbia Suicide Severity Rating Scale	Questions used to assess suicidal ideation	Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266e77.[467] Used in Olsavsky et al. 2023[116]
CD-RISC	Connor-Davidson Resilience Scale	The Connor-Davidson Resilience Scale is a test that measures resilience or how well one is equipped to bounce back after stressful events, tragedy, or trauma. Resilience gives us the ability to thrive in the face of adversity	Neyer et al. Validity, Reliability, and Differential Item Functioning of English and French Versions of the 10-Item Connor-Davidson Resilience Scale in Systemic

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
			Sclerosis: A Scleroderma Patient-Centered Intervention Network Cohort Study. Arthritis Care Res. 2023.[468]
N/A	Draw -a-person test	Draw-a-Person test-after each youth had drawn a house and a tree, he or she was asked to "draw a person" and to identify its sex. The youth was then asked to draw a person of the sex opposite to that of the first drawing.	Bieliauskas, V. J. (1960). Sexual identification in children's drawings of human figure. *Journal of Clinical Psychology*, *16*, 42–44.[469] Used by Zucker et al. 2012[470]
EDE-Q	Eating Disorder Examination Questionnaire	Tool is designed to assess eating disorder-related psychopathology in TGNB subjects.	(1) Fairburn CG, Beglin SJ. Assessment of eating disorders: Interview of self-report questionnaire? Int J Eat Disord 1994; 16:363-70.[471] (2) Berg KC, Peterson CB, Frazier P, Crow SJ. Psychometric evaluation of the eating disorder examination and eating disorder examination-questionnaire: A systematic review of the literature. Int J Eat Disord 2012;45:428e38.[472] (3) Swenne I. Changes and predictive value for treatment outcome of the compulsive exercise test (CET) during a family-based intervention for adolescents eating disorders. BMC Psychol 2018;6:55.[473] All used by Avila et al. 2019[101]
EROS	Erotic Response and Orientation Scale	Erotic Response and Orientation Scale-a 16-item self-report measure assessing sexual orientation in fantasy over the past six months. Half of the questions pertained to heterosexual fantasy (e.g., for females, "How often have you had any sexual feelings (even the slightest) while looking at a boy?") and the other half pertained to homosexual fantasy (e.g., for females, "How often have you had any sexual feelings (even the slightest) while looking at a girl?"). Each item was rated on a 5-point scale for frequency of occurrence, ranging from "none" to "almost every day."	Storms, M. D. (1980). Theories of sexual orientation. Journal of Personality and Social Psychology, 38, 783–792.[474] Used by Zucker et al. 2012[470]
FBeK	"Fragebofen zur Beurteilung des eisenen	The FBeK is one of the most frequently used multidimensional body questionnaires in the German	Dahne A, Assmann B, Ettrich C, Hinz A. [Norm values for the questionnaire to assess the own body (Fragebogen

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
	Körpers" (Body image assessment questionnaire)	language, providing an assessment of body experience that is especially relevant to the study of the importance of body image in clinical samples. It is a self-report measure with response options of either 1 ("I agree") or 0 ("I disagree").	zur Beurteilung des eigenen Korpers, FBeK) for adolescents]. Prax Kinderpsychol Kinderpsychiatr. 2004;53(7):483-496.[475] Used by Becker et al. 2018[103]
GIQ-Ad	Gender Identity Questionnaire for Adolescents	Gender Identity Questionnaire for Adolescents -13- item parent-report questionnaire pertaining to various aspects of concurrent sex-typed behavior (e.g., sex-of-peer affiliation preference, masculine vs. feminine interests, cross-dressing, the desire to be of the other sex). Eleven of the items were rated on a 5-point scale (e.g., from "never" to "every day"), one item was rated on a 4-point scale, and one item was calculated as a difference score based on the number of male versus female close friends.	Johnson LL, Bradley SJ, Birkenfeld-Adams AS, Kuksis MA, Maing DM, Mitchell JN, Zucker KJ. A parent-report gender identity questionnaire for children. Arch Sex Behav. 2004;33(2):105-116. doi:10.1023/b:aseb.0000014325.68094.f3[476]
GIDYQ	Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults	Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults -Item content was based on prior measures, expert panels, and clinical experience. There are parallel versions for males and females. Each item was rated on a 5-point response scale ranging from Never to Always based on a time frame of the past 12 months. Item examples include: "In the past 12 months, have you felt unhappy about being a boy?" and "In the past 12 months, have you wished to have an operation to change your body into a man's (e.g., to have your breasts removed or to have a penis made)?" Participants' GIDYQ total score was calculated by summing scores on the completed items and dividing by the number of marked responses.	Deogracias, J. J., Johnson, L. L., Meyer-Bahlburg, H. F. L., Kessler, S. J., Schober, J. M., & Zucker, K. J. (2007). The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults. Journal of Sex Research, 44, 370–379.[477] Used by Zucker et al. 2012[470]
GMSR-A	Gender Minority Stress and Resilience Measures for Adolescents	This tool assesses social stigma and psychosocial resilience related to gender minority identity. The GMSR-A is comprised of nine subscales, six of which were employed in this study. Included were four minority stress subscales (i.e., gender identity non-affirmation; internalized	Hidalgo MA, Petras H, Chen D, Chodzen G. The Gender Minority Stress and Resilience Measure: Psychometric validity of an adolescent extension. Clinical Practice in

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
		transphobia; negative expectations for the future; non-disclosure of gender identity/history) and two resilience subscales (i.e., pride in being a gender minority individual; community connectedness). Items were rated on a 5-point scale. Sample items include "People don't respect my gender identity because of my appearance or body" (non-affirmation), "If I express my gender history, I could be a victim of crime or violence" (non-disclosure), "It is a gift that my gender identity is different from my designated sex at birth" (pride), and "I feel connected to other people who share my gender identity" (community connectedness). Subscale item responses are summed, with higher scores indicating greater minority stress or resilience.	Pediatric Psychology. 2019;7(3):278–290. [PubMed: 33224698][478] Used by Chen et al. 2021[104] and Conn et al. 2023[105]
GAD-7	General Anxiety Disorder-7	Designated to assess anxiety symptoms, 7-item screening measure of anxiety. Items are rated on a 4-point scale for how often each symptom has occurred in the past 2 weeks from 0 (Not at All) to 3 (Nearly Every Day).	Lowe, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med Care*. 2008; 46:266–274.[479] Used in Cantu et al. 2020[74]
GWBS	General Well-being Schedule	A questionnaire used to assess psychological well-being.	Fazio AF. A concurrent validational study of the NCHS General Well-Being Schedule. Vital Health Stat 2. 1977, (73):1-53. https://www.ncbi.nlm.nih.gov/pubmed/610049[480] Used by Allen et al. 2019[56]
SPPA	Harter Self Perception Profile for Adolescents	The SPPA is an instrument designed to measure an adolescent's overall self-esteem and feelings of competence in eight specific domains, namely: scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, romantic appeal, job competence and close friendship	Van den Bergh BR, Van Ranst N. Self-concept in children: equivalence of measurement and structure across gender and grade of Harter's Self-Perception Profile for Children. J Pers Assess. 1998;70(3):564-582. doi:10.1207/s15327752jpa7003_13[481] Used by Durwood et al. 2017[109]

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
K6	Kessler Psychological Distress Scale	The Kessler Psychological Distress Scale (K6) is a simple measure of psychological distress which involves 6 questions about a person's emotional state. Each question is scored from 0 (None of the time) to 4 (All of the time).	Kessler RC, Green JG, Gruber MJ, Sampson NA, Bromet E, Cuitan M, et al. Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative. International journal of methods in psychiatric research. 2010; 19(01):4.[482] Used by Turban et al. 2022[122]
(n/a)	KIDSCREEN-27	Youth self-report tool to assess health related quality of life. Includes 5 subscales.	Ravens-Sieberer U, Herdman M, Devine J, Otto C, Bullinger M, Rose M, Klasen F (2014) The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. Qual Life Res 23:791–803.[483] Used by Becker-Hebly et al. 2021[72]
LSAS	Liebowitz Social Anxiety Scale	Standardized self-reported measure to assess social anxiety	Mennin DS, Fresco DM, Heimberg RG, Schneier FR, Davies SO, Liebowitz MR. Screening for social anxiety disorder in the clinical setting: using the Liebowitz Social Anxiety Scale. J Anxiety Disord. 2002;16(6):661-673. doi:10.1016/s0887-6185(02)00134-2.[484] Used by Grannis et al. 2021[110]
MDS	Modified Depression Scale	The MDS is a self-administered six-item scale designed to assess the frequency of depressive symptoms (e.g., sadness, irritability, hopelessness, sleep disturbance, and concentration difficulties) among adolescents.	Dunn EC, Johnson RM, Green JG. The Modified Depression Scale (MDS): A Brief, No-Cost Assessment Tool to Estimate the Level of Depressive Symptoms in Students and Schools. School Ment Health. 2012;4(1):34-45. doi:10.1007/s12310-011-9066-5[485]
MSPSS	Multi-dimensional Scale of Perceived Social Support	Multi-dimensional Scale of Perceived Social Support The MSPSS assessed support from: (1) family (4 items), (2) friends (4 items), and (3) significant others (4 items). Scores ranged from 1e 7 (1e2.9 1⁄4 low support; 3e4.9 1⁄4 moderate support; 5.1e7 1⁄4 high support). Notably, the	Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the Multidimensional Scale of Perceived Social Support. J Pers Assess. 1990;55(3-4):610-617.

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
		significant other subscale refers to one special individual such as a spouse/partner, friend, professional, or other family member, whereas the family and friend subscales asked participants to describe support from these general categories (with family being open to interpretation, e.g., legal, bio- logical, and/or chosen)	doi:10.1080/00223891.1990.9674095 https://www.ncbi.nlm.nih.gov/pubmed/2280326.[486] Used by Olsavsky 2023
(n/a)	NIH Toolbox-Emotional Battery	Tool used to assess different emotions. Participants are asked to rate how frequently they experienced a variety of positive feelings over the past seven days. Each item was rated on a 5-point scale from 1 = "not at all" to 5 = "very much"; higher scores indicate greater positive affect. Participants are asked to rate how much they agree or disagree with statements about their personal well-being." Each item is rated on a 5-point scale from "strongly disagree" to "strongly agree"; higher scores indicate greater life satisfaction.	Slotkin, et al. NIH Toolbox Scoring And Interpretation Guide. National Institutes of Health. 2012[487] Used in Chen et al. 2023[75], and Chen et al. 2021[104]
OASIS	Overall Anxiety Severity and Impairment Scale	The OASIS is a 5-item measure that assesses frequency of anxiety, intensity of anxiety symptoms, behavioral avoidance, and functional impairment associated with anxiety	Campbell-Sills L, Norman SB, Craske MG, et al. Validation of a brief measure of anxiety-related severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). J Affect Disord. 2009;112(1-3):92-101. doi:10.1016/j.jad.2008.03.014[488]
PHQ-9	Patient Health Questionnaire Modified for Teens	9-item questionnaire for depressive symptoms with scores ranging from 0 to 27. Individual items are scored on a 4-level scale that ranges from 0 (for minimal) to 3 (severe). PHQ-9 scores are interpreted as follows: Minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). The item also has 4 additional questions related to suicide ideation and life problems.	Richardson, et al. Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. *Pediatrics*. 2010;126(6):1117–1123.[489]

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
PROMIS	Patient Reported Outcomes Measurement Information System	There are 3 PROMIS negative affect item banks, consisting of Depression (28 items), Anxiety (29 items), and Anger (29 items). The items in the PROMIS negative affect banks use a 7-day time frame and a 5-point rating scale that ranges from 1 (“Never”) to 5 (“Always”) The questions are used to measure levels of negative affect across its observed continuum.	Irwin DE, Stucky B, Langer MM, et al. An item response analysis of the pediatric PROMIS anxiety and depressive symptoms scales. Qual Life Res. 2010;19:595-607[490] Used by Chen et al. 2021[104] and Durwood et al. 2017[109]
QLES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire	15-item questionnaire for quality of life and enjoyment with scores ranging from 15 to 75. Individual items are scored on a 5-level scale that ranges from 1 (poor) to 5 (very good).	Endicott, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: A new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.[491]
QIDS	Quick Inventory of Depressive Symptoms	Tool is designed to assess depression-related symptoms. Measures symptoms of depression that reflect the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for major depressive disorder. It produces a total score that can also be grouped into clinical categories: not elevated (0–5), mild (6–10), moderate (11–15), and severe (16–27). Clinicians also completed the clinician version of the QIDS.	Rush, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.[492] Used in Kuper et al. 2020[141]
RCGI	Recalled Childhood Gender Identity/Role Questionnaire	Recalled Childhood Gender Identity/Gender Role Questionnaire-a 23-item questionnaire pertaining to various aspects of sex-typed behavior as well as relative closeness to mother and father during childhood. Items were rated on a 5-point response scale.	Veale JF. Factorial Validity and Invariance Assessment of a Short Version of the Recalled Childhood Gender Identity/Role Questionnaire. Arch Sex Behav. 2016;45(3):537-550. doi:10.1007/s10508-015-0684-0 https://www.ncbi.nlm.nih.gov/pubmed/26864871[493] Used by Zucker et al. 2012[470]
RCMAS2	Revised Children's Manifest Anxiety Scale	This tool is designed to assess anxiety. Forty-nine items were rated "yes"/ "no". "Yes" responses were tallied and transformed into a T score; for this scale T scores > 60 are considered clinically significant	Reynolds and Richmond. Revised Children's Manifest Anxiety Scale, 2nd ed. Last updated 2008. Available at https://www.wpspublish.com.[494] Used in Chen et al. 2023[75]

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
SWLS	Satisfaction with Life Scale	The Satisfaction With Life Scale (SWLS) is a five-item self-report instrument intended to assess the respondent's overall life satisfaction (sometimes referred to as global satisfaction)	Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess. 1985 Feb;49(1):71–5.[495] Used by de Vries 2010, chapter 7[78]
SCARED	Screen for Child Anxiety Related Emotional Disorders	Tool is designed to assess anxiety-related symptoms. Produces a total score as well as subscale scores for panic-related, social, separation-related, generalized, and school avoidance–related anxiety symptoms	Birmaher, et al. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): A replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230–1236.[496] Used in Kuper et al. 2020[141], Olsavsky et al. 2023,[116] Grannis et al. 2021[110]
(n/a)	Self-harm Index	Self-harm actions and thoughts were assessed through two questions in each of the CBCL (parent report) and YSR (self-report): Item 18 (I deliberately try to hurt or kill myself) and Item 91 (I think about killing myself). Possible responses for each question were 0 = not true, 1 = somewhat or sometimes true, or 2 = very true or often true. The index was calculated as the sum of the two items in each scale to create an index from 0 to 4 for each of the CBCL and YSR [30–32], a higher score indicating greater self-harm thoughts and behavior.	Aitken, et al. Self-Harm and Suicidality in Children Referred for Gender Dysphoria. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):513–520.[497] Van Meter, et al. Assessing for suicidal behavior in youth using the Achenbach System of Empirically Based Assessment. *Eur Child Adolesc Psychiatry*. 2018;27(2):159–169.[498] Deutz, et al. The Dysregulation Profile in middle childhood and adolescence across reporters: factor structure, measurement invariance, and links with self-harm and suicidal ideation. *Eur Child Adolesc Psychiatry*. 2016;25(4):431–442.[499] All used in Carmichael et al. 2021[73]
SHQ	Sexual History Questionnaire	Sexual History Questionnaire-a 20-item self-report measure assessing sexual orientation in behavior	Langevin, R. (1985). Sexual strands: Understanding and treating sexual anomalies in men. New York: Routledge.[500] Used in Zucker 2012[470]

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
SRS-2	Social Responsiveness Scale-Second Edition	65-item, Likert-scale, caregiver-completed measure of symptoms associated with autistic traits. A total score provides a severity index for social difficulties in the autism spectrum. Subscale scores for social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior are generated.	
TPI	Spielberger's Trait Anger Expression Inventory	Administered to assess the tendency to respond with anger to a threatening or annoying situation. (Scale ranges from 1-4)	Azevedo FB, Wang YP, Goulart AC, Lotufo PA, Bensenor IM. Application of the Spielberger's State-Trait Anger Expression Inventory in clinical patients. Arq Neuropsiquiatr. 2010;68(2):231-234. doi:10.1590/s0004-282x2010000200015[501] Used by de Vries et al. 2011[57] and de Vries et al. 2014[79]
STAI	Spielberger's Trait Anxiety Scale	Administered to assess the tendency to respond with anxiety to a threatening or annoying situation. (Scale ranges from 1-4)	Carey MP, Faulstich ME, Carey TC. Assessment of anxiety in adolescents: concurrent and factorial validities of the Trait Anxiety scale of Spielberger's State-Trait Anxiety Inventory for Children. *Psychol Rep*. 1994;75(1 Pt 1):331-338.[502] Used by de Vries et al. 2011[57] and de Vries et al. 2014[79]
SBQ-R	Suicide Behaviors Questionnaire-Revised	The SBQ-R generates a score between 3 and 18, with higher scores reflecting higher risk for suicide. The score is then collapsed into one of two categories: a score of 3-6 reflects a negative screening for suicide risk, and a score of 7-18 reflects a positive screening for suicide risk.	Osman A, Bagge CL, Gutierrez PM, et al. The Suicidal Behaviors questionnaire-revised (SBQ-R): Validation with clinical and nonclinical samples. Assessment 2001;8:443e54.[503] Used in Olsavsky et al. 2023[116] and Grannis et al. 2021[110]
TCS	Transgender Congruence Scale	Scale to measure appearance congruence. Each item was rated on a 5-point scale from "strongly disagree" to "strongly agree" and averaged. Higher scores reflect greater appearance congruence.	Kozee HB, Tylka TL, Bauerband LA. Measuring transgender individuals' comfort with gender identity and appearance: Development and validation of the transgender congruence scale. Psychol Women Q. 2012;36(2):179-196.[504] Used by Chen et al. 2023[75] and Chen et al. 2021[104]

Return to TOC

Table I.H.1. Psychological assessment tools utilized in included studies

Acronym	Tool	Description	Citations
UGDS/UGS	Utrecht Gender Dysphoria Scale	Tool is designed to assess gender related distress. 12- item, 5-point Likert-scale, self-report measure assessing gender-related distress in over 12 seconds, which is specific to gender assigned at birth.	Steensma TD, Kreukels BP, Jurgensen M, Thyen U, De Vries AL, Cohen-Kettenis PT. The Utrecht Gender Dysphoria Scale: a validation study. Arch Sex Behav. Provisionally accepted Used by de Vries et al. 2014[79]
WISC	Wechsler Intelligence Scale for Children	The Wechsler Intelligence Scale for Children (WISC) is an IQ test and assesses cognitive abilities in children between the ages of 6 and 16 years old.	Canivez GL, Watkins MW, Dombrowski SC. Structural validity of the Wechsler Intelligence Scale for Children-Fifth Edition: Confirmatory factor analyses with the 16 primary and secondary subtests. Psychol Assess. 2017;29(4):458-472. doi:10.1037/pas0000358[505] Used by de Vries et al. 2011[57]
WHO-QOL-Brief	World Health Organization Quality of Life-Brief	The WHO-QOL-Brief comprises 24 questions that belong to one of four domains (Physical Health, Psychological Health, Social Relationships, and Environment), and two questions on overall quality of life and general health. The questions have a 5-point Likert scale. Higher scores indicate a better quality of life.	Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BRIEF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004 Mar;13(2):299–310.[506] Used by de Vries 2010[78]
YSR	Youth Self Report	Tool is designed as a self-report for youth as a general measure of psychological functioning. Part of ASEBA (www.aseba.org). 112-item self-reported measures of psychological and behavioral functioning of young people. Generated scores reflect six DSM-V orientated categories: Depressive, Anxiety, Somatic, Attention Deficit/Hyperactivity, Oppositional Defiant, and Conduct problems. Internalizing behaviors (such as depression and anxiety) and externalizing behaviors (such as aggression and conduct issues) are measured.	Verhulst, et al. Comparisons of problems reported by youths from seven countries. *Am J Psychiatry*. 2003;160(8):1479–1485.[507] Used in Carmichael et al. 2021[73] Achenbach System of Empirically Based Assessment (ASEBA). Updated 2022. Available at https://aseba.org/[455] Used in Lavender et al. 2023[142]

Return to TOC

APPENDIX I.I: RISK OF BIAS ANALYSIS OF EXTRACTED INCLUDED CLINICAL STUDIES

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Achille (2020)[55]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average pediatric TGNB subject seen in a US-based academic endocrine gender dysphoria clinic	While the sample is representative for patients who persist with treatment at the same clinic for at least 12 months and who are willing to complete questionnaires, the sample only included 50 out of 116 possible participants. That suggests that the eligibility criteria were restrictive.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	For the puberty suppression comparison, there were very few untreated MTF participants (N = 2)
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They had clinic records from which to determine whether participants had received the interventions, although they did not specify that it was their information source. They also did not specify that medication exposures were included on the questionnaires that were used to assess outcomes, so I am left to conclude that they used clinic data for exposures.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	They ensured that exposures preceded outcomes, but they did not report the durations of the different treatments at each outcome measurement point.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	They specified that regression analyses controlled for baseline measures for each outcome, psychiatric medication, and engagement in psychotherapy, but they did not specify that models controlled for age. Because of the small sample size, it is possible that they did not. They used stratification to control for sex. They only controlled for 1 of 2 key factors.
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Outcomes were measured at 12 months; however, we do not know when treatments were initiated. Not all participants initiated treatments at baseline.
	Attrition	☆	a) complete follow up - all subjects accounted for	Restricting to subjects who completed all 3 questionnaires means that there was no attrition, but this does introduce selection bias.
Allen (2019)[56]	**Selection**			
	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	Participants were recruited at the Children's Mercy Hospital Gender Pathway Services (GPS) clinic.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants in different groups were recruited from the same clinic.
	Ascertainment of exposure		d) no description	No clear description of how they obtained participants' medication history.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not clearly stated but looks like they did retrospective review.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Not adjusted for age, but assess AFAB vs. AMAB and adjusted for duration of treatment
	Outcome			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome assessment		c) self-report	The data was collected from self-reported questionnaire responses.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	The range of treatment length was 113-1016 days (M = 349, SD = 193). For most of the sample (90%), the duration of treatment was at, or under, 600 days. It means that for some participants, treatment length between two assessments was less than 6 months, but the median treatment was just around a year.
	Attrition	☆	a) complete follow up - all subjects accounted for	Participants were included if they had pretest and final assessment data points.
Arnoldussen (2022)[71]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average adolescent seeking GD treatment at the Center of Expertise on GD in the Netherlands	72 out of 119 eligible adolescents participated
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	b) structured interview	
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	IQ taken at initial assessment, gender affirming treatment given, then educational achievement was assessed.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	They looked at externalizing variables at start of treatment.
	Outcome			
	Outcome assessment		c) self-report	Participants completed a survey.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up occurred around 8 years after initial assessment
	Attrition	☆	a) complete follow up - all subjects accounted for	Based on data in results section, all patients are included in analysis
Becker-Hebly (2021)[72]	**Selection**			
	Representativeness of the exposed cohort		c) selected group of TGNB youth in the Hamburg gender identity service	Almost half of the participants at entry either dropped out during baseline or were excluded and there was further drop out during follow-up with only 37% responding to questionnaires. Sex ratio changed at each step, so sample isn't fully representative of available participants. Also, further exclusion data was introduced when patients were not included for not completing a questionnaire. There is a high probability of selection bias.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcomes were checked again at follow-up.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	They looked at the raw analysis only
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up was at least six months to 4 years; average was 2 years.
	Attrition	☆	a) complete follow up - all subjects accounted for	Data only presented for those that completed the follow-up.
Boogers (2022)[66]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in the Center of Expertise on Gender Dysphoria from Amsterdam	Large retrospective clinical data set was used. Inclusion and exclusion criteria not specified.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	These patients were all seen at the Center of Expertise on Gender Dysphoria from Amsterdam.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medical records were utilized.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	All comparisons had specific timing.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) Study controlled for any additional factor	They did subgroup analyses to somewhat adjust for baseline characteristics.
	Outcome			
	Outcome assessment	☆	b) record linkage	Measurements were performed at center.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	
	Attrition	☆	a) complete follow up - all subjects accounted for	All data was collected retrospectively
Carmichael (2021)[73]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average	small sample size

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

			TGNB subject taking GnRH analog monotherapy being seen by the GIDS	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were referred to the GIDS
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All patients were starting GnRH analog monotherapy
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study divided some data by Tanner stage at baseline and gender
	Outcome			
	Outcome assessment		b) record linkage	BMD was ascertained by clinic visit, but YSR and CGAS were self-report by validated questionnaires
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	This particular comparison was made after 12 months of GnRH analog therapy
	Attrition	☆	a) complete follow up - all subjects accounted for	For this follow-up-all patients were accounted for
Cantu (2020)[74]	**Selection**			
	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	Participants were recruited from an academic medical center in the Northwestern United States between September 2017 and June 2019. Unsure how many were identified and how many were excluded.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants on different treatments were recruited from the same center.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medical chart was reviewed retrospectively to collect medical interventions.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article but they reviewed the chart retrospectively.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	There were no statistical adjustments.
	Outcome			
	Outcome assessment		c) self-report	PHQ-9 and GAD-7 were reported by participants to assess the mental health outcomes.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	The mean (SD) follow-up time in weeks was 20.4 (10.2).
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	A total of 80 subjects were included in analysis. All of them (N = 80) completed PHQ-9 screeners at both time points and N = 78 completed GAD-7 screeners at both timepoints.
Chen (2023)[75]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average Transgender and nonbinary youth presenting to pediatric subspecialty gender programs	Study mentioned that they felt it was generalizable to the entire population although they were overrepresented in transmasculine, non-Latin white and multiracial whereas nonbinary and black participants were underrepresented
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were recruited the same way and divided into subgroups
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Recruited from gender clinics and specifically recruited if initiating GAH
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Trajectories were examined with the use of repeated-measures multivariate analysis of variance and mixed-effect models were used. Covariates included baseline age, designated sex at birth, racial and ethnic identity and early gender-affirming care.
	Outcome			
	Outcome assessment		c) self-report	Participants completed various validated instruments to assess psychosocial functioning.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Measurements were taken at baseline and after 6, 12, 18 and 24 months
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Data was available for 81% of all possible observations over the period of 24 months, with 238 participants (75.6%) competing all 4 visits and 162 participants completing all 5. The analytic sample did not differ substantially from the overall sample.
Chiniara (2018)[76]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Transgender participants were recruited from the Transgender Youth Clinic at The Hospital for Sick Children, Toronto, with their initial visits between January 2014 and June 2016.	Adolescents who did not follow up at the clinic after the first visit were excluded (n = 12). Three adolescents had their initial visit for gender dysphoria at another center and were excluded from this analysis because of missing data.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	AFAB and AMAB participants were recruited from the same transgender clinic.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Use of medications was collected in medical records.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article but they did review retrospectively.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	The study used only univariable tests and there was no statistical adjustment.
	Outcome			
	Outcome assessment	☆	b) record linkage	In a subset of individuals, blood testing was repeated to measure lipid profile and other laboratory data while receiving gender-affirming hormones (after 6–12 months) according to the initial 2009 Endocrine Society guidelines.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Blood testing was repeated to measure lipid profile and other laboratory data while receiving gender-affirming hormones (after 6–12 months).
	Attrition		c) Follow-up loss rate ≥ 5% and no description of those lost	Follow-up lipid profile was only obtained in AFAB (n = 8) and AMAB (n = 4), although n = 156 assigned female and n = 47 assigned male were enrolled in the study.
Costa (2015)[77]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth in the Gender identity development service in London	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Drawn from medical center; not made clear.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcomes were checked again at follow-up with baseline information provided.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	Delayed eligible and immediately eligible would be inherently different.
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up was at 18 months.
	Attrition		c) Follow-up rate ≥ 5% and no description of those lost	When looking at longer follow-up times, the number decreased, but this was not made clear why.
De Vries (2010)[78]	**Selection**			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth from the Amsterdam gender identity clinic of the VU University Medical Center (VUmc).	140 of 196 consecutively referred adolescents were considered eligible for medical intervention between 2000 and 2008 at the clinic.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants in different groups were recruited from the same clinic.
	Ascertainment of exposure		d) no description	No clear description of how they obtained participants' medication history.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not clearly stated but it's a prospective cohort study design.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	Not adjusted for age, but assessed MTFs vs. FTMs
	Outcome			
	Outcome assessment		c) self-report	The data was collected from self-reported questionnaire responses.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Post-treatment was assessed at least 1 year after the treatment
	Attrition	☆	a) complete follow up - all subjects accounted for	A total of 140 adolescents were eligible and 27 were included in analysis. Among 27 included in the analysis, not all of the participants had post-T data for analysis, so only data of adolescents who were administered questionnaires on both assessments could be used for Pre-T/Post-T comparisons (CBCL: 24, IQ: 25, UGS: 21 and BIS: 22).
de Vries (2011)[57]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB adolescent in the Amsterdam gender identity clinic of the VUmc	Some who entered the study did not complete the diagnostic procedures, thereby introducing some selection bias.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Follow-up evaluations done by provider determined if patient was qualified to continue.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcomes were checked again at follow-up with baseline information provided.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Sex was included as a between-subject variable
	Outcome			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	Done when started on puberty suppression
	Attrition		c) Follow-up rate ≥ 5% and no description of those lost	Only a portion finished the questionnaires.
de Vries (2014)[79]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB adolescent in the Amsterdam gender identity clinic of the VUMC	Adolescents belonged to a group of consecutively referred adolescent, and then determined to be considered eligible for medical intervention.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Drawn from medical center
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcomes were checked again at follow-up with baseline information provided.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Gender was addressed.
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up was done at 1 year.
	Attrition		c) Follow-up rate ≥ 5% and no description of those lost	Only a portion finished the questionnaires.
Eitel (2023)[80]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average Subjects with a diagnosis of gender dysphoria receiving leuprolide in the Seattle Children's Gender Clinic	58 charts were reviewed and 48 patients met inclusion criteria with 55 incidents of 1hr Post levels
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from the same community as exposed group - subjects with a diagnosis of gender dysphoria receiving leuprolide in the Seattle Children's Gender Clinic
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Collected via an electronic health record data pull. A chart review of clinician notes, laboratory values, and medications was conducted to identify baseline Tanner stage and laboratory values within 6 months of leuprolide initiation, evidence of clinical puberty progression, leuprolide formulation and dosing, 1hrPost LH and sex steroid level, and other medications including hormone replacement therapy and menstrual suppression

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Retrospective chart review done
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	Does not mention any controls in the article
	Outcome			
	Outcome assessment	☆	b) record linkage	Clinical records and self-reported outcome were both assessed.
	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	Does not mention it clearly in the article, but does provide some follow-up data for some subjects
	Attrition	☆	a) Complete follow-up – all patients accounted for	All patient follow-up accounted for primary objective. One patient lost for further follow-up information.
Grimstad (2021)[81]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB adolescents AFAB or intersex at a Gender Multispecialty Service (GeMS) at Boston Children's Hospital.	Retrospective cohort identified from patients at the hospital who met inclusion criteria
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	They were all seen at the same center, which have the same protocols and similar practices.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medical records were utilized.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Presence or lack of bleeding had to be confirmed with the medical records.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	The analysis was raw, no adjustments were made. Since this is observational, there may be a lot of confounders that were not addressed.
	Outcome			
	Outcome assessment	☆	b) record linkage	This was pulled directly from the medical records.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Patients were on CSHT for at least one year.
	Attrition	☆	a) Complete follow-up – all patients accounted for	Missing data was only for 5 patients, and they were already removed.
	Selection			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Khatchadourian (2014)[82]	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB subjects from a Canadian -based academic adolescent gender dysphoria clinic	All patients that met the broad eligibility criteria were included in the cohort. It was a small sample size, but represents those who visited the clinic during 1998 to 2011.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All patients were sampled in the same manner. Comparator groups were drawn from the same population.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	data was extracted from clinic notes following visits.
	Outcome temporality requirements		b) no, study was not designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	For both items of comparison, there was no exclusion criteria that stated that patients could not have come into the study with those conditions. The aim of the study was to understand the population.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	Descriptive statistics were used and the Fisher exact test was used to determine if differences were significant. No statistical or methodology controlling for confounding was done.
	Outcome			
	Outcome assessment	☆	a) independent blind assessment	Determined via clinic notes
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Followed patients from that attended clinic from 1998 to 2011. Median follow up time for patients was 2.3 years.
	Attrition	☆	a) complete follow up - all subjects accounted for	Number of subjects is consistent throughout the study.
Klaver (2018)[83]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in the Netherlands that started hormone treatment before turning 18	It's most likely that not all TGNB youth in the Netherlands were treated according to the Dutch protocol -- therefore, the results from this study are only applicable to those that have been treated with it. All participants got care at the VU University Medical Center in Amsterdam.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were treated at the VU University Medical Center in Amsterdam.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Investigators determined when participants started hormone treatment by examining the medical records of all adolescents diagnosed with gender dysphoria at the VU University Medical Center in Amsterdam.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Measurements for each of the outcomes were taken when participants started GnRH analogs, when they added CSHT, and at 22 years old, after treatment with both.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Participants were matched to their comparators based on natal sex. Participants were not matched based on age.
	Outcome			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome assessment	☆	b) record linkage	Investigators determined outcome values by retrospectively reviewing participants' medical records.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	All participants started hormone therapy before the age of 18, and final outcomes were determined when they turned 22.
	Attrition		c) Follow-up loss rate ≥ 5% and no description of those lost	Anthropometric data were missing for 11% of MTF and 18% of FTM for the start of GnRH analogs, 10% of MTF and 13% of FTM for the start of CHT, and 71% of MTF and 76% for the visit at 22 years of age. Data from measurements of body composition determined by whole-body dual-energy x-ray absorptiometry (DXA) were missing for 12% of MTF and 11% of FTM for the start of GnRH analogs, 36% of MTF and 45% of FTM for the start of CHT, and 64% of MTF and 65% of FTM for the visit at 22 years of age. These high values indicate significant attrition/confounding bias, but authors said that the missing data were missing at random and that analyses between people with missing data vs. not did not indicate bias. They also said that their statistical analysis using linear mixed model regression "properly deal(s) with missing data."
Laurenzano (2021)[84]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of transmasculine youth in a US based gender clinic	This study included all participants that met the criteria to begin T therapy.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Same sampling methods for exposed and comparator
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medication was given at their clinic
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcome include those without additional menstrual suppression
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	study did not control for any confounding factors
	Outcome			
	Outcome assessment		c) self-report	This information was most likely collect via patient at the clinic
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	
Lee (2020)[85]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth in four Children's hospitals (Children's Hospital Los Angeles, Lurie Children's Hospital, Boston Children's Hospital, and	TGNB patients who met criteria were prospectively enrolled from the 4 study sites.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

			University of California San Francisco Benioff Children's Hospital)	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Pretreatment and post-treatment scores were analyzed
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Results were stratified by sex designated at birth or whether low BMD was present. Patient characteristics were compared among the 4 sites using ANOVA.
	Outcome			
	Outcome assessment	☆	b) record linkage	
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	
	Attrition		c) Follow-up rate loss ≥ 5% and no description of those lost	After initial eligibility, patients were excluded for not being assessed within the baseline time period, not getting their DXA or QCT done, and because they were at Tanner stage 4 of puberty.
Martinez-Martin (2023)[86]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Outpatient Gender Identity Clinic since its opening in March 2000	Most patients who are treated with estradiol plus LHRH analogs were previously treated with LHRH analogs as a puberty suppressor, and typically start estradiol therapy shortly after their 16th birthday, thus earlier than most other patients. Cyproterone acetate is banned in the US.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from the same community as exposed group - a local Outpatient Gender Identity Clinic (not in the US)
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Clinical records were retrospectively reviewed
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specify in the article
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	For risk difference in incidence of HTN, adjusted for perceived gender, age and calendar year at the onset of gender-affirming hormonal therapy, changes in body weight, fasting plasma glucose, creatinine, LDL-cholesterol and triglycerides
	Outcome			
	Outcome assessment	☆	b) record linkage	SBP and diagnosis of HTN were obtained from clinical records.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	They explored a 5-yr follow up.
	Attrition		c) Follow-up rate loss ≥ 5% and no description of those lost	Out of 811 records, 168 were lost to follow-up before completing 5 years of therapy
Marwa (2022)[87]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youths from a multidisciplinary gender affirming clinic in Dallas, Texas, between June 2014 and June 2019	314 patient records were retrospectively reviewed but only 119 patients were included in the analysis
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	TGD youths were selected from a multidisciplinary gender affirming clinic in Dallas, Texas, between June 2014 and June 2019
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They reviewed electronic medical records of children and adolescents evaluated in a multidisciplinary gender-affirming clinic
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article but they did review retrospectively.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Baseline characteristics were collected and included in a multilinear regression model to assess determinants of LS BMD Z-scores adjusted for age and height and accounting for race.
	Outcome			
	Outcome assessment	☆	b) record linkage	Dual energy X-ray absorptiometry was used to assess BMD.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	DXA scans of the LS are performed at baseline and every 1–2 years as part of standard of care guidelines in all patients being started on puberty suppression and/or gender-affirming hormone therapy. Patients were included if they had had a baseline scan within 180 days of starting therapy, and had a follow-up scan done.
	Attrition	☆	a) complete follow up - all subjects accounted for	All patients who met inclusion criteria and were not excluded were included in the analysis.
Millington (2019)[88]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average subjects recruited from the Gender Management Service Program at Boston Children's Hospital from 2007 to 2017. Patients who were prescribed spironolactone for the purposes of gender transition were included in the analysis.	90 gender-diverse adolescents were prescribed spironolactone during the study period, however, only a total of 85 subjects were included in the analysis.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Subjects recruited from the same hospital were compared based on different doses of spironolactone.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They reviewed the chart retrospectively.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article but they did review retrospectively.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	There were no statistical adjustments.
	Outcome			
	Outcome assessment	☆	b) record linkage	Not clearly stated in the article but it looks like they did medical chart review to identify potassium measurements.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	36 subjects (42%) had at least one potassium measurement within the first 3 months of spironolactone therapy, and 48 subjects (56%) had a measurement within the first 6 months. Potassium measurements were available for up to 7 years of spironolactone therapy.
	Attrition	☆	a) complete follow up - all subjects accounted for	A total of 90 subjects were identified and 3 subjects without follow-up measurements were excluded. Then, after excluding subjects for other reasons, a total of 85 were included in analysis (all of them had follow up measurements.)
Millington (2021)[89]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average GD adolescents being seen in large academic medical centers	No information on how many people were eligible vs. how many participated, but a large sample size was included.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Same cohort was compared against each other.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All participants recruited from medical centers
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Youth were recruited prior to initiating GAH
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Data was separated by male and female at birth and then separated by those with and without obesity, also looked at age, race and tobacco as modifiers
	Outcome			
	Outcome assessment	☆	b) record linkage	Noted the laboratory data was collected as part of clinical care as baseline; imagine this would located in the chart.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Lipid levels were taken at six months.
	Attrition		d) No information about attrition	
Millington (2022)[90]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average	Eligible patients from gender clinics that consented to the study were included

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

			transgender youth attending gender clinics in the USA	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	sample population
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Taken from medical record
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Patients were recruited before starting GAH treatment
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study adjusted for age, and adjusted/compared the measurements from trans youth to both male and female peers
	Outcome			
	Outcome assessment	☆	b) record linkage	Laboratory measurement taken from medical record
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Participants were followed for up to 24 months
	Attrition	☆	a) complete follow up - all subjects accounted for	All patients seem to be accounted for
Mullins (2021)[91]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB patient taking GAHT in the Cincinnati children's hospital medical center	All patients eligible for inclusion were included within the study
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	TGM and TGF were drawn from the same cohort of individuals
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medical records were used to ascertain length of time on GAHT
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Thrombotic events were looked at before and after GAHT exposure
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	The age range was rather broad, and while separated by age, the cohorts were not matched in any way
	Outcome			
	Outcome assessment	☆	b) record linkage	Medical records were reviewed retrospectively for information

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Patients were on GAHT for an average of over 550 days
	Attrition	☆	a) complete follow up - all subjects accounted for	Because study was retrospective, all data was included in follow-up
Navabi (2021)[92]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth at an Endocrine diversity clinic at the Children's Hospital of Eastern Ontario (CHEO) from January 2006 to April 2017	Retrospective review of TGNB youth with at least one DXA measurement at the clinic.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	The main analysis is a pre- and post-, so this would be the same population.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	It was stated that medical records were reviewed.
	Outcome temporality requirements		b) no, study was not designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	The GnRH analog use may have preceded the baseline DEXA scan.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	The main analysis is a pre- post- analysis, so each individual serves as their own control.
	Outcome			
	Outcome assessment	☆	b) record linkage	They utilized medical records.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	The duration of treatment has to be at least 18 months
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Earlier on in the study, it was discussed that 172 patients were included but only 170 were included in the baseline characteristics table. There is no information on the 2 patients that were excluded from the analysis.
Olson-Kennedy (2021)[93]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB subjects from a US-based academic adolescent gender dysphoria clinic	Participants were from a hospital in LA, as well as a nationwide study in major cities across the nation. Demographic information can be found in Table I.1. Patients that signed the waiver and met the broad eligibility were included.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All patients were sampled in the same way from their pediatric gender clinics.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Baseline and follow up information were extracted from patient charts and de-identified.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Baseline and follow up labs were taken. Descriptive statistics as well as statistical tests, such as Shapiro–Wilk test, Wilcoxon Signed-Rank test, and Mann Whitney U test, were used to compare the measurements between the two time periods.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	The investigators stratified data by gender at birth, Tanner stage and type of implant. The investigators did not control for variable time period, which was between 2 and 12 months of follow up for patients.
	Outcome			
	Outcome assessment	☆	a) independent blind assessment	Hormone levels were taken from medical record.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Noted timeline was between 2 and 12 months. Implants may be effective up to 24 months. For CPP, puberty progression and development stops after one month on histrelin (Histrelin, Lexicomp).
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Table I.1 describes the demographics for 66 patients. The number of patients in the other tables describe less patients, ranging from 61 to 63 patients. It was not mentioned why there was a difference between the tables, whether there is simply missing data or a loss at follow-up.
Schagen (2018)[147]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average pediatric transgender patient at the VU University Medical Center in Amsterdam between 1998-2009	They had no exclusion criteria and included everyone in the clinic that met the diagnostic criteria.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All were patients of the same clinic and were selected in the same way.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Prospective trial. These patients were seen in clinic as therapy was received.
	Outcome temporality requirements		b) no, study was not designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	there was no controlling for confounding
	Outcome			
	Outcome assessment	☆	b) record linkage	levels of hormone that were measured via lab by unblinded assessors.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	2 years of treatment
	Attrition		d) No information about attrition	
Schagen (2020)[94]	**Selection**			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	No description of how the cohort was sampled or how they were selected.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants appeared to follow the same protocol and be derived from the same source.
	Ascertainment of exposure		d) no description	Data was taken from previous studies. It was not mentioned how original data from participants of this study were collected.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Changes in bone density and bone markers were measured forward in time
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	Full factorial model was conducted that included time, pubertal stage, sex and all possible interactions.
	Outcome			
	Outcome assessment		d) no description	No description of how measurements were taken
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Teens were followed as they transitioned from GnRH analogs to CSHT as determined by physician
	Attrition	☆	a) complete follow up - all subjects accounted for	
Schulmeister (2022)[95]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Participants in treatment group from four gender specialty clinics in the United States.	A relative lack of diversity of participants since primarily non-Hispanic white and recruited at urban academic institutions
	Selection of the nonexposed cohort		b) drawn from a different source	Participants in control group were drawn from the Bone Mineral Density in Childhood Study (BMDCS).
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Anthropometric, laboratory, and Tanner-stage data were abstracted from medical records.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Anthropometric and laboratory data was abstracted from medical recorded and recorded prior to the participant beginning therapy.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Analysis controlled for age was conducted and within group DMAB vs. DFAB was compared. Each cohort was stratified by Tanner stages.
	Outcome			
	Outcome assessment	☆	b) record linkage	HV data were abstracted from medical records.

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Anthropometric data was recorded prior to the participant beginning GnRH analogs (baseline) and at 6- and 12-month follow-up visits.
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Of 92 youth who were enrolled prior to GnRH analog initiation, 9 participants were excluded because they did not receive GnRH analog treatment for at least 10 months, 12 were excluded from analysis because they did not have a documented height after 10 to 14 months of GnRH analog treatment, and 16 participants were excluded because they started CSH prior to 12 months of GnRH analog treatment.
Tordoff (2022)[96]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender youths from a Urban multidisciplinary gender clinic.	Family support and access to care are associated with protection against poor mental health outcomes, and thus actual rates of depression, anxiety, and suicidality in nonclinical samples of TNB youths may differ. Primarily included white and transmasculine youths, limiting the generalizability of our findings.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants in the untreated group were drawn from the same community - a Urban multidisciplinary gender clinic.
	Ascertainment of exposure	☆	c) written self-report	Self-reported receipt ever of PBs or CSHs at baseline or through the end of the study period.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified how they attained this information.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Temporal trends and potential confounders were adjusted in the model and time-varying exposure of PBs or CSHs was also controlled in model.
	Outcome			
	Outcome assessment		c) self-report	Measures of outcome were symptom-based. Depression was assessed using the Patient Health Questionnaire 9-item scale (PHQ-9), and anxiety was assessed using the Generalized Anxiety Disorder 7-item scale (GAD-7). Self-harm and suicidal thoughts were assessed using PHQ-9 question 9.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	The association between mental health outcomes and access to PBs or CSHs was assessed over a relatively short time frame of 1 year.
	Attrition		c) Follow-up loss rate ≥ 5% and no description of those lost	The final sample included 104 youths. Of these individuals, 84 youths (80.8%), 84 youths (80.8%), and 65 youths (62.5%) completed surveys at 3, 6, and 12 months, respectively.
Valentine (2021)[97]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Transgender youth from a large Midwestern pediatric academic center with a multidisciplinary program serving transgender and gender-diverse youth.	In transgender cohort, participants were predominantly white. Lack of Asian and Hispanic participants.
	Selection of the nonexposed cohort		b) drawn from a different source	Cisgender cohort was drawn from 13 primary care centers.
	Ascertainment of exposure		d) no description	Does not specify, but looks like they collected testosterone usage based on clinical records or notes

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specify in the article
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	BMIs of the transgender male cohort, and a random number generator used these matched patients to create a 2:1 match of cisgender females to the transgender males.
	Outcome			
	Outcome assessment	☆	b) record linkage	BMI data and lipid profile parameters were obtained from clinical records based on visits.
	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	Both short- and long-term follow-ups were evaluated, with short-term follow-up assessing changes in BMI between each clinic visit, and long-term follow-up assessing changes in BMI between first and final follow-up clinic visits (on average longer than 10 months) - for adverse effects, it's not long enough.
	Attrition		c) Follow-up rate loss ≥ 5% and no description of those lost	N = 42 were seen at least twice and, therefore, included in assessment of BMI changes. Only 28 of them had lipid panels drawn, and 18 had laboratories both pre- and post-testosterone.
Valentine (2022)[98]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth from a Pediatric Learning Health System Network	The data for all TGNB youth that met inclusion criteria and at least one outpatient visit were extracted from the database
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	The PedsNET resource was used for all. A random sample of patients with at least one outpatient visit during the same time period who did not have a diagnosis of GD were used as controls.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They used prescription records.
	Outcome temporality requirements		b) no, study was not designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	The timing between the description and the diagnosis code was unclear.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	They did propensity score matching and had an adjusted analysis to address for confounders.
	Outcome			
	Outcome assessment	☆	b) record linkage	They utilized the diagnosis codes.
	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	Duration of therapy was unclear.
	Attrition	☆	a) complete follow up - all subjects accounted for	All data was collected retrospectively, so all subjects were accounted for
Vlot (2017)[99]	**Selection**			

Return to TOC

Table I.I.1. Risk of bias in extracted cohort studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Representativeness of the exposed cohort	☆	b) somewhat representative of the average adolescents diagnosed with gender dysphoria who were treated with GnRH analog and CSHT were recruited at the clinic the Centre of Expertise on Gender dysphoria at the VU University Medical Centre, Amsterdam, the Netherlands.	After applying these criteria to an eligible patient group of 85 transwomen and 130 transmen, a cohort of 28 transwomen and 42 transmen were included in the study.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All 28 transwomen and 42 transmen which were included in this study were recruited from the same clinic and they were just categorized into a young and old pubertal group, based on their bone age.
	Ascertainment of exposure		d) no description	No related description of how they obtained participants' medication history.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article but they did review retrospectively.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Eligible participants were categorized into four groups based on their sex and bone ages - young transwomen, old transwomen, young transmen and old transmen.
	Outcome			
	Outcome assessment	☆	b) record linkage	Associated laboratory data such as a serum BTM measurement of P1NP, osteocalcin or carboxy terminal cross linked telopeptide of type I collagen were reviewed to assess the outcomes.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow up 24 months after CSHT
	Attrition	☆	a) complete follow up - all subjects accounted for	Eligible subjects were restricted to those who have data for all baseline and follow-ups.

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Arnoldussen (2020)[100]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average adolescents seeking GD treatment at the Center of Expertise on GD in the Netherlands	They included all patients who were referred to the clinic in the time period
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Initial year of assessment evident based on the chart documentation
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	They used natal gender as a comparator
	Outcome			
	Outcome assessment		c) self-report	The CBCL and the YSR were the main outcomes.
	Duration of follow-up		N/A	
	Attrition		N/A	
Avila (2019)[101]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB subjects from a US-based academic adolescent gender dysphoria clinic in the community	Response applies to the inferential finding for the overall population, but not to the subgroup comparison, which was based on the subset of all participants who did not skip the relevant items. The highest rating is given because authors specified that only 1 subject declined to participate.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	c) written self-report	Surveys were written and self-reported in surveys given onsite during clinic visit. While the investigators may have had access to information from the chart, they specified that data about exposures were collected in the survey instrument.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	The study used only univariable tests, so there was no statistical adjustment. The study did not use matching. While they restricted the study to young people (age range 13 to 22 years, the range is too broad to qualify as adequate. While some of the descriptive results were stratified on natal sex (but not age), none of the observational comparisons were stratified on either age or natal sex.
	Outcome			
	Outcome assessment		c) self-report	The EDE-Q survey and additional items were self-administered via an online data collection instrument.
	Duration of follow-up		N/A	

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Attrition		N/A	
Bauer (2021)[102]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB subjects from a Canadian-based academic adolescent gender dysphoria clinics	The recruitment process differed by each clinic location. The exact number in the population that were invited to participate is unknown. We know that 174 patients enrolled. Patients come from various walks of life from various locations throughout Canada.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Information regarding exposure was taken in the same manner for all patients.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Information was taken both from a structured interview and medical record. Medications were most likely from medical record.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) no controls for most important confounders or additional factors	P values were taken from Rao-Scott X^2 test. They did not control for confounding with methods or statistical adjustment.
	Outcome			
	Outcome assessment	☆	a) independent blind assessment	They used both structured interviews and medical records to extract their information. Most likely objective data was confirmed with medical record.
	Duration of follow-up		N/A	
	Attrition		N/A	
Becker (2018)[103]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in Germany	The process of collecting data from each department in Germany was not standardized because each location had different clinical procedures, so the results cannot be generalized to TGNB populations outside of Germany. Additionally, this study only included TGNB who sought gender-affirming medical care, and thus does not apply to TGNB not seeking gender-affirming medical care. Finally, the authors did not consider non-binary identities, and thus cannot generalize their results to non-binary/gender-nonconforming people.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participation in the study was offered to anyone applying for gender-affirming treatment.
	Ascertainment of exposure		c) written self-report	Age and gender identity was self-reported. Medical interventions for gender affirmation was drawn from participants' medical history.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	The study controlled for age and treatment duration in months by treating them as covariates, and used a 2 (sample) x 2 (gender) x 3 (interventions) analysis of covariance (ANCOVA). Investigators performed Levene tests to confirm that parametric assumptions were met.
	Outcome			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome assessment		c) self-report	Participants' FBeK scores were compared using a 2 (sample) x 2 (gender) x 3 (interventions) ANCOVA test.
	Duration of follow-up		N/A	
	Attrition		N/A	
Chen (2021)[104]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth in a pediatric academic center in the US	Patients recruited from 4 pediatric medical centers in the US who met specific criteria
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Drawn from academic medical centers for those seeking therapy.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	They looked at the raw analysis. Transgender subjects were subgrouped based on medication taken and designated female or male at birth.
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up		N/A	
	Attrition		N/A	
Conn (2023)[105]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth living in major metropolitan areas of the US	Major metropolitan areas of the US are considered more liberal, inclusive, and supportive for TGNB individuals. As such, these results are not generalizable to more rural and/or discriminatory parts of the US. The youth are truly representative from the areas that they re from as a large cohort was gathered.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were drawn from the same cohort originating from the Trans Youth Care Study.
	Ascertainment of exposure		c) written self-report	Internalized transphobia was determined using the internalized transphobia subscale of the Gender Minority Stress and Resilience Measure for Adolescents (GMSR-A), a self-report measure that assesses social stigma and psychosocial resilience associated with gender minority identity that has been adapted for adolescents.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Age, natal sex, and perceived parental support were included as covariates.

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome			
	Outcome assessment		c) self-report	Data on anxiety and depression were collected using self-report questionnaires.
	Duration of follow-up		N/A	
	Attrition		N/A	
De Graaf (2022)[108]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in large cities (Toronto, Amsterdam, London)	Data was collected from 3 different sites around the world-all cities are large and metropolitan. Sampling data was not provided, so we don't know if all youth that were seen in these time periods were included or a subset of youth.
	Selection of the nonexposed cohort		b) drawn from a different source	Youth from each clinic were compared to each other. While they are all TGNB youth, data was collected from a wide range of years, with London having a cohort that had been seen much more recently than the other two which could greatly impact data as views on TGNB youth and treatments have changed drastically in the last 30 years.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Records seem to have been used to identify youth with gender dysphoria.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Predictors of suicidality were used to compare between groups. 9 predictors were used between the Toronto and Amsterdam group, and 6 predictors were used in the other comparisons.
	Outcome			
	Outcome assessment		c) self-report	While record linkage was used to ascertain the data, the CBCL and YSR are self-reported measures.
	Duration of follow-up		N/A	
	Attrition		N/A	
de Vries (2011)[106]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender youth in Amsterdam	Note: only multidisciplinary clinic in the Netherlands
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Sex at birth and whether or not a patient is immediately eligible or delayed eligible for puberty suppression would be available from the clinic records.
	Outcome temporality requirements		N/A	
	Comparability			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Adolescents were compared by natal sex and then by those that were immediately eligible for puberty suppression vs. those that were delayed eligible. Natal groups were similar based on baseline characteristics, so no additional statistical analysis was done when comparing the groups. The immediately and delayed eligible groups had some statistically different baseline characteristic, but these were not taken into account in the analysis of the outcomes.
	Outcome			
	Outcome assessment	☆	b) structured interview	Adolescents underwent a standardized clinical assessment and completed a DISC interview and psychological assessment.
	Duration of follow-up		N/A	
	Attrition		N/A	
De Vries (2016)[107]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in Amsterdam and Toronto	No sampling method was listed, and not all of the data was available for all of the participants.
	Selection of the nonexposed cohort		b) drawn from a different source	Youth were compared from 2 different clinics which may have different treatment methods. The time frames were also different for each sample.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Youth were identified as having been diagnosed with gender dysphoria
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	7 different predictors were used to predict the outcome of CBCL and YSR scores. Sex was also used in other comparisons. Age was similar between groups.
	Outcome			
	Outcome assessment		c) self-report	While record linkage was used to ascertain the data, the CBCL and YSR are self-reported measures.
	Duration of follow-up		N/A	
	Attrition		N/A	
Durwood (2017)[109]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average pediatric TGNB subject seen in a US-based academic gender study	A small sample size (n = 63) completed the mental health portion of this study. 116 participants completed the self worth component of the study. This study did include children from all around the nation, but due to small sample size of this comparison it most likely doesn't represent the entire TGNB population for the US. They also reported that this population had a higher income than the average US population, which may play a role in their mental health resources.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All transgender participants were sampled in the same way.
	Ascertainment of exposure		c) written self-report	Participants answered whether they were on medication and what type.
	Outcome temporality requirements		N/A	
	Comparability			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	There was no additional statistical adjustment for any factors or methods that would control for confounding factors.
	Outcome			
	Outcome assessment		c) self-report	Participants selected answer on PROMIS scale that aligned with how they felt in the past 7 days.
	Duration of follow-up		N/A	
	Attrition		N/A	
Grannis (2021)[110]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average minors recruited from a gender clinic	Reliance on caregivers for transportation and financial support may suggest an inflated level of support compared to the transgender youth population at large.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from the same community as exposed group - a gender development clinic at a large children's hospital
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Medical chart review
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Sex was controlled by sample restriction. Age was included as a covariate for all other group comparisons. Results were reported after controlling for age. However, it is not possible to truly control for all possible factors that may differentiate treatment groups, and some of these factors may contribute to differential mental health profiles independent of drug treatment.
	Outcome			
	Outcome assessment		c) self-report	Standardized self-report measures were used and neuroimaging was used as well.
	Duration of follow-up		N/A	
	Attrition		N/A	
Green (2022)[111]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in the US	Large scale survey with participants from all areas of the US were part of the study. Recruitment was targeted to reach all demographics. It was a long 142 question survey and was done on a volunteer basis, so survey reflects participants that completes the survey. There was also a lower number of trans girls that responded to the survey than trans boys.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were from the same survey.
	Ascertainment of exposure		c) written self-report	Surveys were completed on volunteer basis by participants that saw targeted ads on social media. Answers about mental health were dichotomized. Questions about demographics and additional questions were multiple choice.
	Outcome temporality requirements		N/A	
	Comparability			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	Multivariate adjusted logistic regression was performed to adjust for age, socioeconomic status, region, gender identity, sexual orientation, race/ethnicity, parent support, gender based victimization, gender identity conversion efforts and history of puberty blocker use
	Outcome			
	Outcome assessment		c) self-report	Survey was self-administered online
	Duration of follow-up		N/A	
	Attrition		N/A	
Karakilic Ozturan (2023)[112]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in Turkey	The data for this study was collected from a single tertiary pediatric endocrinology clinic in Istanbul, the most populous city in Turkey. People living here have more access to healthcare compared to more rural parts of the country -- therefore, their clinical and laboratory findings may not reflect the experiences of TGNB youth in the rest of the country.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All participants were drawn from patients referred to the same tertiary pediatric endocrinology clinic.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Investigators retrospectively reviewed the medical records of all adolescents diagnosed with GD that had at least 6 months of psychiatric follow-up and were referred to their GD outpatient clinic from 2016-2022.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Natal sex defined comparator groups, and age was a measured outcome.
	Outcome			
	Outcome assessment	☆	b) record linkage	Investigators determined outcome values by retrospectively reviewing participants' medical records.
	Duration of follow-up		N/A	
	Attrition		N/A	
Mirabella (2022)[113]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average GD adolescent seeking treatment in Rome/Florence	The GDQ was administered to all adolescents who had been consecutively referred to the clinic, usually during their second of three appointments.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Comparisons were made between the cohort
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	
	Outcome temporality requirements		N/A	

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Youth were compared by gender and whether they were trans-binary or non-binary.
	Outcome			
	Outcome assessment		c) self-report	Study used a questionnaire to assess outcomes
	Duration of follow-up		N/A	
	Attrition		N/A	
Morningstar (2023)[114]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average GAH+ transgender boy from a multidisciplinary gender development clinic at an academic pediatric center in the Midwest of the US.	A sample of transgender boys was recruited from the clinic
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	GAH- transgender subjects were recruited from the same community as GAH+ group - a multidisciplinary gender development clinic at an academic pediatric center in the Midwest of the US.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Information provided on medication doses and length of therapy, assumed from their medical records at the clinic.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Whole-brain analysis was controlled for age. However, variations in dose and duration of GAH administration were not controlled in the analyses.
	Outcome			
	Outcome assessment	☆	b) record linkage	fMRI data were obtained and transgender subjects also self-reported relative closeness to peers and parents.
	Duration of follow-up		N/A	
	Attrition		N/A	
Nahata (2017)[115]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth in a large, urban, midwestern pediatric gender program from 2014-2016	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	EMRs were used to assess ICD 9/10 code

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) or (b)	Only separated by gender
	Outcome			
	Outcome assessment		c) self-report	Medical records were used-but all data came from self-report of subjects to psychiatrists
	Duration of follow-up		N/A	
	Attrition		N/A	
Olsavsky (2023)[116]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB adolescents in a large midwestern gender-affirming clinic in the Midwest	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Patients were recruited based on their diagnosis of GD
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Study used a multivariate linear regression model testing association between nonbinary identity, GAH, family and friend social support. Also initially tested correlation among age, race, and male vs female identity.
	Outcome			
	Outcome assessment		c) self-report	Validated instruments were used to ascertain data
	Duration of follow-up		N/A	
	Attrition		N/A	
Segev-Becker (2020)[117]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB adolescent in the gender dysphoria clinic at the Dana-Dwek Children s hospital in Tel, Aviv Israel from 2013-2018	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Patients were recruited based on their referral to the GD clinic
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study separated data by age and gender
	Outcome			
	Outcome assessment		c) self-report	All data was from medical records, but all data was self-reported
	Duration of follow-up		N/A	
	Attrition		N/A	
Sorbara (2020)[118]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average transgender youth seen at a gender clinic in Toronto, CA	Broad inclusion criteria to include those at the gender clinic that were seeking medication therapy and were diagnosed with gender dysphoria
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All were from the same cohort
	Ascertainment of exposure	☆	b) structured interview	Information was taken from both interview with patients during their visits to the clinic and their medical record. Medical history, including mental health screening was taken from patient.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s) and additional confounders	Logistic regression has performed to since which factors were associated with reported mental illness. Factors included were early or late pubertal, age at first visit, date cohort, social transition and assigned sex
	Outcome			
	Outcome assessment		c) self-report	Mental health outcomes were self-reported
	Duration of follow-up		N/A	
	Attrition		N/A	
Staphorsius (2015)[119]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender youths from VU University Medical Center in Amsterdam.	Adolescents with gender dysphoria were recruited to participate in study. Sample size was small, so there may be some selection bias.

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	They were recruited from VU University Medical Center in Amsterdam, which is the same location.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Not really specified, but they are all located at the same medical center. Thus, medical records should be available.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	They controlled for IQ.
	Outcome			
	Outcome assessment		d) no description	They did perform the TOL test and the MRI, but it is unclear if the assessor was blinded.
	Duration of follow-up		N/A	
	Attrition		N/A	
Tollit (2023)[120]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average pediatric gender diverse patient at an Australian clinic	Broad inclusion criteria seems to include most patients that would be seen at the clinic. Purpose of the study was to get info on demographics.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All were from the same cohort
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Data was collected from both face to face interviews as patients were seen in clinic as well as their medication record.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) or (b)	study did not control for confounding
	Outcome			
	Outcome assessment	☆	b) record linkage	Both medical record and face to face methods were used
	Duration of follow-up		N/A	
	Attrition		N/A	
Turban (2020)[121]	**Selection**			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB subjects completed the 2015 US Transgender Survey (USTS) conducted by the National Center for Transgender Equality (NCTE) with respondents from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas	Eligibility criteria was restricted to participants who were 36 or younger at the time of the survey, since given that pubertal suppression for transgender youth was not available in the United States until 1998, participants who were 17 or younger in 1998 would not have had health care access to GnRH analogs for pubertal suppression. The USTS data set contains responses from 27,715 US transgender adults; however, only a sample of 20,619 participants was included in analysis.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Pubertal suppression treated group (N = 89, 2.5%) vs. pubertal suppression untreated group (N = 3405, 97.5%)
	Ascertainment of exposure		c) written self-report	Exposure status was examined based on self-reported history of pubertal suppression during adolescence.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s) and additional confounders	Baseline demographic variables (including level of family support, sexual orientation, education level, employment status, total household income, gender identity, race and relationship status) were controlled for multivariate regression models. The analysis was stratified based on age.
	Outcome			
	Outcome assessment		c) self-report	Associated mental health outcomes were collected and analyzed based on survey results.
	Duration of follow-up		N/A	
	Attrition		N/A	
Turban (2022)[122]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Transgender person in the USA	Participants were recruited from organizations to complete a voluntary survey. Data is dependent on those that participated, although they were able to recruit a sizeable sample.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Sampled in the same way/ same population
	Ascertainment of exposure		c) written self report	Completed via online survey
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s) and additional confounders	Multivariate logistical regression was performed. All models adjusted for age, partnership status, employment status, K-12 harassment and having experienced gender identity conversion efforts and any additional demographic and potential confounding variables that were found to be associated with each outcome
	Outcome			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome assessment		c) self report	data collected from survey
	Duration of follow-up		N/A	
	Attrition		N/A	
van de Grift (2020)[624]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth in the Netherlands	The study was conducted at a single site/treatment center, and is most likely not applicable to TGNB living in more rural parts of the Netherlands.
	Selection of the nonexposed cohort		b) drawn from a different source	Both TGNB that used PS at Tanner 2/3 vs. 4/5 were selected using the same local registries, but TGNB that did not use PS were selected using hospital records. It is unclear if 'local registries' and 'hospital records' are the same source.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Local registries and hospital records were used to identify eligible participants.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Authors made comparator groups based on natal sex, but did not control for age. There were statistically significant differences between participants' ages at the start of PS and at their first surgery. Comparator groups were also based on puberty level at beginning of treatment.
	Outcome			
	Outcome assessment	☆	b) record linkage	The entire outcome database was completed retrospectively at follow-up during a 6-month period in 2018, using local registries.
	Duration of follow-up		N/A	
	Attrition		N/A	
van der Miesen (2020)[124]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Transgender samples consisted of consecutive referrals to the Center of Expertise on Gender Dysphoria of the VU University Medical Center (VUmc) in Amsterdam, the Netherlands, between 2012 and 2015.	Since it is a single source of transgender adolescents, not sure if it is truly representative for the community.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Transgender adolescents referred to a specialized gender identity clinic and transgender adolescents receiving affirmative care and about to start GAH treatment were recruited from the same transgender clinic.
	Ascertainment of exposure		d) no description	No related description of how they obtained participants' medication history.
	Outcome temporality requirements		N/A	
	Comparability			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Multivariate GLM analysis with assigned gender at birth and a gender by group interaction as additional predictors was used to identify possible gender differences within each group.
	Outcome			
	Outcome assessment		c) self-report	c) self-report
	Duration of follow-up		N/A	
	Attrition		N/A	
Vehmas (2022)[125]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth gender identity services at Helsinki University Hospital	Consecutive adolescents who had been referred to the hospital and met specific inclusion criteria were included. A much higher ratio of FTM to MTF, but that was representative of the clinic at that time.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Male to female and female to male cohorts were compared
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All patients had met criteria of being diagnosed with GD and seeking GHAT.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) Study did not control for any additional factors	Appears just to be a raw analysis.
	Outcome			
	Outcome assessment	☆	b) record linkage	They utilized medical records and some structured interviews
	Duration of follow-up		N/A	
	Attrition		N/A	
Vrouenraets (2021)[126]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Participants were transgender adolescents visiting the Center of Expertise on Gender Dysphoria of the Amsterdam University Medical Centers, Location VUmc in Amsterdam, the Netherlands, between January 1, 2016, and December 31, 2017, or visiting the gender-identity clinic of Leiden University Medical Center, Leiden University Medical Center Curium, in Leiden, the	74 adolescents participated, whereas 206 eligible adolescents were not reached or did not want to or could not participate.

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

			Netherlands, between March 1, 2017, and December 31, 2017.	
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Birth-assigned boys and birth-assigned girls were recruited from the same clinic.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Exposure of puberty suppression was identified through the medical files.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	Not controlled or adjusted for any factors.
	Outcome			
	Outcome assessment		c) self-report	CBCL used to assess behavioral and emotional difficulties were parent-reported.
	Duration of follow-up		N/A	
	Attrition		N/A	
Willemsen (2023)[127]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender youth in Amsterdam	Note: only multidisciplinary clinic in the Netherlands
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Sex at birth and whether or not a patient is immediately eligible or delayed eligible for puberty suppression would be available from the clinic records.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	Adolescents were compared by natal sex and then by those that were immediately eligible for puberty suppression vs. those that were delayed eligible. Natal groups were similar based on baseline characteristics, so no additional statistical analysis was done when comparing the groups. The immediately and delayed eligible groups had some statistically different baseline characteristic, but these were not considered in the analysis of the outcomes.
	Outcome			
	Outcome assessment	☆	b) structured interview	Adolescents underwent a standardized clinical assessment and completed a DISC interview and psychological assessment.
	Duration of follow-up		N/A	
	Attrition		N/A	
Zucker (2010)[65]	**Selection**			

Return to TOC

Table I.I.2. Risk of bias in extracted cross-sectional studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)				
	Representativeness of the exposed cohort	☆	a) truly representative of the average TGNB youth with GID referred to the GIS in Toronto, Canada from 2000-2009	Youth evaluated were consecutively referred from 2000-2009. Those that did not meet the specific criteria of GID were not included
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	The entire group was compared to each other based on demographic, behavioral and psychosocial variables
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All data was from medical records
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	16 different factors were looked at as variables as predictors of the outcome
	Outcome			
	Outcome assessment	☆	b) record linkage	Outcome was assessed from medical records
	Duration of follow-up		N/A	
	Attrition		N/A	

Return to TOC

Table I.I.3. Risk of bias in extracted case-control studies comparing TGNB patients to TGNB patients, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Maru (2021)[128]	**Selection**			
	Adequacy of the case definition	☆	Yes, eg, Record linkage or based on self-reports	Diagnostic codes for Type II DM were used
	Classification	☆	Consecutively or obviously representative series of cases	It appears that all eligible cases (ie, those with the diagnosis) were included
	Selection of controls	☆	Community controls	Controls were the “overall clinic population” (ie, case-cohort sampling)
	Definition of controls		No description of source	With case-cohort sampling, it's likely that the comparison group included subjects who may have had type II DM, which would be an appropriate comparison, but it's unclear.
	Comparability			
	Comparability of (exposure/comparator) cohorts		No controls	They did not control for age or sex
	Exposure			
	Assessment of exposure		No descriptions	They did not specify how they assessed exposures (eg, GD diagnosis, GD treatment)
	Same method of ascertainment for cases and controls		Unclear	They don't specify how exposures were assessed for cases or controls; it's unclear if they used the same for both groups.
	Non-response rate	☆	a) same rate for both groups	They used chart review, so there is no difference in rates. All eligible cases and controls were included.

Return to TOC

Table I.I.4. Risk of bias in extracted cohort studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Beking (2020)[129]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average adolescent with or without gender dysphoria in Amsterdam, the Netherlands.	Trans boys were recruited from the Venter of Expertise on Gender Dysphoria at the VU medical center. No inclusion criteria stated, or how the boys were sampled.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	They were recruited from secondary schools and/or were friends of the recruited transgender boys.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They were being treated there.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Testosterone was started after session 1.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	b) study controls for any additional factor	They were controlled for age.
	Outcome			
	Outcome assessment	☆	b) record linkage	It was not clearly stated whether it was blinded, but they used brain scans for two of the reported groups of outcomes. The other one which is a bit of a baseline characteristic and is self-report is handedness.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Mean duration of testosterone therapy before the measurements taken at session 2 was 9.8 months.
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	All the transgender boys were accounted for, but 3 cisgender boys and 1 cisgender girl dropped out.
Burke (2016)[130]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average youth within the VU medical center	A small cohort was recruited from the Center of Expertise on Gender Dysphoria
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from schools in the same geographical area, also invited friends and relatives of the appropriate age to participate in the control group.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Since patients were recruited within the center, assumption is that health records were used to ascertain exposure.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Patients started on GnRH analogs and then continued onto testosterone and test was repeated
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Study controls for sex, and age and pubertal status. Data was corrected for IQ, as that was significantly different between groups.

Return to TOC

Table I.I.4. Risk of bias in extracted cohort studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome			
	Outcome assessment	☆	b) record linkage	fMRI data was used as well as performance data.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Patients were on treatment for an average of 10 (range 6-15) months
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Some controls did not continue to session, but there was a description of those lost
Costa (2015)[77]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB adolescent at the GIDS in London	Patients who were referred between 2010 and 2014 to GIDS were recruited. Out of 436 referrals, 201completed the GD assessment and psychological interventions and all who did took part in follow-up evaluations.
	Selection of the nonexposed cohort		b) drawn from a different source	They were a naturalistic cohort drawn from the child and adolescent mental health services (CAMHS).
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They were being treated at GIDS so their records were available. They were referred before treatment was initiated.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Puberty suppression was started 6 months after the baseline.
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	Data was not controlled for anything in this comparison
	Outcome			
	Outcome assessment		c) self-report	Participants completed the CGAS to ascertain data
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up was 18 months.
	Attrition		c) Follow-up rate ≥ 5% and no description of those lost	At the end of 18 months, only about a quarter of the original cohort remain.
López de Lara (2020)[62]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB youth getting ready to take CSHT in the pediatric endocrinology clinic in the San Carlos Hospital in Spain.	Sample were volunteers from the clinic that were getting ready to start CSHT. Convenience sample as all were recruited from one clinic and were not randomly selected.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Sample were volunteers from the same clinic as exposed cohort
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Hormone therapy was prescribed by the clinic

Return to TOC

Table I.I.4. Risk of bias in extracted cohort studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	All patients were recruited before the initiation of CSHT and therefore started treatment before outcomes were measured.
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	They matched for age, ethnicity and socioeconomic status. There were no psychiatric comorbidities at baseline.
	Outcome			
	Outcome assessment		c) self report	All measures used were self-reported tools (UGDS, SDQ, STAI, BDI-II)
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Patients were followed up for 12 months after initiation of therapy
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, <5% lost to follow-up), or a description of those lost was provided.	All patients were accounted for in follow-up
Millington (2022)[90]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average transgender youth attending gender clinics in the USA	Eligible patients from gender clinics that consented to the study were included
	Selection of the nonexposed cohort		b) drawn from a different source	Drawn as references from a National study (NHANES)
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Taken from medical record
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	TGNB participants were sampled before and after GAH therapy
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study adjusted for age, and adjusted/compared the measurements from trans youth to both male and female peers
	Outcome			
	Outcome assessment	☆	b) record linkage	Laboratory measurement taken from medical record
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Compared after 12 months of GAH therapy
	Attrition		d) No information about attrition	Unclear because no given information about the NHANES study
Nokoff (2020)[131]	**Selection**			

Return to TOC

Table I.I.4. Risk of bias in extracted cohort studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Representativeness of the exposed cohort	☆	b) somewhat representative of the average pediatric transgender patient in TRUE center for diversity at the Children's hospital in Colorado	They excluded patients with significant medical or psychiatric comorbidities and the examples they gave were diabetes or antipsychotic treatment,
	Selection of the nonexposed cohort		b) drawn from a different source	Controls were selected from two studies at the same institution: RESISTANT and HIP.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	They secured information about the controls from the studies, and patients at their clinic from their medical record.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Patients with exposure had to be on therapy for at least 3 months
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Controls were match on age and BMI. They also stratified results based on spironolactone exposure.
	Outcome			
	Outcome assessment	☆	b) record linkage	investigators were not blinded. Lab values were drawn and taken from medical records.
	Duration of follow-up	☆	a) yes	Average treatment duration for TM was 11 months and 12 months for TF
	Attrition		d) no information about attrition	
Schulmeister (2022)[95]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Participants in treatment group from four gender specialty clinics in the United States.	relative lack of diversity of participants since primarily non-Hispanic white and recruited at urban academic institutions
	Selection of the nonexposed cohort		b) drawn from a different source	Participants in control group were drawn from the Bone Mineral Density in Childhood Study (BMDCS).
	Ascertainment of exposure		d) no description	No related description of how they obtained participants' medication history.
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specified in the article
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	The HV of BMDCS and TGD youth were compared controlling for mid-age, the midpoint between the ages of the two visits used to calculate the HV. Growth data from the Centers for Disease Control and Prevention were used to determine participant height z-scores based on sex designated at birth. Comparison was stratified by Tanner stages.
	Outcome			
	Outcome assessment	☆	b) record linkage	Anthropometric and laboratory data collected in the course of clinical care were abstracted from the medical record.

Return to TOC

Table I.I.4. Risk of bias in extracted cohort studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Anthropometric and laboratory data were recorded prior to the participant beginning GnRH analogs (baseline) and at 6- and 12-month follow-up visits.
	Attrition	☆	b) subjects lost to follow-up are unlikely to introduce bias (ie, < 5% lost to follow-up), or a description of those lost was provided.	Of 92 youth who were enrolled prior to GnRH analog initiation, 9 participants were excluded because they did not receive GnRH analog treatment for at least 10 months, 12 were excluded from analysis because they did not have a documented height after 10 to 14 months of GnRH analog treatment, and 16 participants were excluded because they started GAH prior to 12 months of GnRH analog treatment. A total of 55 individuals were included in the analysis and it looks like all of them had follow up data.
Valentine (2021)[97]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender males from a large Midwestern pediatric academic center with a multidisciplinary program serving transgender and gender-diverse youth.	Retrospective study of transgender males taking testosterone from 2014-2018 at center who had been seen at least twice
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Cisgender cohort was drawn from 13 primary care centers within the same hospital system
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Does not state it in the article but looks like they collected testosterone records based on clinical records or notes
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	BMIs of the transgender male cohort, and a random number generator used these matched patients to create a 2:1 match of cisgender females to the transgender males.
	Outcome			
	Outcome assessment	☆	b) record linkage	BMI data and lipid profile parameters were obtained from clinical records based on visits.
	Duration of follow-up		b) no, follow-up was not long enough for outcome to occur	Both short- and long-term follow-ups were evaluated, with short-term follow-up assessing changes in BMI between each clinic visit, and long-term follow-up assessing changes in BMI between first and final follow-up clinic visits (on average longer than 10 months) - for adverse effects, it doesn't meet the criteria of a one-year follow-up to ascertain effect.
	Attrition	☆	a) complete follow up - all subjects accounted for	N = 42 were seen at least twice and, therefore, included in assessment of BMI changes. Only 28 of them had lipid panels drawn, and 18 had laboratories both pre- and post-testosterone. For BMI measures, all of them had follow-up data.

Return to TOC

Table I.I.5. Risk of bias in extracted cross-sectional studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Alvares (2022)[132]	**Selection**			
	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	Authors did not describe how the sample of transgender subjects were recruited. It is unclear whether they were sampled at random from all eligible clinic patients, whether they were consecutive eligible patients, etc.
	Selection of the nonexposed cohort		c) no description of the derivation of the non-exposed cohort	There was no description of how cisgender controls were recruited.
	Ascertainment of exposure	☆	b) structured interview	Exposures were assessed by trained interviewers
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Authors matched transgender patients to cisgender controls on age and activity levels
	Outcome			
	Outcome assessment		d) no description	No choices really apply. No outcomes assessment was blinded except for the cardiopulmonary exercise tests, which we did not extract.
	Duration of follow-up		N/A	
	Attrition		N/A	
Burke (2015)[133]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average adolescent with or without gender dysphoria in Amsterdam, the Netherlands.	Authors had minimal description of how cohorts were recruited, however the GD cohort was recruited from the clinic and peers were recruited from a nearby geographical area.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from schools in the same geographical area. They also invited friends and relatives of the appropriate age to participate in the control group.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Since patients were recruited within the center, assumption is that health records were used to ascertain exposure.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study controlled for natal sex. Age was generally matched within about a year
	Outcome			
	Outcome assessment	☆	b) record linkage	MRI data was assessed
	Duration of follow-up		N/A	
	Attrition		N/A	
	Selection			

Return to TOC

Table I.I.5. Risk of bias in extracted cross-sectional studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Durwood (2017)[109]	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	Transgender participants were enrolled in the Trans Youth Project, a national, longitudinal study of socially transitioned transgender children. No information on how this cohort was selected.
	Selection of the nonexposed cohort		b) drawn from a different source	The matched controls were recruited through a university database of families interested in participating in child development research.
	Ascertainment of exposure		d) no description	Unclear how they obtained medical records including whether they were on hormonal intervention.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Controls were age- and gender-matched.
	Outcome			
	Outcome assessment		c) self-report	Participants reported outcomes using PROMIS scale.
	Duration of follow-up		N/A	
	Attrition		N/A	
Nokoff (2021)[134]	**Selection**			
	Representativeness of the exposed cohort		d) no description of the derivation of the cohort	All transgender females and five transgender males were recruited from the same cross-sectional study. An additional four transgender males were recruited from a separate longitudinal study. Unclear whether they were sampled at random from all eligible clinic patients
	Selection of the nonexposed cohort		b) drawn from a different source	Data on healthy cisgender controls were obtained from two studies performed at the institution: the RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study and the Health Influences in Puberty (HIP) study.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Participants being on GnRH alone was one of eligibility criteria, but they did not state how they obtained GnRH administration records. Assumed since they were within a health system, records could be used to ascertain exposure.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	Transgender participants were matched to cisgender controls on age (within a year or less), BMI (within category), and sex assigned at birth.
	Outcome			
	Outcome assessment	☆	b) record linkage	BMI data and other cardiovascular parameters were obtained at each visit.
	Duration of follow-up		N/A	
	Attrition		N/A	
	Selection			

Return to TOC

Table I.I.5. Risk of bias in extracted cross-sectional studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Staphorsius (2015)[119]	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Transgender youth associated with VU medical center in Amsterdam	Adolescents were recruited from the clinic, but no data was given for how they were recruited. Their peers were recruited from the same community.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Selection was from friends and peers of participants, which could introduce selection bias, but is from the same community
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆	a) study controls for the most important confounder(s)	Study controlled for sex
	Outcome			
	Outcome assessment	☆	b) record linkage	fMRI data was used to assess data
	Duration of follow-up		N/A	
	Attrition		N/A	
Valentine (2022)[98]	**Selection**			
	Representativeness of the exposed cohort	☆	a) truly representative of the average Youth within the PedsNET health community	All EHRs in the time period were reviewed for data on TGNB youth with GD diagnosis and then matched with a large cohort of peers
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	EHRs were reviewed from the same network and time period.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	EHRs were reviewed for diagnosis
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts	☆ ☆	b) study controls for any additional factor	Propensity scores were used to match control to cases (approximately 4:1.) A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. Additional adjustments were done for data to control for overweight/obesity, depression, and antipsychotic prescription.
	Outcome			
	Outcome assessment	☆	b) record linkage	EHRs were reviewed for data
	Duration of follow-up		N/A	
	Attrition		N/A	

Return to TOC

Table I.I.5. Risk of bias in extracted cross-sectional studies comparing TGNB patients to their cisgender peers, using the Newcastle-Ottawa Quality Assessment Scale (NOS)

Van der Miesen (2020)[124]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average transgender youth from the Center of Expertise on Gender Dysphoria of the VU University Medical Center (VUmc) in Amsterdam, the Netherlands, between 2012 and 2015.	transgender samples consisted of consecutive referrals to the Center of Expertise on Gender Dysphoria of the VU University Medical Center (VUmc) in Amsterdam, the Netherlands, between 2012 and 2015.
	Selection of the nonexposed cohort		b) drawn from a different source	Cisgender adolescents from the general population were recruited by means of the help of different secondary schools in different provinces in the Netherlands.
	Ascertainment of exposure		d) no description	No related description of how they obtained participants' medication history.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/comparator) cohorts		c) neither (a) nor (b)	Although a multivariate GLM analysis with assigned gender at birth and a gender by group interaction as additional predictors was used to identify possible gender differences within each group, it is not used in TGNB vs. cisgender comparison.
	Outcome			
	Outcome assessment		c) self-report	The Dutch version of the YSR was used to assess internalizing and externalizing problem behavior, self-harm/suicidality, and peer relations.
	Duration of follow-up		N/A	
	Attrition		N/A	

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

Achille (2020)[55]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described eligibility, including who was invited to participate, and how many ultimately completed 3 questionnaires.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear. Fewer than half of participants who completed at least 1 survey persisted until the 3rd survey was complete. There is likely selection bias, and it is unclear how those who persisted for 3 months may differ from the rest of the population.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible participants who were invited and who completed 3 questionnaires were included.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Other	Unclear: They did not talk about a power calculation, which is common for these types of studies. It's likely that 50 patients is a sufficient sample to see some changes in mental health outcomes after 12 months if the treatments are effective.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	Some patients received puberty suppression with an unspecified agent, some patients received CSHT, some patients received both, and some patients received none. Treatment durations were also unclear.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Loss to follow-up was more than 50%.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	The answer is given for CESD-R, PHQ-9, and QOL instrument. The answer would be "no" for suicide ideation outcomes.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Unclear	Unclear. There were 3 measurement points: baseline, 6 months, and 12 months. The 6-month findings were published, but not considered in hypothesis tests. Patterns over time were consistent with a real treatment effect, but there were only 3 measures, which is inadequate for a true ITS design.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Allen (2019)[56]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria were clearly described.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear; don't know how many subjects were excluded.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	They state that a total of 47 participants were eligible and were included in analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	No specific descriptions about CSHT and GnRH analogs they were receiving.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated questionnaires to assess the outcomes. The outcome measures were clearly defined and assessed consistently across all study participants.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Looks like all included participants had follow-up data.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Two mixed repeated-measures ANCOVAs were used to ascertain within-subject differences between pretest (T0) and final assessment (T1) suicidality and general well being scores.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	They mention that participants were assessed at least 2 times; however, for analysis they only considered two time points (baseline - before start of GAH; follow up - at least 3 months after treatment)
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Arnoldussen (2022)[135]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Self-perception changes over the course of irreversible medical gender-affirming treatments in TGNB adolescents was measured
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	Unclear-adolescents were only included if pretreatment data on self-perception was available, Out of 513 referred adolescents, 179 were eligible, and only 70 had pretreatment data on self-perception.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible candidates that also had the pretreatment data on self-perception were enrolled
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Did not report a power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	Some patients had received puberty suppression at pretreatment assessment, and some had not. Patients may have received a variety of GAH treatments and surgeries.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	all patients were evaluated on the same screening questionnaire-the SPSS
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All participants had received PS, CSH and gender affirming surgery
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Since data was retrospectively obtained, all patients had all data points
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P values and confidence intervals were calculated, and multilevel modeling was conducted to determine the effect of time. Possible confounders were also added to the model.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	ITS design was not used
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

Alvares (2022)[132]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Investigators measured mean TT levels of TGNB women 12 months before the study vs. the moment of the study, in order to better demonstrate the extent of suppression on TT values over time.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	All inclusion/exclusion criteria are clearly listed
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All participants were adult women seeking gender-affirming care at the Gender Dysphoria Unit. The study's results will not be applicable to those under the age of 25.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	The investigators do not include how many women were screened against the inclusion/exclusion criteria and excluded based on it.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	Only 15 TGNB women were included, and the authors do not discuss the power of the study.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	All participants were using estrogen at the time of the study, but could have been using other CSHT (like cyproterone acetate) as well. Participants were also using different doses of estrogen.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Unclear	Blood tests were taken on the day of the study, but it's unclear when/how consistently blood tests were taken 12 months before the study.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Evaluators were not blinded.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	No participants were lost to follow-up; no description is given.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Unclear	It's unclear what statistical analysis the authors used for this comparison.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	A single blood test was conducted at T1; it's unclear how many blood tests were taken at T0.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Becker-Hebly (2021)[72]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Can extract population, intervention, comparison and outcome from the abstract.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Criteria listed on P5.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Other	Only 75 out of 204 participants agreed to participate, meaning that this was a response rate of 37%. There is likely selection bias.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible participants were invited.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. No power calculation was discussed.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	It is unclear if the GnRH analog and the CSHT regimen was consistent across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear	Unclear- they only mentioned people who had follow-up results; it was not clear what the full amount at baseline was.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	They provided P-Values.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	There were only two measurement points.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Beking (2020)[129]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	They are looking at the effects of testosterone on amygdala lateralization.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Unclear	They specifically list the exclusion criteria but do not really have specific inclusion criteria.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	They are part of that group, but this looks like a convenience sample.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	This was a convenience sample.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Power was not defined.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The protocol was provided in the study
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	The protocol was provided in the study
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Not specified
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Follow-up was 100%
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Measurements only taken twice
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

Boogers (2022)[66]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Reported data are a bit convoluted, but they still state their aim: "This work aims to investigate the effects of GnRHa [analogs] and GAHT [CSHT] on growth, and the efficacy of growth-reductive treatment."
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Noted in the "Participants" section
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Significant proportion were not included in the final analysis.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible participants were thought to be included.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. No power calculation was discussed.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Treatment protocol and timing was clearly defined under "Measurements" and "Laboratory Investigations."
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Treatment protocol and timing was clearly defined under "Measurements" and "Laboratory Investigations"
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No blinding was noted
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Not clear how follow-up changed over time but a significant proportion were not included in the final analysis.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Some provided P-values, some did not provide P-values.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	There were multiple measurement points provided in the figures, but outcomes were not taken multiple times before the intervention
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Cantu (2020)[74]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and recruitment process.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	They state that all youth ages 11 and older complete anxiety and depression screeners at every visit regardless of mental health diagnoses or symptom severity.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	Participants were 80 youths and all of them completed PHQ-9 screeners at both time points; however, only 78 youths completed GAD-7 screeners at both time points. They did not mention why 2 out of 80 participants did not complete GAD-7.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	In the limitation part, they stated that power analyses revealed that the current sample would have been well powered to detect large effects, but not small-to moderate effects, which are more likely when looking at shorter time frames.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	Unclear about the exact time of HT initiation given the variability in how and where individuals received their treatments. Participants who started on hormone blockers only were not included in this analysis. No analyses were conducted to examine differences between which hormone was started or for those that also initiated puberty blockers.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Validated screening measures of mental health were used to assess outcomes.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Validated surveys were answered by participants and they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	One of the eligibility criteria was that participants had attended both initial visits and first follow-up appointment.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	For both PHQ-9 and GAD-7, paired sample t-tests were used to examine overall changes from initial visit to follow-up, and independent sample t-tests were used to examine simple differences across groups. ANOVA was used to examine the role of potential moderators (ie, initiation of HT and distance from clinic) in the changes in distress over time. P values were used for pre-to-post changes.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Except for baseline visit, only first follow-up appointment was analyzed.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Carmichael (2021)[73]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	They very clearly stated all of their objectives and procedures for obtaining them.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly stated how they recruited their participants, the specific eligibility criteria and who was selected.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Participants were selected from a group of TNGB youth who attended GIDS an wanted to commence hormone therapy who met specific criteria. Unclear if the group that would attend this clinic is representative of the TGNB population as a whole
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Everyone who wished to participate that met the eligibility requirements was enrolled in the study. There were some who did not meet the criteria initially but were enrolled several months later when they did meet it.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Did not report a power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	All patients were given GnRH analog triptorelin for pubertal suppression together with psychosocial support and therapy, from study entry until the end of the GnRH analog monotherapy pathway at age 16 or older. 3.75mg by IM injection given every 28 days during treatment period. 2 Participants given 11.25 mg every 10 weeks.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Each outcome had clearly defined procedures and measurements.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients received the same treatments.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear	Patients aged out of the study at the age of 16, but when comparing data at longer interval points, the baseline mean of the participants that were followed up was calculated. There were several instances where 1,2 or 3 participants did not participate in a data point, but it was accounted for and not a large loss for follow up.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Most measurements were taken at baseline, 12,24 and 36 mo. Each measurement was compared to baseline, but measurements could also be compared to each other to detect more or less change. Multiple measurements not taken before intervention.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Chen (2023)[75]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Outcomes clearly stated for this study
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	The study sample was representative of transgender and nonbinary youth presenting to pediatric subspecialty gender programs and generalizable to this population.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Does not clearly state in this study, but it seems like they were
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear-no power calculation stated
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	All patients received GAH, but no data was available of which therapies each patient got.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were receiving GAH
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	At least four out of five total time points were available for 75% of participants. As a result, there was high covariance coverage with data available for the majority of the sample for each variable of interest at all time points. Within sample, data exhibited skew and were determined to be missing at random(Little's MCAR test: $\chi 2$ [751] = 803.25, p = 0.09). This type of missing data can be appropriately handled using maximum likelihood estimation method. Of those missing too much data, they were excluded from analytical sample (n = 14)
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Latent growth curve model was used
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Data taken at 6,12,18 and 24 months and then put into a latent growth curve model. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Costa (2015)[77]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Can extract population, intervention, comparison and outcome from the abstract.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Clearly stated
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All participants agreed to participate;.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All participants agreed to participate; from T0 to T1, there was no loss of patients. Patients started to fall off after then.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There were no power calculations.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	No, this was unclear because the GnRH analog regimen was not specified.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Patients were lost to follow-up after T1; initial was 201 and final was 71.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	There were four time periods from baseline and P-Values were provided for each one. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
De Vries (2010)[78]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	Not clearly stated inclusion eligibility.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	140 of 196 consecutively referred adolescents were considered eligible for medical intervention between 2000 and 2008 in the clinic.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	A total of 140 adolescents were eligible and 27 were included in analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated questionnaires to assess the outcomes. The outcome measures were clearly defined and assessed consistently across all study participants.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Not clearly stated but it looks like it is not a double-blinded study
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Not all of the participants had post-treatment data for analysis, so only data of adolescents who were administered questionnaires on both assessments could be used for Pre-treatment-Post-treatment comparisons (CBCL: 24, IQ: 25, UGS: 21 and BIS: 22).
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Repeated measures ANOVA was used to ascertain within subject differences between gender dysphoria and body satisfaction at baseline functioning (Pre-T, before the start of GnRH analogs) and after GRS (Post-T) with gender entered as a between-subject variable. Pearson correlations were used to determine relationships between Pre-T and Post-T measures. P value is provided for comparisons.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Except for the baseline visit, only one follow-up assessment was analyzed.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
De Vries (2014)[79]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Can extract population, intervention, comparison and outcome from the abstract.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Located on P2- other study provides additional detail on those who were eligible
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	First 70 were included, not the whole sample. Potential selection bias.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	Limited to the first 70
	5. Was the sample size sufficiently large to provide confidence in the findings?	Other	There were no power calculations.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	Some were on CSH; the treatment regimen was not clearly provided.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Noted when you look at the n provided by the individual results provided in the results tables.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	There were three time periods and a time linear quadratic P-value test was also provided. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
De Vries (2011)[57]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Can extract population, intervention, comparison and outcome from the abstract.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Protocol referenced provides additional detail on those who were eligible
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	First 70 were included, not the whole sample. Potential selection bias
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	Limited to the first 70
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There were no power calculations.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	Some were on CSH; the treatment regimen was not clearly provided.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Noted when you look at the n provided by the individual results provided in the results tables.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided for the main analysis; the other ones had to be inferred.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	There were only two measurement points.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Ghelani (2020)[58]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	They did not describe inclusion eligibility and sampling procedures clearly.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	It looks like they only excluded 4 subjects since they had an incomplete set of body composition data or if any other confounding factor was identified from routine clinic questioning about lifestyle that could affect the results.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Although it is not clearly stated, it looks like all of 36 participants had follow up data.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	They did not mention power calculation in the article. However, in limitation part they state one of limitations is small sample size, especially for the trans girls (N = 11).
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They clearly state the intervention and duration of treatment.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	The outcomes were prespecified and data was recorded from routine clinic monitoring of patients. Validated tools were used for body composition analysis.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes	They state that data was taken from this routine clinic monitoring of patients and subsequently anonymized.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	The participants included in the analysis were those who had completed follow-up data.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Changes in anthropometric and body composition variables between 0 and 12 months were tested using paired t-tests. Statistical significance was considered to be p-value < 0.05.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Outcomes were measured at baseline, 6 months and 12 months of GnRH treatment in TGNB subjects. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

Hannema (2017)[59]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Yes, they wanted to investigate the body changes in 28 trans girls taking long term estrogen.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	The authors stated they invited gender dysphoric adolescents at the VU University Medical Centra in Amsterdam from 1988-2009. They included those that had been taking estrogen for over one year.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	The exact population that was invited to participate and were seen at the clinic is unknown. It is unclear whether this population represents the clinic.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear because they did not mention the numbers for the total population or whether participants were excluded.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	They had 28 participants for the first year, with participants decreasing every year. With a small sample size, it is hard to be confident in the findings.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They took many measures from the population, but they were all described in the methods and appeared to be delivered consistently.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Laboratory values were measured in the same way. They used the same methods and devices to collect other measurements.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	The investigators were not blinded.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	At baseline there were 28 participants. At the first year, all patients are accounted for. The first year is the data they mainly analyzed. They did follow participants for up to three years. By the third year, they only had data for 16 participants. It was not mentioned why there was a change.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	They compared values using a paired t test if normally distributed and Wilcoxon if not normally distributed. They stated that they used these tests on the laboratory values, but p values were not given for lab values. P values that were significant were given for all other measurements
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Baseline was established then they took annual measurements of the patients.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	No, they did not account for confounding factors.
Jarin (2017)[136]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria was clearly described.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All records of patients in that met criteria were reviewed.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All records that met criteria were reviewed
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Previously recorded measurements were retrospectively reviewed.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear if investigators were blinded to participants' intervention.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	For most of cardiovascular parameters, loss to follow-up after baseline was more than 20%.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Repeated measures analysis of variance models were used to evaluate changes in laboratory values and metabolic markers over time for each individual subject. Although P values of pre-to-post changes for each cardiovascular parameter were not reported, statistically significant change (P < .05) was noted.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Values were obtained at or immediately before initiation of therapy (baseline), at 1 to 3 months after initiation, at 4 to 6 months after initiation, and at 6 months and beyond. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Joseph (2019)[137]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	Not clearly stated inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Not clearly stated. 70 patients were referred to clinic, but unclear if that is all referrals to clinic or just the group that was analyzed.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible subjects with adequate data were included in this analysis
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	At the start and then annually during treatment during scheduled clinic visits, the subjects underwent a dual energy X-ray absorptiometry (DXA) scan. BMD and BMAD were valid and reliable measures of bone health outcomes.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear if investigators were blinded to participants' intervention.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	A total of 70 participants had two scans but a total of 31 subjects had three scans. The loss to follow-up rate for scan 3 was more than 20%.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Two analyses were conducted – one assessing pure longitudinal changes in BMD and BMAD (n = 31) in those having three serial DXA scans, and one to extend the observations in the first year on GnRH analog treatment in an additional 39 subjects (total n = 70). As the data followed a normal distribution, paired t tests were used. A p-value less than 0.05 was considered statistically significant.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Some participants had three scans - baseline and 2 subsequent years on GnRH analog treatment. Multiple measures of outcome not taken before intervention.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Kaltiala (2020)[138]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Very clearly stated the aim of the study
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Clearly stated the criteria for which participant's chart they wanted to review.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes-all patient charts that met the criteria within the gender identity service facility were reviewed.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear-no power calculation stated
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	All patients were given cross-sex hormones-but the specific drugs and amounts were not stated.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	For each data point, specific measures were listed to specify definitions and reasons for inclusion or exclusion
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were receiving some sort of treatment
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	This study was done retrospectively, so all patients had competed all of the requirements before chart review.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Comparisons were only done from initial assessment to approximately 12 months later.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Klaver (2018)[83]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Specific aim of retrospective study
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Flowchart of participant inclusion process is given
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All charts that met criteria in institution were used
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear-no power calculation stated
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No, all patients were treated with the same protocol
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Percentages of missing data for anthropometrics were 11% in transwomen and 18% in transmen for start of GnRH analogs, 10% in transwomen and 13% in transmen for start of CHT, and 71% in transwomen and 76% for visit at 22 years of age. For measurements of body composition examined by whole-body dual-energy x-ray absorptiometry, percentages of missing data were 12% in transwomen and 11% in transmen for start of GnRH analogs, 36% in transwomen and 45% in transmen for start of CHT, and 64% in transwomen and 65% in transmen at 22 years of age.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Yes	
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Klaver (2020)[139]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear - don't know how many subjects were not eligible
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear - don't know whether all eligible participants were enrolled
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear - power calculation was not mentioned in the article
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Intervention-related information was clearly stated in the treatment protocol part.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated clinical measures and laboratory data collected at each visit.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were taking the same therapy.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Looks like all included participants had follow-up data.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	They performed linear mixed-model regression analyses with time as an independent variable to estimate the change in cardiovascular risk factors over time. P values were used for changes.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Data was obtained at 3 time points - start of GnRH analog treatment, start of CSH treatment, and 22 years. Multiple measurements not taken before intervention.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Klink (2015)[140]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Study subjects were included when they were at least 21 years of age, gonadectomy had taken place in the period from June 1998 to August 2012, and data on BMD at start of GnRH analog treatment, at start of CSH therapy, and at the age of 22 years were available. The34 eligible subjects and their parents or legal representatives gave written consent for follow-up at start of treatment.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	This study was somewhat representative of the group. Some selection bias was likely introduced with a specific set of inclusion criteria and the need for specific metrics to have been included in past medical charts.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	It looks as if all patients who met criteria were included
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear-no power calculation stated
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Patients all followed the same protocol
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Information was given about how all data was collected.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients had been on the same treatment protocol
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Only 34 subjects were analyzed. No data provided about who was lost in follow-up.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Normally distributed data were compared with the paired sample T test with post-hoc Bonferroni correction. With data that were not normally distributed Wilcoxon Signed Rank test was used for comparison. For correlation analyses, the Pearson's correlation coefficient was calculated for normally distributed data. When data were not normally distributed the Spearman's rank correlation coefficient was calculated. P < .05 was considered statistically significant.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	While data was collected at 3 time points, there was no data collected at multiple time points before intervention
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Kuper (2020)[141]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	Approximately 34% of families did not follow-up after the phone intake (eligible subjects must complete phone intake before the initial assessment).
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	A total of 209 eligible participants were screened and included, but there was a large loss in follow-up

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Power calculation was not mentioned in the article.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They clearly described how many patients were on puberty suppression only, masculinizing or femininizing therapy only, or both.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Validated tools of measuring mental health and body imaging were used to assess outcomes. Survey and clinician data was used.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Validated questionnaires were answered by participants, and they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Loss to follow-up was more than 20% since 148 out of 209 eligible participants had follow-up data. They stated reasons for loss to follow-up.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	To examine change over time, QIDS, SCARED, and BIS scores were first tested for normality by using the Kolmogorov-Smirnov test. Changes in normally distributed variables were examined by using paired t tests, and the Wilcoxon rank test was used when the Kolmogorov-Smirnov value was significant. Cohen's d was used as a measure of effect size (0.2 = small, 0.5 = moderate, and 0.8 = large). Changes in clinical groupings on the QIDS were also examined by using the Wilcoxon rank test. P values were provided for associated tests.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Except for the baseline visit, only one follow-up assessment was analyzed.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Lavender (2023)[142]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	The study has low questionnaire completion rates which could negatively affect sample representative of clinic population. Also, authors mentioned that small sample size could affect the study generalizability
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Everyone met prespecified criteria were included. Only those that completed both surveys had their data included
	5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	In methods section, authors state that a power calculation indicated that, for a medium effect size (0.25) at 80% power, a total sample of 28 young people would be required for an ANOVA repeated-measures design (within-between interaction) for two groups with three measurement time points.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	No specific descriptions about CSHT and GnRH analogs they were receiving.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Validated tools of measuring mental health and psychological and behavioral functioning were used to assess outcomes.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Validated questionnaires were answered by participants and they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Loss to follow-up was more than 50% since only 38 out of 109 eligible participants completed psychosocial questionnaires at baseline, 1 year after GnRH analogs, and 1 year after CSH.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	To assess changes in SRS-2 scores, T-scores calculated from the total score and each of the subscales was analyzed in six separate two-factor repeated-measures ANOVAs. Changes in UGDS scores, and BIS total scores and subscale scores were analyzed in separate two-factor repeated-measures ANOVAs. Changes in CBCL and YSR T-scores, and internalizing and externalizing T-scores were analyzed in three two-factor repeated measures ANOVAs. P values were used for group comparisons.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Measures were taken at three time points: at baseline, 1 year after GnRH analogs, and 1 year after CSH. There were not multiple measures taken before baseline.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Laurenzano (2021)[84]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Yes, to describe the safety and efficacy of SC-T in TM/GD youth at their clinic
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	yes, participants were under the age of 21 and had been using SC-T for at least 6 months who were seen at the clinic
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	yes, all participants were taken from the clinic over an 8 year period
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	It is unclear. The study is a retrospective review aimed to include all the patients of the clinic, but the exact population or if anyone was excluded is unknown.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	119 seems like an appropriate size to power to be able to power the study, but no power calculation was done.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	All participants were started on the same dose of SC-T and doses were escalated by their providers at the same clinic. Participants could receive weekly or biweekly T, but the monthly amount were similar. Per chart review, 31.1% of patients slightly deviated from schedule.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Validated tests and instruments were used to measure T levels, BMI and adverse events.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Retrospective study with the exposure as part of the inclusion criteria
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	There was no loss to follow up since the study was retrospective. When number varied in the analysis, this was disclosed.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Paired T test was used to compare pre/post lab values. P values were given.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Unclear	The number of measurements per patient is unclear. They used the most recent lab values, but did not disclose the average office visits/labs taken per patients.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
López de Lara (2020)[62]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	The objectives of our study were to assess the psychosocial status of patients seeking care in the pediatric endocrinology clinic for gender incongruence and the impact on psychosocial status of cross-sex hormone therapy (CSHT) at 1 year of treatment

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Inclusion section stated criteria and selection process
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	While there is some selection bias in that the patients were volunteers and not randomly selected, they still represent the clinic which they came from. The clinic itself may not fuly represent the broader population as those being treated at an earlier age have more parental support.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Only patients that volunteered from clinic participated-there may have been more that met the criteria, but all that volunteered were enrolled (and one criteria was that they be willing to participate)
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	No mention of power, sample size was small
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They mentioned that they use oral estradiol/intramuscular testosterone at Tanner stage 2-3. More detail could be provided, but since they are the same clinic, the same intervention is probably used.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used standardized tools to measure the outcomes (UGDS, SDQ, STAI, BDI-II)
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No mention of blinding and all TGNB participants received treatment.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	It appears that they had all patients followed up, unless they only reported data from those that they received follow-up data from
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-values are provided
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Only baseline and 12 month measures were taken
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Millington (2021)[89]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	To assess the association of CSH with lipid levels
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	Limited detail provided
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Patients seeking CSH (without GnRH analogs) were recruited from 4 children's hospitals from 2016 to 2018.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	It appears that all of them were recruited.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Power calculation was not provided.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	There were four different children's hospitals involved.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Unclear	Unclear, not all the details were provided
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear, not all the details were provided

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear	It was unclear what percentage was lost to follow-up.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	The graph shows three points (0 months, 6 months, 12 months), only 0 and 6 months were provided. No measurements before intervention
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Millington (2022)[90]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Study aims to look at kidney function for transgender youth receiving GAH over a 2 year period
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	Participants were recruited prior to initiating GAH treatment at one of four study sites. Study protocol was published separately, no eligibility criteria listed.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unknown. Study did take place at a clinic, so mostly likely representative but unclear.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unknown from given information
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Sample size was large at 286, but no power calculation was done
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes, followed same guidance for GAH prescribing
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	While each hospital carried out their own clinic's procedure to measure the outcomes, lab measurements are fairly reliable and all followed the same equations for CKD.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Investigators were not blinded
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	More than 20% of participants were lost after the 6 month mark, and continue to decrease from there. Most likely lost to follow up or the patient has not reached that point in their therapy.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P value provided. Logistic regression was used.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	They did not use an ITS design
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Navabi (2021)[92]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Examine the effects of GnRH analogs on bone mass and body composition
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Youth under the age of 18 seen at clinic with at least 1 DXA measurement were included in study

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Patients were screened at the gender diversity clinic.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear-not enough information given about the charts that were reviewed.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	While there was a large sample, a power calculation was not performed
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Treatment protocol and timing was clearly described under the section "CHEO Endocrine Diversity Clinic Management of Youth With GD"
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	All completed at the same facility, and the treatment protocol is the same for all.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were on GnRH analog treatment
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Loss to follow-up was greater than 20%.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Only two time points appear to be provided.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Neyman (2019)[64]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	yes	yes, to study the use of bicalutamide in MTF youth
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes, patients were selected from endocrine clinic from the Riley hospital if they were only taking bicalutamide
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	The patients were taken from an endocrine clinic, but this may represent a small subset that only uses bicalutamide due to insurance rejection.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	yes, population was given (103 patients) and the authors explained how they got to their 13 patients.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	Most likely 13 patients is too small a sample to be confident in the findings.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	All patients received the same intervention and the Tanner stage was used to evaluate the outcome.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	The Tanner Stages are a classification system used among physicians. There may be a bit of gray area as it is based off observation, which may vary between physician.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	no mention of blinding
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Small population, all accounted for.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No	no statistical measured pre/post. No p value given
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Yes	For 5 patients, there was a second visit recorded. There were most likely to be continuous visits as patients continued therapy.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Olson-Kennedy (2021)[93]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	yes	Claims clearly stated
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They stated eligibility and exclusion criteria for patients that they included, but did not included numbers for the whole population.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Patients records were taken from Gender Clinics in major cities around the nation. Although the exact population is unknown and there is a small population (n = 66), the sampling method allows for these participants to represent the population
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Patients who met criteria and who signed informed consent were enrolled in the study.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	It is possible that 66 patients would be enough to be a sufficient sample size. When evaluated in subgroups, such as transfeminine and transmasculine there appears to be some variability and smaller sized groups. For example, when looking at baseline sex hormone levels, there was a range of testosterone levels from 3 to 365 ng/dL.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	Patient information was taken from medical chart, therefore the outcome was not conducted by the study. Since patients were taken from either a hospital or a larger study, mostly likely labs were taken in a similar way. The study specifies that labs had to be taken before implant, but does not specify when labs had to be taken
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	outcome for pre/post were hormone levels with units specified
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	The article does not mention that assessors were blinded to the patient's exposure
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Some of the numbers for the different outcomes varied by 1 to 3 participants, but overall they were consistent. It was not mentioned why the numbers were inconsistent, but it was most like because they may not have had all the data for each participant
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P value is provided. Wilcoxon Signed Ranked tests were used to compare hormone levels at T0 and T1
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Unclear	Unknown when exactly participants hormone levels were taken and how many times they were taken.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Olson-Kennedy (2018)[143]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	yes	Claims stated- prospective trial evaluating metabolic parameters of gender diverse youth
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	yes	They clearly stated their inclusion criteria

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes, they selected patients by screening the population at the clinic
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes, they enrolled 101 eligible participants.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	The participants were categorized into transfeminine or transmasculine, with groups the size of 25 and 34 people. No power calculation was mentioned
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	The intervention was unclear. It appeared that GAH was personalized based on affordability and patient characteristics. Therapy seemed consistent in the transmasculine group, but varied greatly in the transfeminine group as some were on puberty blockers, some were taking injectable estrogen and some took oral.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	outcomes were physiological parameters that were taken from patient's medical record
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Prospective study. No mention of blinding
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	101 patients enrolled in the study, there was data for 59 patients. Unclear why there was data for so few patients.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes, they used a t test to evaluate if there was a difference from baseline to 2 years of therapy.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Unclear	Unknown how many measurements were taken. Looks like they used the values from the specified time frame.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Perl (2020)[144]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	Very specific inclusion criteria. Of the total of 48 cases, 15 fulfilled these study inclusion criteria and 33 were excluded, leaving room for selection bias less generalizability.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Everyone who met the inclusion criteria was included
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear: They did not talk about a power calculation. However, they only included 15 participants in the analysis.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They clearly described how many patients were puberty suppression and how many patients were added to take testosterone.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated tools to measure blood pressure. However, the BP measurements were taken at the start of each clinic visit and might have been affected by factors, such as anticipation and stress, associated with the visit. 24-hour ambulatory BP monitoring to determine circadian rhythm and variability had not been performed.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were undergoing hormone therapy.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	All patients accounted for. A total of 15 participants were included in the analysis (taking GnRH analogs) and 9 out of 15 had continued to receive testosterone.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Dynamics of outcome variables over time were analyzed with repeated measures analysis of variance or, when correcting for baseline covariate(s), with repeated measures analysis of covariance. A two-sided p-value < 0.05 was considered significant.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	The outcomes were measured after the initiation of GnRH analogs and after the addition of testosterone in those that continued on that therapy.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Perl (2021)[145]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clear measures were collected from charts
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Clear inclusion criteria
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All charts of this population were reviewed for inclusion in review for this clinic-so represents this clinics population
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All patients whose charts that met criteria were enrolled
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	No power calculation was stated, but it was a relatively small sample size
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Dosage of medication clearly defined
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes, all measures were reliable such as BP, hormone levels and weight/height. Although noted that sometimes BP is elevated when patients are nervous at appointments.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients received GnRH analogs and some received CSH
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Since data was retrospectively obtained, all patients had all data points
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	The Kolmogorov–Smirnov test and the Shapiro–Wilk test were applied to test the normal distribution of continuous parameters.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Data was only measured at baseline and follow-up
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Roy (2023)[146]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Cardiovascular parameters were evaluated in patients on testosterone therapy
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	No description of selection process

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	Very small sample size
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear. There was no specific information on how everyone was chosen and included
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Description of testosterone dosage clearly stated
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients were receiving testosterone
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	All patients accounted for in data
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Unclear	Unclear-significance was listed in results section, but no P values provided
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Multiple readings not taken before starting testosterone therapy
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Schagen (2018)[147]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	yes	assess the effects of GnRH analogs and CSH therapy on adrenal androgen levels in adolescents with GD
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes, they had broad inclusion criteria to include those that had diagnosed GD and were legible for treatment.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	yes, they had a broad inclusion criteria with no exclusion criteria. It looks like they included everyone who qualified.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	With no exclusion criteria, it appears that all eligible participants were enrolled.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	They used either a t test (if the sample size was n > 30 or large enough to determine a statistical difference) or the Mann Whitney U test. They did not have data for a few participants, so they used a linear mixed model to increase power.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They followed a consistent protocol among all participants based on age and gender.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes, blood samples were taken every 6 months. Androstenedione levels were determined by a coated tube radioimmunoassay with a limit quantification of 0.5 nmol/L. DHEAS was determined by radioimmunoassay Coat-A-Count.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Prospective study.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear	It is unclear if there was loss to follow up. They stated that one reason for the linear mixed model was that they didn't have data at certain time points for some participants.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	p value was provided. Independent t test or Mann Whitney U test was used.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	They took multiple measurements after intervention had started (every 6 months). They did not take multiple before the intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Schagen (2016)[148]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	There is an aim section.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Listed under the protocol section.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	These patients were being seen at a gender identity clinic from a set time frame.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	It appears that all of them were enrolled.
	5. Was the sample size sufficiently large to provide confidence in the findings?	No	Power calculation was not provided.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	There is a treatment protocol at this clinic.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	There is a treatment protocol at this clinic.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Blinding was not noted.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Other	There were different populations numbers used for different parameters as data was missing from some of the patients. So there was 100% follow-up for some parameters and less for others.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-Values were provided.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Only two time points appear to be provided.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Schagen (2020)[94]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	general research objective was clearly stated.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No	Mentioned that patients must have met DSM-IV criteria for gender dysphoria, but does not mention how or where patients were selected. The data from 45 patients was taken from Vlot et al. and Klink et al.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unsure because it is not clear how these patients were selected. Demographic information not given.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear because not sure how patients were selected to be a part of the study. Eligible population unknown.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There were 121 participants enrolled in the study. This may be enough to correctly power the study, but no information given.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes, bone density scans were calculated from DXA scans and serum bone markers were taken from blood samples.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes, they used aBMD and BMAD calculations. They also got their reference information for the z-scores from reliable sources.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	all participants were subject to the same exposure.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear	There were 121 patients, but the data they had varied since they used data from another study. Also, not all participants continued to GAH during the timeline of the study.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	The p value was provided for all pre/post outcome. BMAD changes were analyzed using linear mixed model. Differences in aBMD was analyzed using Wilcoxon Signed Ranked test.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	They took annual measurements. They had data at baseline, 12 mo, 24 mo and 35 mo. They did not take multiple measurements before treatment/intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Stoffers (2019)[149]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	A total of 64 patients were eligible and 2 of whom declined participation and were excluded. As a result, a total of 62 subjects were included in the analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Power calculation was not mentioned in the article.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	They clearly described how many patients were testosterone.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated clinical measures and laboratory data.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear. Don't know if investigators were blinded to participants' interventions.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Although a total of 62 subjects were included in the analysis, at T12, only 37 subjects had follow-up data and at T24, only 15 had data. The loss to follow-up was more than 20%.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Data were verified for normal distribution using the Shapiro-Wilk test. Differences between time points were analyzed by paired samples t-test for normally distributed data and by the Wilcoxon signed-rank test for data that were not normally distributed. Results were considered statistically significant if P < .05.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Except for the baseline, they also assessed multiple times during 24 months of testosterone treatment (T0, T6, T12, and T24). Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Tack (2017)[150]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria were clearly described.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear; don't know how many subjects were excluded.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	Unclear - don't know whether all eligible participants were enrolled
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population (see details in methods part)
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated clinical measures and laboratory data obtained at each visit.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear if investigators were blinded to participants' intervention.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	A total of 27 subjects were included (treated with CA for at least 6 months), however, 21 participants had been added with E and were included in the analysis of CA + E data.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Statistical tests were aimed at detecting changes in anthropometric, biochemical, and hormonal parameters at 6 and 12 months of treatment with CA + E compared with values before the start of CA + E. A P value less than or equal to 0.05 was considered significant.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Two follow-up time points - change after 6 or 12 months of treatment with CA + E compared with before the start of the treatment. There were not additional measurements taken before baseline.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?		
Tordoff (2022)[96]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	A total of 169 subjects were screened for eligibility and 161 subjects were eligible.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	A total of 161 subjects were eligible, however, the final sample only included 104 youths.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Power calculation was not mentioned in the article.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Validated tools for measuring mental health were used to assess outcomes.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Validated questionnaires were answered by participants and they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Of these individuals included in the final sample, 84 youths (80.8%), 84 youths, and 65 youths (62.5%) completed surveys at 3, 6, and 12 months, respectively.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	They assessed the prevalence of outcomes over time and P values were reported for the pre-to-post changes.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	Yes	Outcomes were measured at baseline, 3, 6, and 12 months of follow-up.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Valentine (2021)[97]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria were clearly described.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	A total of 53 TGNB males were identified and of these, 42 were included in analysis since they were seen at least twice; only 18 had laboratories both pre- and post-testosterone.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	A total of 53 TGNB males were identified and of these, 42 were included in analysis since they were seen at least twice; only 18 had laboratories both pre- and post-testosterone.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	While they did not clearly state lipid parameters, they retrospectively reviewed valid laboratory data for lipid profiles.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear if investigators were blinded to participants' intervention.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	28 participants had lipid panels drawn, and only 18 had laboratories both pre- and post-testosterone.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P values were used for changes.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Except for the baseline visit, only one follow-up assessment was analyzed.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Van der Loos (2021)[69]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated in abstract
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Listed under "Study Design and Population"
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	These patients were all who visited the gender clinic between 1972 and 2018.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Noted in text
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Power calculation was not provided.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	There is a treatment protocol at this clinic.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes, patients were chosen that had the outcomes available. Measures were consistent across patient population.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Blinding was not noted.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Having appropriate measures was an inclusion criterion.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Implicitly- P-values do not seem to be provided but confidence intervals are.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Only three time points
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Vlot (2017)[99]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	Clearly stated population, intervention, comparison and outcome
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	They clearly described inclusion eligibility and sampling procedures.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear; don't know how many subjects were excluded.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool

	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	After applying these criteria to an eligible patient group of 85 transwomen and 130 transmen, a cohort of 28 transwomen and 42 transmen were included in the study.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Power calculation was not mentioned in the article.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Unclear. Don't know if investigators were blinded to participants' interventions.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	A total of 28 transwomen and 42 transmen were included in the study, but only some of them have follow-up data. For example, only 15 transwomen (9 young transwomen and 6 old transwomen) had P1NP measurements for all three time points.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Changes in percentages of bone turnover markers and BMAD between D0, C0 and C24 were calculated as deltas (Δ) with corresponding 95% CI and p-values.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Data was collected at three moments in time: (1) D0: at start of GnRH analog treatment to suppress puberty, (2) C0: at start of CSHT and (3) C24: at 24 months after C0. No other measurements taken before intervention.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Willemsen (2023)[127]	**Question**	**Answer**	**Details and notes**
	1. Was the study question or objective clearly stated?	Yes	The study aimed to evaluate the effect of GnRH analogs and testosterone (CSHT) treatment on growth in transgender boys; and the impact of timing, tempo of dose increase, and BMI on growth.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Data were taken from the Amsterdam Cohort of Gender Dysphoria (ACOG) study, which includes the complete population of all ages seen at the gender identity clinic of Amsterdam University Medical Center from 1972 to December 2018.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	For the most part, all eligible participants were included. One participant was excluded because they were treated with oxandrolone.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	The authors include their reasons for including 146 eligible TGNB boys (based on the inclusion/exclusion criteria), but did not discuss statistical power.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	All participants were treated using the same treatment protocol, but treatments were still individualized by treating clinicians. This could be a potential source of information bias.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	No	Parental height and BA were not routinely obtained in participants in whom it was clinically obvious that they had reached adult height -- no description of how investigators determined clinical obviousness is given.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	There is no mention of blinding in the study design; data was collected retrospectively.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	No participants were evidently lost to follow up since this was a retrospective study, but 31% of the participants in the postpubertal group were missing values for midparental height.

Return to TOC

Table I.I.6. Risk of bias in extracted studies with no control group comparing TGNB patients before and after intervention (pre-post), using the NIH Quality Assessment Tool			
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No	Statistical methods examined changes in outcome measures from before to after the intervention, but no p-values were included. Confidence intervals were used
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?	No	Height and weight were measured every 3-6 months from the start of PS, but BA was only determined at the start of PS and the start of CSHT. Blood draws were untimed in relation to the administration of medication since they were taken on the day of the appointment with the clinician.
	12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	

Return to TOC

APPENDIX I.J: DATA EXTRACTED FROM STUDIES COMPARING TGNB PATIENTS TO OTHER TGNB PATIENTS, ORGANIZED BY OUTCOME

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Achille (2020)[55] A US [redacted] NY) pediatric endocrine gender dysphoria clinic	TGNB adolescents (N = 50) **Eligibility:** Participants were recruited at the clinic, and a vast majority consented/assented. **Sampling method:** Participants must have completed 3 waves of questionnaires at 6-month intervals, for a total of approximately 12 months of observation **Subset definition:** Comparisons were made between **treated and untreated MTF (n = 17)** and **FTM (n = 33)** adolescents	• Mean age (yr, SD): ○ MTF: 15.5 (1.6) ○ FTM: 16.6 (2.5) • Depressed in the prior year: ○ MTF: 12 (70.6) ○ FTM: 20 (60.6) • Reported suicidality: ○ MTF: 2 (11.8) ○ FTM: 3 (9.1) • Seeing a therapist: ○ MTF: 16 (94.1) ○ FTM: 29 (87.9) • Taking psychiatric medications: ○ MTF: 5 (29.4) ○ FTM: 17 (34.0)	• Puberty suppression using: ○ GnRH analogs and/or antiandrogens for MTF youth (n = 15) ○ GnRH analog or medroxyprogesterone for FTM youth (n = 8) • CSH using: ○ Estrogen for MTF youth (n = 7) ○ Testosterone for FTM youth (n = 28)	• No puberty suppression ○ MTF: n = 2 ○ FTM: n = 25 • No CSH ○ MTF: n = 10 ○ FTM: n = 5	Self-reported measures: • CESD-R questionnaire • PHQ-9 questionnaire **Cohort**: outcomes were measured at 12 months (wave 3)	Difference in change from baseline CESD-R: • Puberty suppression vs. none: ○ MTF: Coefficient −2.41, P value = 0.008, R^2 = 0.52 ○ FTM: Coefficient −0.02, P value NS, R^2 = 0.09 • CSH vs. none: ○ MTF: Coefficient −0.56, P value NS, R^2 = 0.21 ○ FTM: Coefficient −0.43, P value NS, R^2 = 0.11 Difference in change from baseline PHQ-9: • Puberty suppression vs. none: ○ MTF: Coefficient −1.89, P value NS, R^2 = 0.28 ○ FTM: Coefficient −0.16, P value NS, R^2 = 0.04 • CSH vs. none: ○ MTF: Coefficient −0.92, P value NS, R^2 = 0.29 ○ FTM: Coefficient −0.23, P value NS, R^2 = 0.04
Allen (2019)[56] [redacted] clinic	**N = 47** TGNB adolescents **Eligibility**: Adolescents and young adults (age range 13–20 years) who received services for GD at the clinic. Participants were included if they had pretest and final assessment data points and were treated with CSH for at least 3 months **Sampling method**: A total of 47 eligible participants had pretest and final assessment data. The pretest	• The age of the participants ranged from 13.73 to 19.04 years (mean = 16.59, SD = 1.19). • The range of treatment length was 113-1016 days (mean = 349, SD = 193). • For most of the sample (90%), the duration of treatment was at, or under, 600 days.	**CSH** treatment	**CSH** with previous **GnRH analog** treatment	• The ASQ was used to measure suicidality **Cohort:** outcomes are measured after the exposure has been measured (retrospective review)	Suicidality: • The findings between CSH-only and GnRH analogs + CSH were statistically significant at T1 ($P < 0.05$), with the GnRH analog + CSH cohort having lower ASQ scores than the CSH-only group. ○ The estimated adjusted mean (standard error) of ASQ scores for CSH-only group was 1.06 (1.3) at T0 and .33 (.77) at T1. The estimated adjusted mean (standard error) of ASQ scores for GnRH analogs + CSH group was 1.08 (1.49) at T0 and .01 (.02) at T1.

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	for 23 participants occurred at their first contact with the clinic (the other participants' pretest assessment was completed at a subsequent visits to clinic but prior to starting CSH). Thirteen of the participants first presented to our clinic in 2015; 19 in 2016; 14 in 2017; and one in 2018. Patients are administered questionnaires and screeners at the beginning of their clinic visit, either at the time of the diagnostic evaluation or during a follow-up appointment with the multidisciplinary team. Responses are reviewed by the mental health professional prior to meeting with the patient. **Subset definition**: Of the 47 participants, Comparisons were made between those that were administered GnRH analogs prior to beginning CSH (GnRH analogs + CSH subgroup) (n = 8) and those that were not received GnRH analogs prior to being administered CSH (CSH-only subgroup) (n = 39).	• Assigned female at birth was n = 33 (70.2%) and assigned male at birth was n = 14 (29.8%). • The majority of participants were white N = 39 (83%).				
	Subset definition: Comparisons were made between youth AMAB (n = 33) and AMAB (n = 14)		**AFAB**	**AMAB**		Suicidality: • A significant effect was not observed for sex assigned at birth with regard to suicidality scores, after controlling for duration of treatment, F(1, 44) = .08, *P* = .79, partial η^2 = .002.

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• The estimated adjusted mean (standard error) of ASQ scores for AFAB group was 1.01 (.23) at T0 and .29 (.13) at T1. The estimated adjusted mean (standard error) of ASQ scores for AMAB group was 1.21 (.36) at T0 and .24 (.19) at T1.
Bauer (2021)[102] 10 Canadian medical clinics located across Canada (eg, [redacted] All clinics had ≥ 1 pediatric specialist, and resources to mental health physicians.	Pubertal and post-pubertal youth (N = 174) **Eligibility:** GD diagnosis, < 16 yrs of age, no previous use of estrogen, testosterone, or GnRH analogs (except contraceptives), and referred for hormone use **Sampling method:** Recruitment processes differed due to the site location and requirements set by the Research Ethics Board. Potential eligible participants were invited to contact the research investigator prior to their first visit **Subset definition:** Comparisons were made between **transfeminine (n = 37)** and **transmasculine (n = 137)** participants	**Assigned sex at birth:** • AMAB: 37 (21.3) • AFAB: 137 (78.7) **Age**, *P* = NS • 10–13 yrs old: ○ Transfeminine: 14 (40.6) ○ Transmasculine: 40 (28.7) • 14–15 yrs old: ○ Transfeminine: 23 (59.4) ○ Transmasculine 97 (71.3) **Gender identity,** *P* < .001 • Male or primarily a boy: ○ Transfeminine: 1 (2.4) ○ Transmasculine: 125 (92.2) • Female or primarily a girl: ○ Transfeminine: 32 (87.1) ○ Transmasculine: 0 (0) • Nonbinary: ○ Transfeminine: 3 (10.5) ○ Transmasculine: 11 (7.8)	Pubertal and post-pubertal transfeminine youth (n = 37)	Pubertal and post-pubertal transmasculine youth (n = 137)	Self-reported measures: • 5-item MDS questionnaire • 5-item OASIS questionnaire • Suicidal ideation and attempts were evaluated using the Canadian Community Health Survey **Cross-sectional:** exposures/outcomes were measured at the same time	There was a significant difference in the MDS questionnaire scores between the cohorts, with transmasculine youth feeling depressed more often than transfeminine youth, *P* = .03. There were no significant differences between the cohorts on any other reported measures for mental health. Self-assessed mental health (n, weighted %), *P* = NS: • Excellent or very good: ○ Transfeminine: 16 (38.8) ○ Transmasculine: 27 (19.0) • Good: ○ Transfeminine: 8 (23.4) ○ Transmasculine: 34 (22.6) • Fair or poor: ○ Transfeminine: 13 (37.7) ○ Transmasculine: 75 (58.4) • MDS ≥ 4 (depressed often or always; n, weighted %), *P* = .03 ○ Transfeminine: 4 (7.6) ○ Transmasculine: 29 (22.0) • OASIS ≥ 8 (probable anxiety; asked only participants ≥ 12 years of age; n, weighted %), *P* < .001: ○ Transfeminine: 10 (35.0) ○ Transmasculine: 84 (71.4) • Self-harm in the past year (n, weighted %), *P* = NS:

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		Living in their identified gender, *P* < 0.001 • All the time: ○ Transfeminine: 24 (58.1) ○ Transmasculine: 122 (90.1) • Some of the time: ○ Transfeminine: 11 (37.8) ○ Transmasculine: 13 (9.9) • Not at all: ○ Transfeminine: 2 (4.1) ○ Transmasculine: 0 (0) **Other providers** whom the adolescent and family had met with to discuss gender with prior to the clinic visit: • Family physician, *P* = NS: ○ Transfeminine: 23 (68.2) ○ Transmasculine: 85 (68.6) • Pediatrician or adolescent medicine, *P* = NS: ○ Transfeminine: 13 (33.4) ○ Transmasculine: 39 (30.5) • Psychologist or psychiatrist, *P* = NS ○ Transfeminine: 18 (46.2) ○ Transmasculine: 64 (45.4) • Counselor, elder, religious leader, *P* = NS:				○ Transfeminine: 18 (61.5) ○ Transmasculine: 92 (69.0) • Suicidal ideation (n, weighted %): ○ Ever, *P* = NS ▪ Transfeminine: 19 (58.8) ▪ Transmasculine: 76 (58.0) ○ In the past year, *P* = NS ▪ Transfeminine: 11 (35.1) ▪ Transmasculine: 45 (34.4) • Suicide attempt (n, weighted %): ○ Ever, *P* = NS ▪ Transfeminine: 9 (30.8) ▪ Transmasculine: 44 (37.3) ○ In the past year, *P* = NS ▪ Transfeminine: 4 (12.4) ▪ Transmasculine: 20 (17.9)

[a] Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)

[b] Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).

[c] Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ Transfeminine: 17 (50.7) ○ Transmasculine: 64 (45.6)				
Cantu (2020)[74] An academic medical center in the Northwestern United States between September 2017 and June 2019	**N = 80** TGNB adolescents **Eligibility**: Youth were included in the current study if they (1) were between the ages of 11 and 18 years, (2) had attended both an initial visit and one follow-up appointment, and (3) completed measures assessing acute distress (PHQ-9 and GAD-7) at both visits **Sampling method**: All youth ages 11 and older complete anxiety and depression screeners at every visit regardless of mental health diagnoses or symptom severity. Second visit is recommended 3–4 months after the initial visit. **Subset definition**: • N = 80 TGNB adolescents (N = 80 youth completed PHQ-9 screeners at both time points and N = 78 youth completed GAD-7 screeners at both time points) • Comparisons were made between Participants who received HT between their initial visit, and follow-up appointment (n = 28 for PHQ-9, n = 27 for GAD = 7), and those who did not (n = 51 for PHQ-9, n = 50 for GAD-7)	Full cohort: • Mean (SD) age was 15.1 (1.8) • affirmed male gender, n (%), was 58 (72.5) • follow-up time in weeks, mean (SD) was 20.4 (10.2) • Only N = 1 (1.3%) individual initiated HT before the initial visit • 28 youth initiated HT between initial visit and first follow-up ○ Of those 28 youth, 6 were started on feminizing hormones and 22 were started on masculinizing. ○ A total of 17 youth initiated hormone blockers between their initial visit and first follow-up, 4 of which also initiated HT. • N = 77 (96.2%) received neither HT nor hormone blockers at initial visit • N = 38 (47.5%) received neither HT nor hormone blockers at follow up appointment.	Participants **receiving HT** between initial visit and first follow-up appointment (n = 28 for PHQ-9, n = 27 for GAD = 7)	Participants **not receiving HT** between initial visit and first follow-up appointment (n = 51 for PHQ-9, n = 50 for GAD-7)	• PHQ-9: a 9-item screening measure of depression. • GAD-7: a 7-item screening measure of anxiety **Cohort**: outcomes are measured after the exposure has been measured (retrospective chart review)	A repeated measures factorial ANOVA did not reveal any significant differences in depression and anxiety scores among youth who did versus did not initiate HT following their intake visit. **PHQ-9:** • There was no significant difference in scores between the HT initiated subjects, with a mean score (SD) of 9.8 (7.1) at initial visit and 10.3 (7.3) at follow-up appointment compared to those who had not initiated HT with a mean score (SD) of 11.1 (6.3) at initial visit and 10.1 (5.9) at follow-up appointment, *P* = NS **GAD-7:** • There was no significant difference in scores between the HT initiated subjects, with a mean score (SD) of 8.4 (6.4) at initial visit and 8.5 (5.5) at follow-up appointment, compared to those who had no HT, with a mean score (SD) of 9.6 (5.9) at initial visit and 9.1 (5.8) at follow-up appointment, *P* = NS

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Chen (2021)[104] Four pediatric academic medical centers in the US	Adolescents seeking GnRH analog therapy (N = 95) **Eligibility:** Patients aged 8 to 20 yrs old, diagnosed with GD, eligible to start GnRH analogs or CSH as deemed by the primary treatment team, proficient in English, and seeking care at one of the study clinic locations **Sampling method**: Patients presenting at one of the four medical centers between July 2016 and September 2018, desiring to start GnRH analogs or CSH treatment for GD **Subset definition:** Comparisons were made between **AFAB (n = 46)** and **AMAB (n = 49)**	Mean age (yr, SD), P value = 0.002: • AFAB: 10.76 (1.43) • AMAB: 11.65 (1.36) **Gender identity**, P value = 0.000: • Transmasculine/Male: ○ AFAB: 40 (87) ○ AMAB: 1 (2) • Transfeminine/Female: ○ AFAB: 1 (2.2) ○ AMAB: 44 (89.8) • Nonbinary: ○ AFAB: 5 (10.9) ○ AMAB: 4 (8.2)	AFAB patients seeking GnRH analog therapy (n = 46)	AMAB patients seeking GnRH analog therapy (n = 49)	Self-reported measures: • BDI-Y questionnaire • RCMAS-2 questionnaire • Suicide attempts and suicidal ideation **Cross-sectional:** exposures/outcomes were measured at the same time	There was a significant difference in total anxiety and worry scores between the AFAB and AMAB cohorts, but no other significant differences between groups in reported measures were found. • BDI-Y (n = 91; n, %), *P* = NS: ○ Severe depression: ▪ AFAB: 2 (4.7) ▪ AMAB: 5 (10.4) ○ Moderate depression: ▪ AFAB: 5 (11.6) ▪ AMAB: 5 (10.4) ○ Mild depression: ▪ AFAB: 4 (9.3) ▪ AMAB: 5 (10.4) ○ Minimal depression: ▪ AFAB: 32 (74.4) ▪ AMAB: 33 (68.8) • Mean RCMAS-2 T-score (n = 84; SD): ○ Total anxiety, *P* = .047: ▪ AFAB: 45.67 (11.65) ▪ AMAB: 51.2 (13.38) ○ Physiological anxiety T-score, *P* = NS: ▪ AFAB: 45.49 (10.6) ▪ AMAB: 49.15 (12.07) ○ Worry T-score, *P* = .029: ▪ AFAB: 47.11 (11.57)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ AMAB: 53.2 (13.42) ○ Social anxiety T-score, *P* = NS: ▪ AFAB: 45.53 (10.57) ▪ AMAB: 49.88 (12.87) • Suicidal ideation (n, %): ○ Experienced lifetime suicidal ideation (n = 89), *P* = NS: ▪ AFAB: 7 (7.9) ▪ AMAB: 14 (15.7) ○ Experienced lifetime suicidal ideation with plan (n = 21), *P* = NS: ▪ AFAB: 3 (3.4) ▪ AMAB: 5 (5.6) ○ Experienced suicidal ideation in the past 6 months (n = 20), *P* = NS: ▪ AFAB: 3 (3.4) ▪ AMAB: 9 (10.1) ○ Experienced suicidal ideation in the past 6 months with plan (n = 8), *P* = NS: ▪ AFAB: 1 (1.1) ▪ AMAB: 3 (3.4) • Suicide attempt (n, %): ○ Experienced lifetime suicide attempt (n = 18), *P* = NS: ▪ AFAB: 1 (1.1) ▪ AMAB: 6 (33.3) ○ Experienced suicide attempt in the past 6 months (n = 8), *P* = NS:

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ AFAB: 0 (0) ▪ AMAB: 2 (2.2)
	Adolescents seeking CSH therapy (ie, testosterone or estrogen) (N = 316) **Eligibility:** Same as above **Sampling method**: Same as above **Subset definition:** Comparisons were made between **AFAB (n = 205)** and **AMAB (n = 111)**	• Mean age (yr, SD), *P* = NS ○ AFAB: 15.87 (1.76) ○ AMAB: 16.23 (2.08) • **Gender identity**, *P* = 0.000: ○ Transmasculine/Male: ▪ AFAB: 191 (93.72) ▪ AMAB: 0 (0) ○ Transfeminine/Female: ▪ AFAB: 1 (0.5) ▪ AMAB: 105 (94.6) ○ Nonbinary: ▪ AFAB: 13 (6.3) ▪ AMAB: 6 (5.4)	AFAB patients seeking CSH therapy (n = 205)	AMAB patients seeking CSH therapy (n = 111)	Self-reported measures: • BDI-II • RCMAS-2 questionnaire • Suicide attempts and suicidal ideation **Cross-sectional:** exposures/outcomes were measured at the same time	• Youth designated female at birth attempted suicide at a significantly higher rates than youth designated male at birth. There were no other statistically significant differences between groups in mental health measures. • BDI-II (n = 308; n, %), *P* = NS: ○ Severe depression: ▪ AFAB: 26 (13.1) ▪ AMAB: 22 (20.2) ○ Moderate depression: ▪ AFAB: 37 (18.6) ▪ AMAB: 20 (18.3) ○ Mild depression: ▪ AFAB: 35 (17.6) ▪ AMAB: 18 (16.5) ○ Minimal depression: ▪ AFAB: 101 (50.8) ▪ AMAB: 49 (44.9) • Mean RCMAS-2 T-score (n = 309; SD): ○ Total anxiety, *P* = NS: ▪ AFAB: 40.32 (11.52) ▪ AMAB: 59.12 (11.47) ○ Physiological anxiety T-score, *P* = NS: ▪ AFAB: 55.66 (11.51) ▪ AMAB: 54.05 (9.99)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ Worry T-score, *P* = NS: ▪ AFAB: 61.89 (11.53) ▪ AMAB: 61.41 (11.94) ○ Social anxiety T-score, *P* = NS: ▪ AFAB: 58.41 (10.74) ▪ AMAB: 57.36 (11.69) • Suicidal ideation (n, %): ○ Experienced lifetime suicidal ideation (n = 305), *P* = NS: ▪ AFAB: 133 (43.6) ▪ AMAB: 70 (23.0) ○ Experienced lifetime suicidal ideation with plan (n = 204), *P* = NS: ▪ AFAB: 62 (20.3) ▪ AMAB: 27 (8.9) ○ Experienced suicidal ideation in the past 6 months (n = 207), *P* = NS: ▪ AFAB: 67 (22.0) ▪ AMAB: 41 (13.4) ○ Experienced suicidal ideation in the past 6 months with plan (n = 89), *P* = NS: ▪ AFAB: 20 (6.6) ▪ AMAB: 12 (3.9) • Suicide attempt (n, %): ○ Experienced lifetime suicide attempt (n = 207), *P* = .001 ▪ AFAB: 60 (19.7) ▪ AMAB: 15 (4.9)

[a] Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)

[b] Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).

[c] Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ Experienced suicide attempt in the past 6 months (n = 74), *P* = NS: ▪ AFAB: 9 (3.0) ▪ AMAB: 2 (0.7)
Chen (2023)[67] USA- Gender clinics at the [redacted] from July 2016 through June 2019	TGNB adolescents (N = 315) Eligibility: Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating GAH as part of their clinical care. For minors, parental consent was required to initiate treatment. Sampling Method: Youth were recruited from 4 different sites at the start of GAH therapy. They were enrolled if they met inclusion criteria Subset definition: • Comparisons were made between those designated female at birth(n = 204) and those designated male at birth (n = 111) • Comparisons were made between those identifying as white (n = 210) and those not identifying as white (n = 105) • Comparisons were made between those who started GAH in early puberty (n = 24)	• participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) • Higher percentage of those designated female at birth (64.8%) then male. • Mostly Non-Latinx or non-Latin white (58.1%) Tanner stage at GAH initiation: no (%) • Early n = 24 ○ Stage 1: 2 (0.6) ○ Stage 2: 14 (14.1) ○ Stage 3: 9 (2.9) • Late n = 291 ○ Stage 4: 29 (9.2) ○ Stage 5: 262 (83.2)	TGNB youth starting GAH in early puberty (Tanner stages 1-3) (n = 24)	TGNB youth starting GAH in later puberty (Tanner stages 4-5) (n = 291)	• **Depression symptoms** were assessed using the 21-item BDI-II. • **Anxiety symptoms** were assessed by the RCMAS2 **Cohort:** outcomes were measured at baseline, 6, 12, 18 and 24 months of GAH treatment	Depression: • Those that had initiated GAH in early puberty had a significantly lower score of 9.57 (8.26) compared to 17.00 (12.21) for those who initiated GAH in later puberty at baseline. *P* < .001 Anxiety • Those that had initiated GAH in early puberty had a significantly lower score of 51.54 (12.20) compared to 60.75 (11.15) for those who initiated GAH in later puberty at baseline. *P* < .001
			TGNB youth identifying as white (n = 210)	TGNB youth of color (n = 105)		Depression: • White youth had a greater decrease in depression scores over 24 months of GAH therapy than youth of color with a time-invariant effect on slope of 1.70, 95% CI (0.23 to 3.15) • Racial and ethnic identity were not associated with any other outcomes at baseline or over time
			TGNB youth DFAB (n = 204)	TGNB youth DMAB (n = 111)		Depression: • Scores decreased over 24 months of GAH among those designated female at birth, but not among those designated male at birth with a time-invariant effect of 1.91, 95% CI (0.33 to 3.50) Anxiety • Scores decreased over 24 months of GAH among those designated female at birth, but not among those designated

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	and those who started in later puberty (n = 291)					male at birth with a time-invariant effect on slope of 1.56, 95% CI (0.01 to 3.10)
Conn (2023)[105] Four pediatric gender clinics located in major metropolitan areas of the US [redacted]	N = 315 TGNB youth aged 12-20 **Eligibility:** Participants had gender dysphoria as determined by a clinician, have English proficiency, and be psychiatrically and cognitively able to give informed consent/assent to participation. The use of gender affirming hormones (GAH) must be appropriate and the participant must be ready to start CSH (cross-sex hormones; estrogen or testosterone) as determined by the clinical team. **Sampling method**: Data was collected using a computer-assisted survey instrument. The data for this study came from the larger Trans Youth Care Study, an ongoing, multisite, observational study of TGNB initiating medical treatment with CSH. Investigators only used the CSH cohort baseline data of the study, which were collected before participants started CSH. The baseline survey included 316 individuals, but one was excluded due to not meeting inclusion criteria.	• Age: • Mean (SD) age was 16.01 (1.87) • Gender: • 60.3% transmasculine/male • 33.6% transfeminine/female • 3.8% nonbinary • 3% other	TGNB youth with internalized transphobia	TGNB youth without internalized transphobia	• Anxiety was measured using the Revised-Children's Manifest Anxiety Scale • Depressive symptoms were measured using the Beck Depression Inventory-II • Internalized transphobia and gender-identity pride was measured using the Gender Minority Stress and Resilience Measure for Adolescents • Perceived parental support was measured using 4 items adapted from the Family subscale of the MSPSS Cross-sectional: exposures/outcomes were measured at the same time before participants initiated CSH	Anxiety • Higher levels of anxiety were associated with greater internalized transphobia. rho = 0.427, *P* < 0.01 • Internalized transphobia was significantly associated with greater anxiety. b = 0.47 (95% CI = 0.15-0.79), *P* < .01 Depression • Higher levels of depression were associated with greater internalized transphobia. rho = 0.436, *P* < 0.01 • Internalized transphobia was significantly associated with greater depression. b = 0.53 (95% CI = 0.37-0.69), *P* < .01
			TGNB youth AFAB (n = 204)	TGNB youth AMAB (n = 111)		• Gender Identity pride • Being AFAB was associated with lower levels of gender identity pride compared to those AMAB (rho = 00.178, *P* < .01)
			TGNB youth with greater perceived parental support	TGNB youth without greater perceived parental support		• Internalized transphobia • Greater perceived parental support was significantly associated with lower internalized transphobia (rho–0.252, *P* < .01) • Anxiety • Greater perceived parental support was significantly associated with lower anxiety (rho = -0.209, *P* < .01) • Depression

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• Greater perceived parental support was significantly associated with lower depression (rho = -0.259, *P* < .01)
De Graaf (2022)[108] [redacted], Ontario; the [redacted] the Netherlands; and [redacted] UK.	**Population N = 2771 TGNB adolescents** • **Eligibility:** Patients referred and assessed for GD at one of the three clinic sites between 1978 and 2017 • **Sampling method:** Not specified • **Subset definition:** Total population (N = 2771) patients were seen at 3 clinic sites: ○ Gender Identity Service at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario (*n* = 260) ○ The Center of Expertise on Gender Dysphoria at the Amsterdam University Medical Centers, VUmc site in Amsterdam, the Netherlands (*n* = 266) ○ The Gender Identity Development Service at the Tavistock and Portman National Health Service Trust in London, UK (*n* = 2245)	• Age (in years), mean (SD), *P* < .001 ○ Toronto: 16.66 (1.75) ○ Amsterdam: 15.91 (1.42) ○ London: 15.93 (1.07) • Birth-assigned sex, N (%), *P* < .001 ○ Male ▪ Toronto: 129 (49.6) ▪ Amsterdam: 123 (46.2) ▪ London: 685 (30.5) ○ Female ▪ Toronto: 131 (50.4) ▪ Amsterdam: 143 (53.8) ▪ London: 1560 (69.5) • Year of assessment, mean (SD), range, *P* < .001 ○ Toronto: 2004.72 (7.59), 1978-2012 ○ Amsterdam: 2004.87 (5.77), 1990-2012 ○ London: 2014.99 (1.77), 2009-2017 • Full-Scale IQ, mean (SD), *P* = .005 ○ Toronto:102.08 (18.85) ○ Amsterdam: 97.16 (16.37) ○ London: N/R	TGNB youth seen at the Toronto clinic	TGNB youth seen at the Amsterdam or London clinic	Demographic information and CBCL and YSR scores were obtained at the time of baseline measurement prior to any hormonal treatment for GD. Linear regression analysis was used to examine correlations and predictors of suicidality (Items 18 and 91 from CBCL and the YSR.) Cross sectional: Exposures/outcomes were measured at the same time, at time of baseline assessment, prior to any hormonal treatment for GD.	**Demographic and General Child Behavior Checklist/ Youth Self-Report Metrics-univariable comparison** • On average, the Toronto clinic adolescents were significantly older than both the Amsterdam and London clinic adolescents. • The percentage of birth-assigned females in the London clinic was significantly higher than the percentage in the Toronto and Amsterdam clinics. • The year of assessment for the London clinic adolescents was, on average, significantly more recent than both the Toronto and Amsterdam adolescents. • For IQ, social class, and parent's marital status, data were available only from the Toronto and Amsterdam clinics. On average, the adolescents from the Toronto clinic had a significantly higher IQ than the adolescents from the Netherlands but did not differ significantly with regard to parent's social class or marital status. • On the CBCL, the adolescents from the Toronto clinic had, on average, more behavior problems than the adolescents from the London clinic who, in turn had more behavior problems than the adolescents from the Amsterdam clinic. • On the YSR, the adolescents from the London clinic had, on average, more behavior problems than the adolescents from the Toronto clinic who, in turn, had more behavior problems than the adolescents from the Amsterdam clinic. • On the CBCL (poor) peer relations scale, the adolescents from the Toronto clinic had, on average, a higher score than

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• Social Class, N(%), *P* = NS ○ 1–2 ▪ Toronto: 201 (77.3) ▪ Amsterdam: 171 (78.1) ▪ London: N/R ○ 3 ▪ Toronto: 59 (22.7) ▪ Amsterdam: 48 (21.9) ▪ London: N/R • Parent's marital status, N (%), *P* = NS ○ Both Parents ▪ Toronto: 116 (44.6) ▪ Amsterdam: 117 (51.1) ▪ London: N/R ○ Other ▪ Toronto: 144 (55.4) ▪ Amsterdam:112 (48.9) ▪ London: N/R • CBCL Gender N (%), *P* < .001 Item 110 ("Wishes to be of opposite sex"/ "I wish I were of the opposite sex") ○ 0 ▪ Toronto: 13 (5.8) ▪ Amsterdam: 16 (6.4) ▪ London: 25 (1.8)				the adolescents from both the Amsterdam and the London clinic. • On the YSR (poor) peer relations scale, the adolescents from the Toronto clinic and the London clinic had, on average, a higher score than the adolescents from the Amsterdam clinic. • For the CBCL gender identity item, the percentage of adolescents from the London clinic who received a rating of a 1 or a 2 was significantly higher than the percentage of adolescents from the Toronto and Amsterdam clinics, although in all clinics the percentage was ≥ 93% • On the YSR, the between-clinic difference was not significant, with all percentages ≥ 95%. • For the suicidality composite based on parent-report, the adolescents from the Toronto and London clinics had, on average, a higher score than the adolescents from the Amsterdam clinic. **Correlation between the CBCL and YSR suicidality sum score as a function of clinic and birth-assigned sex.** • In the Toronto sample, the correlation for the birth-assigned males (r = 0.12) was not significant, but was significant for the birth-assigned females (r = 0.52, *P* < .001). • In the Amsterdam sample, the correlation for the birth-assigned males (r = 0.61) and birth-assigned females (r = 0.63) were both significant, *P* < .001. • In the London sample, the correlation for the birth-assigned males (r = 0.02) and birth-assigned females (r = 0.07) were both not significant. **Predictors of Suicidality-logistic regression**

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ 1 or 2 ▪ Toronto: 211 (94.1) ▪ Amsterdam: 233 (93.5) ▪ London: 1399 (98.2) • YSR Gender, N(%), *P* = NS Item 110 ("Wishes to be of opposite sex"/"I wish I were of the opposite sex") ○ 0 ▪ Toronto: 10 (4.2) ▪ Amsterdam: 8 (3.3) ▪ London: 27 (2.0) ○ 1 or 2 ▪ Toronto: 228 (95.7) ▪ Amsterdam: 233 (93.5) ▪ London: 1337 (98.0) • CBCL Poor Peer Relations Scale (Sum), mean (SD), *P* < .001 ○ Toronto (n = 239): 2.42 (1.88) ○ Amsterdam (n = 250): 1.38 (1.57) ○ London (n = 1594): 1.60 (1.60) • YSR Poor Peer Relations Scale (Sum), mean (SD), *P* < .001 ○ Toronto (n = 244): 2.09 (1.68) ○ Amsterdam (n = 242): 1.40 (1.49) ○ London (n = 1553): 2.04 (1.70)				Toronto vs. Amsterdam: • Predictor of CBCL Suicidality, *B, P,* (95% CI) ○ The adolescents from the Toronto clinic had higher reports of suicidality than the adolescents from the Amsterdam clinic. ○ A higher degree of suicidality was associated with birth-assigned female transgender adolescents, adolescents who lived in a family configuration classified as "Other," a lower social class background, and more behavioral and emotional problems in general. ▪ Clinic: -0.260, *P* = .005, (-0.441, -0.078) ▪ Birth-assigned sex: 0.170, *P* = 0.050, (0.000, 0.341) ▪ YOA: − 0.013, 0.056, (− 0.025, 0.000) ▪ Age at assessment:0.000, *P* = NS ▪ Full-scale IQ:− 0.001, *P* = NS ▪ Parent's marital status: − 0.200, *P* = 0.026, (− 0.375, − 0.025) ▪ Parent's social class: 0.266, *P* = 0.020, (0.042, 0.490) ▪ Poor peer relations: 0.016, *P* = NS ▪ General behavior problems: 0.014, *P* < .001, (0.011, 0.018 • Predictor of YSR Suicidality, B, *P*, (95% CI) ○ A higher degree of suicidality was associated with birth-assigned female transgender adolescents, poor peer relations, and more behavioral and emotional problems in general. ▪ Clinic: -0.035, *P* = NS ▪ Birth-assigned sex: 0.212, *P* = .025 (0.041, 0.383)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• CBCL sum of items, mean (SD), *P* < .001 ○ Toronto (n = 240): 59.51 (30.91) ○ Amsterdam (n = 250): 47.48 (27.32) ○ London (n = 1603): 49.24 (30.15) • YSR sum of items, mean (SD), *P* < .001 ○ Toronto (n = 244): 63.92 (27.19) ○ Amsterdam (n = 242): 52.93 (24.59) ○ London (n = 1562): 68.24 (30.21) • CBCL sum of suicidality items, mean (SD), *P* < .001 ○ Toronto (n = 237): 0.83 (1.09) ○ Amsterdam (n = 250): 0.43 (0.75) ○ London (n = 1562): 0.98 (1.17) • YSR sum of suicidality items, mean (SD), *P* < .001 ○ Toronto (n = 244): 0.82 (1.06) ○ Amsterdam (n = 242): 0.57 (0.93) ○ London (n = 1515): 1.29 (1.33)				▪ YOA: 0.001, *P* = NS ▪ Age at assessment: -0.01, *P* = NS ▪ Full-scale IQ: -0.001, *P* = NS ▪ Parent's marital status:0.022, *P* = NS ▪ Parent's social class: -0.028, *P* = NS ▪ Poor peer relations: 0.066, *P* = 0.034, (0.005, 0.127) ▪ General behavior problems:0.020, *P* < .001, (0.016,0.024) **Toronto vs. London** • Predictor of CBCL Suicidality, *B, P,* (95% CI) ○ The adolescents from the London clinic had a higher degree of suicidality than the adolescents from the Toronto clinic. ○ A higher degree of suicidality was associated with birth-assigned female transgender adolescents and more behavioral and emotional problems in general. ▪ Clinic: 0.207, *P* < 0.001, (0.107, 0.307) ▪ Birth-assigned sex: 0.254, *P* < 0.001, (0.157, 0.352) ▪ YOA: − 0.014, *P* = 0.059, (− 0.029, 0.001) ▪ Age at assessment: 0.035, *P* = 0.076, (− 0.004, 0.073) ▪ Poor peer relations: 0.024, *P* = NS ▪ General behavior problems: 0.021, *P* < .001, (0.019, 0.023) • Predictor of YSR Suicidality, β, *B, SE, t, P,* (95% CI) ○ The adolescents from the London clinic had higher reports of suicidality than the adolescents from the Toronto clinic

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						and a higher degree of suicidality was also associated with more behavioral and emotional problems in general. ▪ Clinic: 0.203, *P* < .001, (0.091, 0.315) ▪ Birth-assigned sex: 0.097, *P* = 0.077, (− 0.204, 0.010) ▪ YOA: − 0.007, *P* = NS ▪ Age at assessment:.015, *P* = NS ▪ Poor peer relations: − 0.019, *P* = NS ▪ General behavior problems: 0.027, *P* < .001, (0.025, 0.029) **Amsterdam vs. London** • Predictor of CBCL Suicidality, β, B, SE, t, P, (95% CI) o The adolescents from the London clinic had higher reports of suicidality than the adolescents from the Amsterdam clinic. o A higher degree of suicidality was associated with birth-assigned female adolescents and more behavioral and emotional problems in general. ▪ Clinic: 0.540, *P* < .001, (0.336, 0.744) ▪ Birth-assigned sex: 0.252, *P* < .001, (0.157, 0.347) ▪ YOA: − 0.013, *P* = NS ▪ Age at assessment: 0.026, *P* = NS ▪ Poor peer relations: 0.017, *P* = NS ▪ General behavior problems: 0.021, *P* < .001, (0.019, 0.023) • Predictor of YSR Suicidality, *B, P,* (95% CI) o The adolescents from the London clinic reported a higher degree of suicidality than the adolescents from the Amsterdam clinic and a higher degree of suicidality was

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						also associated with more behavioral and emotional problems in general. ▪ Clinic: 0.331, *P* = .006, (0.096, 0.566) ▪ Birth-assigned sex: 0.073, *P* = NS ▪ YOA: 0.000, *P* = NS ▪ Age at assessment: 0.031, *P* = NS ▪ Poor peer relations: − 0.025, *P* = NS ▪ General behavior problems: 0.028, *P* < .001, (0.026, 0.030)
de Vries (2011)[106] [redacted]	**N = 105 TGNB adolescents** **Eligibility**: diagnosed with GD and seen between April 2002-December 2009. **Sampling method**: 105 out of 201 adolescents consecutively enrolled • 17 dropped out of the diagnosis procedure • 18 were not invited since they were included • 61 declined **Subset:** Comparisons were made between TGNB natal males (n = 53) vs TGNB natal females (n = 52)	• Full cohort: • mean (SD) age was 14.6 years (2.2) • mean (SD) full-scale IQ was 97.4 (14.2); for • living arrangements, ○ 51.5% lived with both parents ○ 48.5% lived with other • parents' education status ○ 15.5% had high ○ 68.0% had medium ○ 16.5% had low • Natal male: • mean (SD) age was 14.5 years (2.2) • mean (SD) full-scale IQ was 95.4 (13.1) • living arrangements ○ 56.6% lived with both parents	TGNB natal male adolescent	TGNB natal female adolescent	• Intelligence (IQ)_ was measure by the Dutch versions of the Wechsler Intelligence scale for Children (WISC) • Behavior Problems were measured using T scores from the CBCL • Psychiatric comorbidities were assessed using the DISC IV Cross-sectional: exposures/outcomes were measured at the same time around the time of intake	Natal males suffered more often from two or more comorbid diagnoses, mood disorders, and social anxiety disorder. No other significant differences were found. • **Full Scale IQ**, *P* = NS ○ Natal male, mean (SD): 95.4 (13.1) ○ Natal female, mean (SD): 99.5 (15.0) • **Anxiety conditions**_OR, *P value* • Any condition, 0.64, *P* = NS ○ Natal male, % (n): 24.5 (13) ○ Natal female, % (n): 17.3 (9) • Specific phobia, 1.0, *P* = NS ○ Natal male, % (n): 4.5 (4) ○ Natal female, % (n): 4.5 (4) • Social phobia, 0.26, *P* = 0.049 ○ Natal male, % (n): 15.1 (8) ○ Natal female, % (n): 3.8 (2) • Agoraphobia, N/A *P* = NS

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ 44.0% lived with other • parents' education status, ○ 11.5% had high ○ 71.2% had medium ○ 17.3% had low • Natal female: • mean (SD) age was 14.6 years (2.2) • mean (SD) full-scale IQ was 99.5 (15.0) • living arrangements ○ 43.3% lived with both parents ○ 56.0% lived with other • parents' education status ○ 19.6% had high, 6 ○ 4.7% had medium ○ 15.7% had low ○ There were no significant differences between the groups				○ Natal male, % (n): 1.1 (1) ○ Natal female, % (n): 0 (0) • Separation anxiety, 3.2, *P* = NS) ○ Natal male, % (n): 1.9 (1) ○ Natal female, % (n): 5.8 (3) • Generalized anxiety, N/A, *P* = NS ○ Natal male, % (n): 0 (0) ○ Natal female, % (n): 1.9 (1) • **Mood conditions,** OR, P value ○ Any, 0.15, *P* = .008 ▪ Natal male, % (n): 20.8 (11) ▪ Natal female, % (n): 3.8 (2) ○ Major depression, 0.26, *P* = NS ▪ Natal male, % (n): 13.2 (7) ▪ Natal female, % (n): 3.8 (2) ○ Dysthymia, N/A, *P* = NS ▪ Natal male, % (n): 7.5 (4) ▪ Natal female, % (n): 0 (0) • **Disruptive conditions,** OR, P value ○ Any, 0.47, *P* = NS ▪ Natal male, % (n): 15.1 (8) ▪ Natal female, % (n): 7.7 (4) ○ ADHD combined, 2.1, *P* = 0.50 ▪ Natal male, % (n): 1.9 (1) ▪ Natal female, % (n): 3.8 (2)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ ADHD inattentive, 1.0, *P* = NS ▪ Natal male, % (n): 1.9 (1) ▪ Natal female, % (n): 1.9 (1) ○ ADHD hyperactive, N/A, *P* = NS ▪ Natal male, % (n): 1.9 (1) ▪ Natal female, % (n): 0 (0) ○ Oppositional defiant, 0.48, *P* = NS ▪ Natal male, % (n): 11.3 (6) ▪ Natal female, % (n): 5.8 (3) • **Any substance use**, OR, *P value* ○ Any, N/A, *P* = NS ▪ Natal male, % (n): 1.9 (1) ▪ Natal female, % (n): 0 (0) • **Number of DSM-IV diagnoses,** OR, P value ○ One or more, 0.51 *P* = NS ▪ Natal male, % (n): 39.6 (21) ▪ Natal female, % (n): 25 (13) ○ Two or more, 0.29, *P* = 0.03 ▪ Natal male, % (n): 22.6 (12) ▪ Natal female, % (n): 7.7 (4) ○ Three or more, 0.50, *P* = NS ▪ Natal male, % (n): 3.8 (2) ▪ Natal female, % (n): 1.9 (1)
	N = 89 TGNB adolescents **Eligibility:** diagnosed with GD and seen between April 2002-December	• Full cohort: • mean (SD) age was 14.5 years (2.2)	TGNB adolescents immediately eligible for treatment	TGNB adolescents with delayed eligibility for treatment	• Intelligence (IQ)_ was measure by the Dutch versions of the Wechsler	**Baseline comparisons,** mean (SD) • Immediately eligible patients were younger (14.1 (2.2) vs 15.6 (1.6) years, *P* = .001), and had a higher percentage living

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	2009. **Sampling method:** 105 out of 201 adolescents consecutively enrolled • 17 dropped out of the diagnosis procedure • 18 were not invited since they were included • 61 declined **Subset:** Comparisons were made between TGNB adolescents immediately eligible for treatment (n = 63) and delayed eligible adolescents (n = 26)	• mean (SD) full-scale IQ was 96.9 (13.1) • living arrangements ○ 51.7% lived with both parents ○ 48.3% lived with other • parents' education status ○ 12.6% had high ○ 69.0% had medium ○ 18.4% had low • Immediately eligible • mean (SD) age was 14.1 years (2.2) • mean (SD) full-scale IQ was 99.1 (12.8) • living arrangements, ○ 63.9% lived with both parents ○ 36.1% lived with other • parents' education status ○ 19.0% had high ○ 68.3% had medium ○ 12.7% had low • Delayed eligible • mean (SD) age was 15.6 years (1.6) • mean (SD) full-scale IQ was 91.6 (12.4) • living arrangements ○ 23.1% lived with both parents			Intelligence scale for Children (WISC) • Psychiatric comorbidities were assessed using the DISC IV • Cross-sectional: exposures/outcomes were measured at the same time around the time of intake	with both parents (64% vs 23%, *P* < .001) compared to delayed eligible adolescents. **Full Scale IQ,** *P* = 0.011 • Immediately eligible, mean (SD): 99.1 (12.8) • Delayed eligible, mean (SD): 91.6 (12.4) ○ Immediately eligible participants had a significantly higher IQ than delayed eligible patients **Anxiety conditions,** OR, *P* value There were no significant differences in comorbidities between cohorts • **Any Condition**, 1.7, *P* = NS ○ Immediately eligible % (n): 17.5 (11) ○ Delayed eligible, % (n): 26.9 (7) • **Specific phobia**, 0.80, *P* = NS ○ Immediately eligible % (n): 4.8 (3) ○ Delayed eligible, % (n): 3.8 (1) • **Social phobia**, 2.8 *P* = NS ○ Immediately eligible % (n): 7.9 (5) ○ Delayed eligible, % (n): 19.2 (5) • **Agoraphobia**, N/A, *P* = NS ○ Immediately eligible % (n): 1.6 (1) ○ Delayed eligible, % (n): 0 (0) • **Separation anxiety**, 1.2, *P* = NS ○ Immediately eligible % (n): 3.2 (2) ○ Delayed eligible, % (n): 3.8 (1) • **Generalized anxiety**, N/A, *P* = NS

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ 76.9% lived with other • parents' education status, ○ 16.7% had high ○ 70.8% had medium ○ 12.5% had low				○ Immediately eligible % (n): 1.6 (1) ○ Delayed eligible, % (n): 0 (0) **Mood conditions**, OR, P value There were no significant differences in comorbidities between cohorts • **Any**, 1.5, *P* = NS ○ Immediately eligible % (n): 11.1 (7) ○ Delayed eligible, % (n): 15.4 (4) • **Major depression**, 1.5, *P* = NS ○ Immediately eligible % (n): 7.9 (5) ○ Delayed eligible, % (n): 11.5 (3) • **Dysthymia**, 1.2, *P* = NS ○ Immediately eligible % (n): 3.2 (2) ○ Delayed eligible, % (n): 3.8 (1) **Disruptive conditions**, OR, P value There were no significant differences in comorbidities between cohorts • **Any,** 3.5, *P* = NS ○ Immediately eligible % (n): 6.3 (4) ○ Delayed eligible, % (n): 19.2 (5) • **ADHD combined**, 1.2, *P* = NS ○ Immediately eligible % (n): 3.2 (2) ○ Delayed eligible, % (n): 3.8 (1) • **ADHD inattentive**, 2.5, *P* = NS ○ Immediately eligible % (n): 1.6 (1)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ Delayed eligible, % (n): 3.8 (1) • **ADHD hyperactive**, N/A, *P* = NS ○ Immediately eligible % (n): 0 (0) ○ Delayed eligible, % (n): 3.8 (1) • **Oppositional defiant**, 5.5, *P* = NS ○ Immediately eligible % (n): 3.2 (2) ○ Delayed eligible, % (n): 15.4 (4) ○ **Number of DSM-IV diagnoses**, OR, P value • **One or more**, 1.6, *P* = NS ○ Immediately eligible % (n): 28.6 (18) ○ Delayed eligible, % (n): 38.5 (10) • **Two or more**, 2.9, *P* = NS ○ Immediately eligible % (n): 9.5 (6) ○ Delayed eligible, % (n): 23.1 (6) • **Three or more**, N/A, *P* = NS ○ Immediately eligible % (n): 0 (0) ○ Delayed eligible, % (n): 7.7 (2)
de Vries (2011)[57] [redacted]	Transgender adolescents (N = 70) **Eligibility:** N/R **Sampling method**: First 70 transgender adolescents who were referred for medical treatment (ie, puberty suppression) between 2000 and 2008	• Mean age at assessment (yr, SD), *P* = .028 ○ Natal males: 13.14 (1.55) ○ Natal females: 14.10 (1.99) • Mean age at start of GnRH analogs (yr, SD), *P* = .036 ○ Natal males: 14.25 (1.79) ○ Natal females: 15.21 (1.95)	Natal males (n = 33)	Natal females (n = 37)	Self-reported measures: • BDI-II • TPI • STAI **Cohort:** outcomes were measured before (T0) and while on puberty suppression, before CSH (T1)	• Compared with natal males, natal females reported significantly more feelings of anger and anxiety. There was not a significant effect between sex on depression scores. Mean BDI-II score (SD), (n = 41): • Before starting puberty suppression (T0): ○ Natal males: 5.71 (4.31) ○ Natal females: 10.34 (8.24) • While taking puberty suppression (T1):

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	Subset definition: Comparisons were made between **natal males (n = 33)** and **natal females (n = 37)**	• Mean age at start of CSH (yr, SD), *P* = .008 ○ Natal males: 16.24 (1.21) ○ Natal females: 16.99 (1.07) • Mean time between start of GnRH analogs and CSH (yr, SD), P value = 0.405 ○ Natal males: 1.99 (0.94) ○ Natal females: 1.78 (1.16)				○ Natal males: 3.50 (4.58) ○ Natal females: 6.09 (7.93) • Between-sex significance: 3.85, *P* = NS: Mean TPI score (SD), (n = 41): • Before starting puberty suppression (T0): ○ Natal males: 5.22 (2.76) ○ Natal females: 6.43 (2.78) • While taking puberty suppression (T1): ○ Natal males: 5.00 (3.07) ○ Natal females: 6.39 (2.59) • Between-sex significance: 5.70, *P* = .022 Mean STAI score (SD), (n = 41): • Before starting puberty suppression (T0): ○ Natal males: 4.33 (2.68) ○ Natal females: 7.00 (2.36) • While taking puberty suppression (T1): ○ Natal males: 4.39 (2.64) ○ Natal females: 6.17 (2.62) • Between-sex significance: 16.07, *P* < .001
de Vries (2014)[79] [redacted] Netherlands)	Transgender adults who had received puberty suppression during adolescence, and completed gender reassignment surgery (N = 55) **Eligibility:** Prescribed puberty suppression at the clinic as an adolescent with GD, and received	• Mean age at assessment before treatment is started (yr, SD): ○ Transgender women: 13.6 (1.8) ○ Transgender men: 13.7 (2.0) • Mean age at start of GnRH analogs (yr, SD):	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Self-reported measures: • BDI • TPI • STAI Cohort: outcomes were measured before the start of puberty suppression (pre-	• Over time, trans men showed reduced anger and anxiety, whereas trans women were more stable. There was not a significant effect between sex on depression scores. Mean depression (BDI) score (SD): • At the start of CSH (T1): ○ Transgender women: 2.25 (3.54)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	gender reassignment surgery between 2004 and 2011 **Sampling method**: This group of adolescents belonged to a larger group of adolescents (n = 196) who were referred for treatment between 2000 and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery **Subset definition:** Comparisons were made between **transgender women (n = 22)** and **transgender men (n = 33)**	○ Transgender women: 14.8 (2.0) ○ Transgender men: 14.9 (1.9) • Mean age at start of CSH (yr, SD): ○ Transgender women: 16.5 (1.3) ○ Transgender men: 16.8 (1.0) • Mean age at gender reassignment surgery (yr, SD): ○ Transgender women: 19.6 (0.9) ○ Transgender men: 19.0 (0.8) • Mean age at assessment after gender reassignment surgery (yr, SD): ○ Transgender women: 21.0 (1.1) ○ Transgender men: 20.5 (0.8) • Mean pre-treatment BDI score (SD): ○ Transgender women (n = 12): 4.73 (4.20) ○ Transgender men (n = 20): 10.09 (8.34) • Mean pre-treatment anger TPI score (SD): ○ Transgender women (n = 12): 14.17 (3.01) ○ Transgender men (n = 20): 19.55 (5.96) • Mean pre-treatment anxiety (STAI) score (SD):			treatment; T0), at the start of CSH (T1), and at least 1 year after gender reassignment surgery (T2)	○ Transgender men: 5.05 (7.08) • At least 1 year after gender reassignment surgery (T2): ○ Transgender women: 3.38 (4.40) ○ Transgender men: 6.95 (9.83) Mean anger (TPI) score (SD): • At the start of CSH (T1): ○ Transgender women: 14.00 (3.36) ○ Transgender men: 19.25 (5.69) • At least 1 year after gender reassignment surgery (T2): ○ Transgender women: 5.58 (3.92) ○ Transgender men: 16.56 (6.06) Mean anxiety (STAI) score (SD): • At the start of CSH (T1): ○ Transgender women: 31.71 (8.36) ○ Transgender men: 41.59 (9.03) • At least 1 year after gender reassignment surgery (T2): ○ Transgender women: 35.83 (10.22) ○ Transgender men: 39.20 (10.53)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ Transgender women (n = 12): 31.87 (7.42) ○ Transgender men (n = 20): 44.41 (9.06)				
Durwood (2017)[109] Part of a longitudinal study (Trans Youth Project)	Socially transitioned transgender youth (6 to 14 years of age) enrolled in the Trans Youth Project who completed the depression and anxiety measurements (N = 63) **Eligibility:** Participants needed to identify as a gender opposite their natal sex in everyday life, socially transitioned, and enrolled in the Trans Youth Project from March 2015 to February 2016 **Sampling method**: Participants were from the larger Trans Youth Project. Participants were recruited into the Trans Youth Project by national and local support groups, summer camps, online forums, and word of mouth **Subset definition:** Comparisons were made between **transgender youth taking hormone blockers (n = 18), CSH (n = 5), and no treatment (n = 39)**. One untreated child was excluded from the comparison.	• Mean age (yr, SD; N = 63): 10.8 (1.3) • Asserted gender: ○ Boys: 33 (52.4) ○ Girls: 30 (47.6) • Race or ethnicity (N = 63): ○ White, non-Hispanic: 37 (58.7) ○ Hispanic: 8 (12.7) ○ Asian: 4 (6.3) ○ Black: 1 (1.6) ○ Multiracial/other: 13 (20.6)	Youth taking hormonal treatment: • CSH (n = 5) • Hormone blockers (n = 18)	Untreated youth (n = 39)	• Child-reported depression and anxiety measured by NIH's PROMIS • Parent-reported depression and anxiety measured by a proxy version of NIH's PROMIS • Answers were converted to a Likert type scale and then a standardized T score. **Cross-sectional:** exposures/outcomes were measured <u>at the same time</u>	Mean depression T-score (SD), *P* = NS: • Youth taking CSH: ○ Child-reported: 48.7 (8.1) ○ Parent-reported: 49.3 (9.5) • Youth taking hormone blockers: ○ Child-reported: 48.6 (9.1) ○ Parent-reported: 50.9 (8.3) • Youth not taking CSH or hormone blockers: ○ Child-reported: 48.4 (9.8) ○ Parent-reported: 49.9 (9.3) Mean anxiety T-score (SD), *P* = NS: • Youth taking CSH: ○ Child-reported: 48.7 (8.8) ○ Parent-reported: 51.0 (10.5) • Youth taking hormone blockers: ○ Child-reported: 51.4 (8.3) ○ Parent-reported: 54.0 (8.2) • Youth not taking CSH or hormone blockers: ○ Child-reported: 52.6 (10.4) ○ Parent-reported: 55.7 (9.4)

[a] Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)

[b] Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).

[c] Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Grannis (2021)[110] A gender developmental clinic at a children's hospital	FTM adolescents (N = 42) **Eligibility:** Diagnosis of GD, 9 to 21 yrs of age, and able to participate in MRI-based research **Sampling method**: Study sample was drawn from a larger study of transgender youth receiving gender affirming medical care (both PB and CSH). All participants were receiving gender affirming behavioral support and had not been prescribed PBs previously. **Subset definition:** Comparisons were made between **treated (n = 19)** and **untreated (n = 23)** FTM adolescents	• Mean age (yr, SD), P value < 0.01: ○ Treated FTM: 17.0 (1.2) ○ Untreated FTM: 15.8 (1.5) • History of anxiolytics/anti-depressant use: ○ Treated FTM: 10 (52.6) ○ Untreated FTM: 18 (78.3) • Birth control use: ○ Treated FTM: 15 (79.0) ○ Untreated FTM: 15 (65.2) • Mean duration of testosterone use (months, SD): ○ Treated FTM: 13.1 (10.3) • Mean testosterone dosage (mg, SD): ○ Treated FTM: 242.1 (82.3)	Received intramuscular testosterone cypionate (n = 19)	Did *not* receive intramuscular testosterone cypionate (n = 23)	Self-reported measures: • SCARED questionnaire • LSAS questionnaire • CDI assessment • SBQ-R **Cross-sectional:** exposures/outcomes were measured at the same time	• Compared to untreated participants and after controlling for age, those who received testosterone cypionate had significantly lower mean symptom severity for: ○ generalized anxiety: F(1,39) = 6.99 (measured by SCARED, P = .01; η^2 = 0.16) ○ social anxiety: F(1,39) = 17.21 (measured by LSAS, P < .001; η^2 = 0.32) ○ depression: F(1,39) = 7.39 (measured by CDI, P = .01; η^2 = 0.16) • Lower rates of suicidality in the prior year trended towards significant in those treated with testosterone (F[1,39] = 3.85, P = .06; η^2 = 0.09) • No significant differences emerged between treated and untreated participants for lifetime suicidality (P = 0.27), and non-suicidal self-injury in the past year (P = .42) or during the participant's lifetime (P = .15)
Green (2022)[111] Large US nationwide online survey conducted between October and December 2020	TGNB youth aged 13 to 17 (N = 3,235) **Eligibility:** Youth aged 13 to 24 residing in the US who identified as LGBTQ or gender questioning. Excluded participants included those who lived outside of the US, were < 13 or > 24 years of age, and reported being both cisgender and heterosexual **Sampling method**: Targeted ads from social media (ie, Instagram, Snapchat, Facebook) were used to	• Mean age (yr, SD), P < .001 ○ Received CSH: 16.00 (1.03) ○ Did not receive CSH: 15.09 (1.36) • **Gender identity**, P < .001 • Nonbinary: ○ Received CSH: 42 (15.3) ○ Did not receive CSH: 1,382 (46.7) • Transgender boy/man: ○ Received CSH: 205 (74.8) ○ Did not receive CSH: 1,377 (46.5)	Survey participants, aged 13 to 17, who had received CSH therapy (n = 274)	Survey participants, aged 13 to 17, who had *not* received CSH therapy (n = 2,961)	Self-reported measures: • 2-item PHQ (PHQ-2) • Suicidal thoughts and behaviors (from the CDC's Youth Risk Behavior Survey) **Cross-sectional:** exposures/outcomes were measured at the same time	• Receiving CSH therapy was associated with lower odds of recent depression and attempting suicide in the past year **Depression** (measured by PHQ-2): • Multivariate logistic regression (aOR[a]; 95% CI): 0.61 (0.43 to 0.86); P < .01 **Seriously considered suicide**: • Multivariate logistic regression (aOR[a]; 95% CI): 0.74 (0.52 to 1.03), P = NS **Attempted suicide**: • Multivariate logistic regression (aOR[a]; 95% CI): 0.62 (0.40 to 0.97), P = .04

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	recruit participants. Eligible participants had to complete a secured questionnaire with validity checks. Participation was voluntary and informed consent was obtained **Subset definition:** TGNB youth aged 13 to 17 was a subset of the overall survey population (N = 34,759). Comparisons were made between TGNB youth (aged 13 to 17) **who received CSH therapy (n = 274)** and **those who desired CSH therapy but did not receive it (n = 2,961)**	• Transgender girl/woman: ○ Received CSH: 27 (9.9) ○ Did not receive CSH: 202 (6.8) • **History of PBs**, *P* < .001: ○ Received CSH: 66 (24.4) ○ Did not receive CSH: 37 (1.3) • **Depression**, *P* < .001: ○ Received CSH: 167 (60.9) ○ Did not receive CSH: 2,294 (77.9) • Seriously considered suicide, *P* < .001: ○ Received CSH: 135 (51.1) ○ Did not receive CSH: 1,674 (61.6) • **Attempted suicide**, *P* < .001: ○ Received CSH: 42 (16.0) ○ Did not receive CSH: 733 (27.7)				
Khatchadourian (2014)[82] [redacted]	Adolescents diagnosed with GD (N = 84) **Eligibility:** Pubertal development of at least Tanner stage 2, previously seen by a mental health professional at the British Columbia Transgender Clinical Care Group, and confirmed diagnosis of GD **Sampling method**: Data was extracted from clinic notes of patients that were seen in clinic	• Mean age at first clinic visit (yr, SD): ○ MTF: 16.8 (2.4) ○ FTM: 16.4 (2.1) • Mean age at start of GnRH analog treatment (yr, SD): ○ **MTF (n = 11)**: 14.7 (1.7) ○ **FTM: (n = 15)**: 14.8 (2.1) • Tanner stage at start of GnRH analog treatment: • 2 to 3:	Presence of comorbid psychiatric conditions in MTF adolescents	Presence of comorbid psychiatric conditions in FTM adolescents	• Psychiatric comorbidities diagnosed by a mental health professional (psychologist or psychiatrist) **Cross-sectional:** exposures/outcomes were measured at the same time	Presence of psychiatric comorbidities (n, %): • Mood disorder, *P* = 0.01: ○ MTF: 7 (19) ○ FTM: 20 (44) • Anxiety disorder, *P* = .02: ○ MTF: 4 (11) ○ FTM: 15 (33) • Attention-deficit/hyperactivity disorder, *P* = NS: ○ MTF: 6 (16) ○ FTM: 2 (4)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	from January 1998 to December 2011 **Subset definition:** Comparisons were made between **MTF (n = 37)** and **FTM (n = 45)** adolescents	○ MTF: 5 (45) ○ FTM: 4 (27) • 4 to 5: ○ MTF: 6 (55) ○ FTM: 10 (67) • Mean age at start of CSH (yr, SD): ○ **MTF (n = 24)**: 14.7 (2.2) ○ **FTM (n = 39)**: 17.0 (1.6) • Tanner stage at start of CSH: • 2 to 3: ○ MTF: 1 (4) ○ FTM: 6 (15) • 4 to 5: ○ MTF: 21 (88) ○ FTM: 32 (82) • Mean age at start of spironolactone (yr, SD): ○ MTF: 17.6 (1.9) ○ FTM: N/A • Tanner stage at start of spironolactone: • 2 to 3: ○ MTF: 0 (0) ○ FTM: N/A • 4 to 5: ○ MTF: 25 (100)				• Eating disorder, *P* = NS: ○ MTF: 2 (5) ○ FTM: 2 (4) • Pervasive developmental disorder/autism spectrum disorder, *P* = NS: ○ MTF: 4 (11) ○ FTM: 2 (4) • ≥ 2 DSM-IV diagnoses, *P* = NS: ○ MTF: 9 (24) ○ FTM: 12 (27) • Substance abuse, *P* = NS: ○ MTF: 4 (11) ○ FTM: 2 (4) • Suicide attempt resulting in an emergency department visit, *P* = NS: ○ MTF before first clinic visit: 2 (5) ○ FTM before first clinic visit: 6 (13) ○ MTF after first clinic visit: 1 (3) ○ FTM after first clinic visit: 3 (7) • Psychiatric hospitalization for posttraumatic stress disorder, substance abuse, depression, psychosis, behavioral issues, or anxiety, *P* = NS: ○ MTF before first clinic visit: 3 (8) ○ FTM before first clinic visit: 7 (16) ○ MTF after first clinic visit: 0 (0) ○ FTM after first clinic visit: 1 (1)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ FTM: N/A				• Prescribed CSH (n, %), *P* < .02: ○ MTF (oral micronized 17β-estradiol): 24 (65) ○ FTM (injectable testosterone enanthate and/or cypionate): 39 (87)
Nahata (2017)[115] large urban, Midwestern, pediatric academic center from 2014-2016	TGNB adolescents (N = 79) **Eligibility**: Patients had the ICD 9/10 codes for gender dysphoria in their medical records **Sampling method:** Patients records were reviewed from 2014-2106 for participants with the ICD 9/10 codes for gender dysphoria, referred to a pediatric endocrinology multidisciplinary gender program for hormone therapy. **Subset definition:** Comparisons were made between transgender males (n = 51) and transgender females (n = 28)	• 51 (64.6%) trans gender males • 28 (35.4%) transgender females • None of the subjects identified as nonbinary or genderqueer. • Median age at first endocrinology visit was 15 years (range 9–18 years). • Majority of patients were white, N = 66 (83.5%) • Gender-affirming hormone therapy was initiated in N = 40 subjects	TGNB males (n = 51)	TGNB females (n = 28)	• Mental health conditions were documented if they were formally diagnosed by a psychiatrist through standard clinical practice at any time in the EMR since receiving care in the institution. Conditions reviewed were: ○ depression ○ anxiety ○ post-traumatic stress disorder (PTSD) ○ eating disorders ○ autism spectrum disorder (ASD) ○ bipolar disorder ○ self-injurious behavior (including suicidal ideation, self-harm, and suicide attempts) ○ The presence of and frequency of suicidal ideation, self-harm, and suicide attempts were recorded based on what	**Mental health conditions** n(%) • There was no significant difference in the rate of depression between transgender males: 42 (82.4%) and transgender females: 20 (71.4%), *P* = NS • There was no significant difference in the rate of Anxiety between transgender males: 34 (66.6%) and transgender females: 26 (57.1%), *P* = NS • There was no significant difference in the rate of PTSD between transgender males: 13 (25.6%) and transgender females: 5 (17.9%), *P* = NS • There was no significant difference in the rate of eating disorders between transgender males: 5 (9.8%) and transgender females: 5 (17.9%), *P* = NS • There was no significant difference in the rate of ASD between transgender males: 3 (5.9%) and transgender females: 2 (7.1%), *P* = NS • There was no significant difference in the rate of bipolar disorder between transgender males: 3 (5.9%) and transgender females: 1 (3.6%), *P* = NS **Self-injurious behaviors** • There was no significant difference in the rate of Suicidal ideation between transgender males: 40 (78.4%) and transgender females: 19 (67.9%), *P* = NS

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
					was documented by their psychiatrist. **Cross-sectional study:** measurements/outcomes were taken at the same time	• There was no significant difference in the rate of Self-harm between transgender males: 31 (60.7%) and transgender females: 13 (46.4%), *P* = NS • There was no significant difference in the rate of having one or more suicide attempts between transgender males: 15 (29.4%) and transgender females: 9 (32.1%), *P* = NS ○ There were no statistical differences between genders in any mental health outcomes
Olsavsky (2023)[116] Gender affirming multidisciplinary clinic in a large, Midwestern children's hospital	TGNB adolescents (N = 75) **Eligibility:** Adolescents were eligible if they had a GD diagnosis, were 9-21 years old and were able to participate in MRI-based research. **Sampling Method:** TGNB adolescents were recruited from the clinic between Dec 2018-March 2020, March 2021-Feb 2022. Adolescents who met the inclusion criteria were reimbursed via a prepaid gift card. Of 101 approached, 82 participated (81%) and 7 were excluded due to incomplete surveys. All adolescents provided informed consent/assent; parental consent was obtained for minors. **Subset definition:** • Comparisons were made between TGNB youth	Mean age: • 16.39 ± 1.62 SD range (11-18) Gender at birth: • N = 43 (57.3%) assigned female at birth • N = 32 (42.7%) assigned male at birth Gender Identity: • N = 41 (54.7%) Identify as male • N = 28 (37.3%) Identify as female • N = 6 (8%) identify as nonbinary Hormone therapy • N = 39 (52.0%) receiving GAHT ○ N = 32 (42.7%) receiving CSHT (testosterone, estrogen) ○ N = 9 (12%) receiving puberty blockers Majority (77.3%) identify as white	TGNB youth with nonbinary identity (n = 6)	TGNB youth with binary gender identity (n = 69)	• Anxiety Symptoms measured by adolescents competing the SCARED screening questionnaire • Depressive symptoms measure by adolescents completing the CDI • NSSI measured by 1 question based on the SBQ-R and the C-SSRS, "How often have you harmed yourself without the intent of killing yourself in the past year?" (rated from 1-never to 5-very often) • Suicidality was measured by asking 1 question from the SBQ-R, "How often have you thought about killing yourself in the last year?" (rated from 1-never to 5-very often)	Anxiety • There was no significant correlation between TGNB youth identifying as binary and not identifying as binary for anxiety scores (*P* = NS), accounting for all other variables[c]. • Depression • There was no significant correlation between TGNB youth identifying as binary and not identifying as binary for depressive symptoms (*P* = NS), accounting for all other variables[c]. NSSI • TGNB youth identifying as a nonbinary was correlated with higher scores of NSSI of 0.29 compared to TGNB youth not identifying as nonbinary. *P* < .05 • When accounting for all other variables[c], identifying as nonbinary was significantly associated with fewer reports of NSSI (b = 0.30, *P* = .008) Suicidality • There was no significant correlation between TGNB youth identifying as binary and not identifying as binary for suicidality scores, accounting for all other variables[c]. (*P* = NS)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	identifying as non-binary (n = 6) and TGNB youth identifying as a gender (n = 69) • Comparisons were made between GNB youth that received GAHT (n = 39) and those that were untreated (n = 36)		TGNB youth receiving GAHT (n = 39)	Untreated TGNB youth (n = 36)	• Social support was measured using the MSPSS • Bivariate correlations were examined and then those with a significant correlation were included in a hierarchical linear regression model. • Cohort: Outcomes were measured after exposure	Anxiety • TGNB youth taking gender-affirming hormonal intervention use were each associated with fewer anxiety symptoms, accounting for all other variables[c]. (b = -0.23, *P* = .046) Depression • Receiving gender-affirming hormonal interventions was significantly correlated with fewer depressive symptoms compared to those not receiving GAHT, with a correlation of -0.23 ,*P* < .05 • Fewer depressive symptoms was marginally associated with gender-affirming hormonal intervention use, accounting for all other variables[c]. (b = -0.21, *P* = .05) NSSI • There was no significant correlation between TGNB youth taking GAHT vs not taking GAHT for NSSI scores, accounting for all other variables[c]. (*P* = NS) Suicidality • There was no significant correlation between TGNB youth taking GAHT vs not taking GAHT for suicidality scores, accounting for all other variables[c]. (*P* = NS)
			TGNB youth receiving greater social support (from friends, family, and significant others)	TGNB youth not receiving greater social support		Anxiety • TGNB youth with greater friend support was correlated with fewer anxiety symptoms than those without friend support, with a correlation of -0.28, *P* < .05 • TGNB youth with greater friend support was associated with fewer anxiety symptoms, accounting for all other variables[c] (b = -0.32, *P* = .007) Depression

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• TGNB youth with greater significant other support was correlated with less suicidality than those without significant other support, with a correlation of -0.29, *P* < .05 • TGNB youth with greater family support was correlated with fewer depressive symptoms than those without family support, with a correlation of -0.39, *P* < .01 • Fewer depressive symptoms was significantly associated with family support for TGNB youth, accounting for all other variables[c] (b = -0.33, *P* = .003) NSSI • TGNB youth with greater family support was correlated with less reports of NSSI than those without family support, with a correlation of -0.25, *P* < .05 • TGNB youth with greater family support was significantly associated with fewer reports of NSSI, accounting for all other variables[c], (b = -0.27, *P* = .019) Suicidality • TGNB youth with greater friend support was correlated with less suicidality than those without friend support, with a correlation of -0.26, *P* < .05 • TGNB youth with greater significant other support was correlated with less suicidality than those without significant other support, with a correlation of -0.32, *P* < .01 • TGNB youth with greater family support was correlated with less suicidality than those without family support, with a correlation of -0.28, *P* < .05 • TGNB youth with greater friend support was significantly associated with less suicidality, accounting for all other variables[c], (b = -0.25, *P* = .03)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ No other significant correlations or associations were found between social support and mental health outcomes
Segev-Becker (2020)[117] [redacted] Israel	pubertal TGNB adolescents (N = 95) **Eligibility:** All patients who were referred to the clinic between March 2013 and December 2018 were eligible **Sampling Method:** All consecutive patients younger than 18 years of age who were referred to the clinic between March 2013 and December 2018 were included in the study. The majority of patients had been evaluated by a community MHP and were diagnosed with GD according to the DSM 5 criteria prior to their first visit to the GD clinic. **Subset definition**: comparisons were made between **TGNB females (n = 38**) and **TGNB males (n = 58)**	• The mean age at clinic referral: ○ transgender females: 15.9 ± 1.7 years ○ transgender males: 15.2 ± 1.7 years ○ transgender females were significantly older, *P* = .032 • The mean age at presenting as transgender: ○ transgender females: (13.7 ± 2.7 years [range, 6.5 to 17.4 years] ○ transgender males: 14 ± 1.5 years [range, 10 to 17 years] ○ No significant difference in age *P* > .05 • At the time of referral, n (%) at Tanner stage 4 to 5 of puberty ○ transgender females: 36 (89%) ○ transgender males: 55 (95%) • At the time of referral, 91 (95%) of the pubertal group had completed sexual maturation in their assigned gender at birth. • 77 (80%) pubertal patients began GnRH analog treatment at a mean	Presence of comorbid psychiatric conditions in pubertal TGNB females (n = 38)	Presence of comorbid psychiatric conditions in pubertal TGNB males (n = 58)	Chart reviewed for psychiatric comorbidities as recorded by a mental health professional **Cross-sectional:** exposures/outcomes were measured at the same time	**Depression n(%)** • There was no significant difference in the rate of TGNB girls with depression: 9 (24) compared to TGNB boys: 12 (29), *P* = NS **Suicidal thoughts n(%)** • There was no significant difference in the rate of TGNB girls with suicidal thoughts: 4 (10) compared to TGNB boys: 7 (12), *P* = NS **Suicide attempts n(%)** • There was no significant difference in the rate of TGNB girls with suicide attempts: 3 (8) compared to TGNB boys: 10 (17), *P* = NS **Eating disorders n(%)** • There was no significant difference in the rate of TGNB girls with eating disorders: 3 (8) compared to TGNB boys: 2 (3.5), *P* = NS **School dropouts n(%)** • There was no significant difference in the rate of TGNB girls with school dropouts: 12 (32) compared to TGNB boys: 12 (20), *P* = NS **Substance abuse n(%)** • There was a significant difference in the rate of substance abuse between TGNB girls: 6 (16) compared to TGNB boys: 1 (1.5) *P* = .01 **Psychiatric Medication, n(%)**

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		age of 15.6 ± 1.6 years (range, 11 to 18.5 years). • Sixty-one of the patients who began GnRH analog treatment (83%) were started on CSH treatment either concurrently or later, at a mean age of 16.5 ± 1.3 years (range, 13 to 18.9 years).				• There was no significant difference in the rate of TGNB girls taking psychiatric medication: 12 (32) compared to TGNB boys: 17 (29), *P* = NS **ADD/ADHD, n(%)** • There was no significant difference in the rate of TGNB girls with ADD/ADHD: 8 (21) compared to TGNB boys: 18 (31), *P* = NS **Autistic Spectrum, n(%)** • There was a significant difference in the rate of autism spectrum between TGNB girls: 4 (10) compared to TGNB boys: 0 (0) *P* = .02
Sorbara (2020)[118] Transgender youth clinic in [redacted] Canada	**N = 300 TGNB youth** **Eligibility**: Diagnosis of gender dysphoria and seen by clinic staff. Exclusion criteria was if they were not seeking CSH or had previously been on hormone blockers or CSH. **Sampling method**: patients that were eligible from clinic **Subset definition**: Younger presenting youth (YPY) were < 15 years old at presentation to clinic and were compared to older presenting youths (OPY) were > 15 years when presented to clinic.	• **YPY (n = 116):** ○ Age: 13.9 (range 12.9 to 14.5) ○ AFAB: 87 (75.0) ○ Tanner stage < 3 (early puberty): 24 (20.7) ○ Tanner stage > 4 (late puberty): 82 (70.7) ○ Tanner Stage not reported: 10 (8.6) ○ Socially transitioned: 76 (65.5) • **OPY (n = 184):** ○ Age = 16.3 (range 15.6 to 16.8) ○ AFAB: 142 (77.2) ○ Tanner Stage < 3 (early puberty): 2 (1.1) ○ Tanner Stage > 4 (late puberty): 166 (90.2) ○ Tanner Stage not reported: 16 (8.7)	Younger presenting Youth to clinic (n = 116)	Older Presenting Youth to clinic (n = 184)	• Youth or caregiver reports of formal diagnoses of depressive, anxiety, and autism spectrum disorders were extracted from initial visit documentation. • Reported active use of psychoactive medication, suicidal ideation at the time of or preceding the TYC visit, and history of self-harm or suicide attempt were also recorded. **Cross sectional**: Measures/Outcomes taken at same time at initial visit	• Reported Mental Illness • Depression ○ OPY had a higher rate of depression than YPY, *P* < .05. ○ OPY 46% vs. YPY 30% • Anxiety (Estimated values): ○ No significant difference between OPY and YPY, *P* = NS ○ YPY 44% vs OPY 45% • History of Self-harm ○ OPY had a higher rate of history of self-harm than YPY, *P* < .05 ○ OPY 40% vs. YPY 28%, • Current SI (Estimated values) ○ No significant difference between OPY and YPY, *P* = NS ○ YPY 8% vs. OPY 12% • History of SI

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ Socially transitioned: 149 (81.0)				○ OPY had more history of suicidal ideation compared to YPY, *P* < .05 ○ OPY 52% vs. YPY 40% • Suicide Attempt ○ OPY had significantly more suicide attempts than YPY, *P* < .05 ○ YPY 9% vs. OPY 17% • Use of Psychotropic Medication ○ OPY had significantly higher use of psychotropic medications than YPY, *P* < .05 ○ YPY 23% vs. OPY 36%
			TGNB youth were compared by variables that increased the odds of mental health problems.	TGNB youth were compared by variables that did not increase the odds of mental health problems.	• Pearson's X2 test or Fisher's exact test was used to compare rates of mental health diagnoses between YPY and OPY. • Logistic regression was used to assess whether age at first visit, pubertal stage, date cohort, and social transition were associated with mental health problems. **Cross sectional**: Exposure/Outcomes measured at same time at initial visit	**Logistic Regression Factors Odds Ratio** **Depressive disorders** • Late pubertal stage youth were 5.49 times more likely to report the diagnosis of depressive disorders, *P* = .03. • Factors such as age at first visit, date cohort, social transition, and assigned sex were not found to significantly impact the odds of depression. **Anxiety disorders** • Late pubertal stage youth were 4.18 times more likely to report the diagnosis of anxiety disorders, *P* = .02. • Factors such as age at first visit, date cohort, social transition, and assigned sex were not found to significantly impact the odds of having an anxiety disorder. **History of self-harm** • Youth assigned female at birth were 3.41 times more likely to have a history of self-harm, *P* = .006.

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• Factors such as age at first visit, date cohort, social transition, and pubertal stage were not found to significantly impact the odds of having a history of self-harm. **Suicidal Ideation** • There was no significant multicollinearity that predicted an associated. Conditions for goodness of fit testing were not met for the previous suicide attempt or current SI because there were few events. **Psychoactive medication** • 1 year increases of age at first visit increased the odds of psychoactive medication use by 1.31, *P* = .02 • Factors such as pubertal stage, date cohort, social transition, and assigned sex were not found to significantly impact the odds of using PM.
Tollit (2023)[120] [redacted] gender clinic in Australia.	**N = 359 TGNB youth** **Eligibility**: First appointment with clinic from January 1, 2007 to December 31, 2016, and had a self-reported gender identity which differed from their gender at birth or sough clinical guidance on their gender identity. **Sampling method**: Patients were selected if they met criteria and were a patient of the clinic. **Subset definition**: Comparisons were made between assigned males at birth (n = 166) vs assigned females at birth (n = 193)	**AMAB (n = 166):** • Gender: ○ 139 were transgender, ○ 14 were non binary, ○ 4 were cisgender and 9 weren't sure. • Age: ○ Average age was 12.4 years. at GD diagnosis • Treatment: ○ 126. 39 were on puberty blockers, ○ 7 were on anti androgens ○ 19 were on gender affirming hormones.	Trans females presenting at RCHGS. (n = 166)	Trans males presenting at RCHGS. (n = 193)	• Mental Health data extracted from clinician-recorded notes collected at clinic appointments for: ○ depressive disorder ○ eating disorders ○ PTSD ○ history of self-harm ○ history of suicidal ideation **Cross-sectional:** exposures/outcomes were measured at the same time	**Depression:** • TM = 74, TF = 108 • There were significantly more trans females reporting depression than trans males, *P* = .03 **Eating Disorder:** • TM = 1, TF = 4 • There was no significant difference between trans males and trans females having an eating disorder, *P* = NS **PTSD:** • TM = 1, TF = 4 • There was no significant difference between trans males and trans females having PTSD, *P* = NS **Self-harm:** • TM = 25, TF = 64

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		AFAB (n = 193): • Gender: ○ 174 were transgender, ○ 12 were nonbinary, ○ 2 were cisgender and 5 were not sure. • Age: ○ Average age was 14.8 years. • Treatment: ○ 15 were on puberty blockers ○ 57 were on menses suppression ○ 29 were on gender affirming hormones.				• There were significantly more trans females with a history of self-harm compared to trans males, $P < 0.05$ **Suicidal Ideation:** • TM = 36, TF = 70 • There were significantly more trans females reporting suicidal ideation than trans males, $P < .05$
Tordoff (2022)[96] [redacted]	TGNB adolescents and young adults (N = 104) **Eligibility:** TGNB adolescents and young adults desiring gender-affirming care **Sampling method**: After a referral is received, including those initiated by the patient, a 1-hour phone intake with a clinical social worker was required for the patient, caregiver, or both. After completion of the phone intake, patients were scheduled for a clinic visit with a medical provider. All patients who completed both the phone intake and in-person visit between August	• Mean age (yr, SD; N = 104): ○ 15.8 (1.6) • Gender identity (N = 104): ○ Male or transgender male: 63 (60.6) ○ Female or transgender female: 27 (26.0) ○ Nonbinary or gender fluid: 10 (9.6) ○ Don't know or missing: 4 (3.8) • Pharmacological intervention (at baseline or end of the study period; N = 104): ○ PBs: 19 (18.2)	Transgender adolescents and young adults who had received PBs (eg, GnRH analogs), CSHs (eg, estrogen, testosterone), or both after 12 months (n = 69) • CSHs only: n = 50 (48.1%) • PBs only: n = 5 (4.8%) • PBs + CSHs: n = 14 (13.5%)	Transgender adolescents and young adults who had not received PBs, CSHs, or both after 12 months (n = 35)	Self-reported measures: • PHQ-9 questionnaire • Suicidal thoughts or self-harm were evaluated using the PHQ-9 • GAD-7 questionnaire **Cohort:** outcomes were measured at 3 months (n = 84), 6 months (n = 84), and 12 months (n = 65)	• After adjusting for potential confounders and temporal trends, the odds of **moderate to severe depression (PHQ-9 ≥ 10)** was reduced by 60% in patients treated with PBs or CSHs compared to untreated patients (ie, not yet started PBs or CSHs) ○ aOR: 0.40; 95% CI: 0.17 to 0.95; $P = .04$; E-value: 2.56 • After adjusting for potential confounders and temporal trends, patients treated with PBs or CSHs had a 73% lower odds of **suicidal thoughts or self-harm** compared to those who had not started PBs or CSHs ○ aOR: 0.27; 95% CI: 0.11 to 0.45; $P = .003$; E-value = 3.25 • No significant relationship was observed for **moderate to severe anxiety (GAD-7 ≥ 10)** in patients who received PBs or CSHs compared to untreated patients after adjusting for potential confounders and temporal trends

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	2017 and June 2018 were recruited. A baseline survey was completed within 24 hours of their first appointment, and were invited to participate in follow-up surveys at 3, 6, and 12 months **Subset definition:** Comparisons were made between **treated (n = 69)** and **untreated (n = 35)** transgender youth	○ CSHs: 64 (61.5) ○ Androgen blockers (n = 33): 17 (51.5) ○ Menstrual suppression or contraception: 25 (35.2) • Baseline depression (using PHQ-9; N = 104): ○ Severe (score ≥ 20): 26 (25.0) ○ Moderately severe (score 15 to 19): 11 (10.6) ○ Moderate (score 10 to 14): 22 (21.2) ○ Mild (score 5 to 9): 27 (26.0) ○ Minimal (score 0 to 4): 14 (13.5) ○ Missing: 4 (3.8) • Baseline anxiety (using GAD-7; N = 104): ○ Severe (score ≥ 15): 32 (30.8) ○ Moderate (score of 10 to 14): 20 (19.2) ○ Mild (score of 5 to 9): 28 (26.9) ○ Minimal (score of 0 to 4): 20 (19.2) ○ Missing: 4 (score of 3.8) • Baseline resilience (using CD-RISC, 10-item, higher scores indicate greater resilience; N = 104): ○ Score of 0 to 10: 8 (7.7) ○ Score of 10 to 20: 35 (33.7)				○ aOR: 1.01; 95% CI: 0.41 to 2.51; *P* = .98 • Subgroup analysis among patients aged 13 to 17 yrs (n = 90) on the association between receiving CSH/PBs vs. those who did not, and mental health outcomes: • Moderate to severe depression (PHQ-9 ≥ 10): ○ aOR: 0.51; 95% CI: 0.19 to 1.37, *P* = NS • Any suicidal thoughts/self-harm: ○ aOR: 0.32; 95% CI: 0.12 to 0.88, *P* = .027 • Moderate to severe anxiety (GAD-7 ≥ 10): ○ aOR: 0.84; 95% CI: 0.29 to 2.40, *P* = NS

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ Score of 21 to 30: 15 (14.4) ○ Score of 30 to 40: 34 (32.7) • Baseline suicidal thoughts or self-harm (N = 104): 45 (43.2)				
Turban (2020)[121] Survey respondents were from all 50 US states, American Samoa, District of Columbia, Guam, overseas US military bases, and Puerto Rico	TGNB adults who self-reported wanting pubertal suppression during adolescence (N = 3,494) **Eligibility:** TGNB adults **Sampling method**: Of the 27,715 respondents, 20,619 participants were between 18 to 36 years old. Analysis was further restricted to those who ever wanted pubertal suppression (n = 3,494) **Subset definition:** Comparisons were made between those **who received pubertal suppression with a PB (n = 89)** and **those who desired it, but never received it (n = 3,405)**	• Mean age (yr, SD), P value = 0.001: ○ Received PBs: 21.7 (4.7) ○ Never received PBs: 23.4 (5.0) • Mean age of social transition (yr, SD), P value < 0.001 ○ Received PBs: 15.2 (4.5) ○ Never received PBs: 20.1 (5.5) • Mean age at beginning hormone treatment, P value < 0.001 ○ Received PBs: 15.7 (2.4) ○ Never received PBs: 22.5 (4.3) • Sex assigned at birth, P value = 0.04: • AFAB: ○ Received PBs: 39 (43.8) ○ Never received PBs: 1,874 (55.0) • AMAB: ○ Received PBs: 50 (56.2) ○ Never received PBs: 1,531 (45.0) • **Gender identity**, P value < 0.001: • Woman: ○ Received PBs: 23 (25.8) ○ Never received PBs: 617 (18.2)	Survey respondents who reported receiving PBs during adolescence (9 to 16 years of age; n = 89)	Survey respondents who reported wanting to start a PB, but never received it (n = 3,405)	• Past-month severe psychological distress • Suicidal ideation and suicide attempts • Past month binge drinking • Lifetime illicit drug use **Cross-sectional:** exposures/outcomes were measured at the same time	**Past-month severe psychological distress** (K6 ≥ 13): ○ Univariate analyses (OR; 95% CI): 0.5 (0.3 to 0.8), *P* = .001 ○ Multivariable analyses (aOR[b]; 95% CI): 0.8 (0.4 to 1.4), *P* = NS **Suicidal ideation:** • Suicidal ideation in the past 12 months: ○ Univariate analyses (OR; 95% CI): 0.6 (0.4 to 0.8), *P* = .006 ○ Multivariable analyses (aOR[b]; 95% CI): 0.6 (0.3 to 1.1), *P* = NS • Suicidal ideation with plan in the past 12 months: ○ Univariate analyses (OR; 95% CI): 0.9 (0.5 to 1.6), *P* = NS • Lifetime suicidal ideation: ○ Univariate analyses (OR; 95% CI): 0.3 (0.2 to 0.5), *P* < .001 ○ Multivariable analyses (aOR[b]; 95% CI): 0.3 (0.2 to 0.6), *P* = .001 **Suicide attempt:** • Attempt resulting in inpatient care in the past 12 months: ○ Univariate analyses (OR; 95% CI): 2.8 (0.8 to 9.4), *P* = NS • Suicidal ideation with plan and attempt in the past 12 months: ○ Univariate analyses (OR; 95% CI): 1.2 (0.6 to 2.3), *P* = NS • Lifetime suicide attempts:

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• Man: ○ Received PBs: 19 (21.3) ○ Never received PBs: 383 (11.3) • Transgender women: ○ Received PBs: 25 (28.1) ○ Never received PBs: 720 (21.3) • Transgender man: ○ Received PBs: 16 (18.0) ○ Never received PBs: 795 (23.5) • Nonbinary or genderqueer: ○ Received PBs: 6 (6.7) ○ Never received PBs: 866 (25.6)				○ Univariate analyses (OR; 95% CI): 0.7 (0.4 to 1.0), *P* = NS • Past-month binge drinking (drinking ≥ 5 standard alcoholic drinks during 1 occasion): ○ Univariate analyses (OR; 95% CI): 0.3 (0.8 to 2.0), *P* = NS • Lifetime illicit drug use (excluding marijuana use): ○ Univariate analyses (OR; 95% CI): 1.1 (0.7 to 1.8), *P* = NS
Turban (2022)[122] 2015 U.S. Transgender Survey (USTS) conducted a survey in August-September 2015 in transgender adults (>18 years) online	**N= 21,598 survey participants** **Eligibility:** those enrolled in the survey were >18 years. Study was restricted to only those that responded they had been interested in CSH (n=21,598) **Sampling method:** participants were recruited online through 400 community organizations **Subset definition:** Grouped by age of CSH initiation: (CSH 14-15), (CSH 16-7) and (CSH >18)	**No CSH but wanted (n= 8860)** • 2620 were trans male • 2324 were trans female • 2829 were AFAB/NB • 766 were AMAB/NB • 321 identified as other • 135 were 18-24 • 2653 were 25-44 • 753 were 45-64 • 139 were 65+ years old **CSH 14-15: (n= 119)**	CSH: defined as testosterone and estrogen received at ages 14-17	CSH at age >18	• Survey data was used to compare mental health outcomes: ○ past suicidal ideation in past 12 months ○ past year suicidal ideation with plan ○ past year suicide attempt ○ severe psychological distress measured by the Kessler-6 Psychological Distress Scale (>13)	**Mental Health outcomes after adjusting for confounding:** • Access to CSH ages 14-17 was associated with lower odds of past month severe psychological distress (aOR=0.6, 95% CI= 0.5-0.8, *P* < .001), when compared to access to CSH during adulthood • Access to CSH ages 14-17 was associated with lower odds of past year SI (aOR=0.7, 95% CI= 0.6-0.9, *P* = .007), when compared to access to CSH during adulthood • Access to CSH ages 14-17 was associated with lower odds of past month binge drinking (aOR=0.7, 95% CI= 0.5-0.9, *P* = .001), when compared to access to CSH during adulthood • Access to CSH ages 14-17 was associated with lower odds of lifetime illicit drug use (aOR=0.7, 95% CI =0.5-0.8, *P* = .0003) when compared to access to CSH during adulthood

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• 48 were trans male • 54 were trans female • 13 were AFAB/NB • 4 were AMAB/NB • 75 were 18-24 years • 23 were 25-44, 19 were 45-64 • 2 were 65+ years old **CSH 16-17: (n= 362)** • 214 were trans male • 109 were trans female • 35 were AFAB/NB • 4 were AMAB/NB • 297 were 18-24 years • 54 were 25-44 • 11 were 45-64 **CSH>18: (n= 12,257)** • 4713 were trans male • 6340 were trans female • 834 were AFAB/NB • 330 were AMAB/NB • 40 identified as other • 2856 were 18-24 • 6285 were 25-44 • 2660 were 45-64			○ binge drinking the month prior (more than 5 drinks on a single occasion) ○ lifetime illicit drug use • Multivariable logistic regression was performed, comparing mental health outcomes for participants groups. • All models adjusted for age, partnership status, employment status, K-12 harassment and having experienced gender identity conversion efforts and any additional demographic and potential confounding variables that were found to be associated with each outcome. **Cross sectional/Case-control**-Outcomes and Exposures were measured at the same time	• There was no significant difference (*P* = NS) between access to CSH at ages 14-17 vs. during adulthood when comparing having an SI plan, SI attempt or SI with hospitalization
			Access to CSH during adolescence- both early adolescence (14-15) and late adolescence (16-17)	Wanted CSH but never took		**Mental health outcomes after adjusting for confounders:** • Access to CSH during early adolescence was associated with lower odds of past month severe psychological distress (aOR= 0.3, 95% CI=0.2-0.4,^*P* < .0001), when compared to wanting CSH but never accessing them. • Access to CSH during early adolescence was associated with lower odds of past year SI (aOR=0.4, 95% CI=0.2-0.6, *P* < .001) when compared to wanting CSH but never accessing them. • No other detected difference for other mental health variables comparing early vs no CSH. • Access to CSH during late adolescence was associated with lower odds of past month psychological distress (aOR=0.3, 95% CI=0.3-0.4, *P* < .001) when compared to CSH desiring CSH but never accessing them • Access to CSH during late adolescence was associated with lower odds of past year suicidal ideation (aOR=0.5, 95% CI =0.4-0.7, *P* < .0001) when compared to CSH desiring CSH but never accessing them. • No other difference detected comparing late adolescent CSH treatment vs. no CSH
			CSH: defined as testosterone and estrogen received at ages 14-15	CSH at age 16-17		• No difference in mental health outcomes detected in participants that received CSH in late vs early adolescence (*P* = NS)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• 456 were 65+ **Frequency of Mental Health Outcomes** • No CSH ○ Past year SI: 5144 ○ SI with plan: 2731 ○ SI with attempt: 853 ○ SI with hospitalization: 220 ○ K6>13: 4545 ○ binge drinking: 2083 ○ illicit drug use: 1918 • CSH 14-15 ○ Past year SI: 48 ○ SI with plan: 29 ○ SI with attempt: 8 ○ SI with hospitalization: 1 ○ K6>13: 40 ○ binge drinking: 39 ○ illicit drug use: 40 • CSH 16-17 ○ Past year SI: 40 ○ SI with plan: 39 ○ SI with attempt: 40 ○ SI with hospitalization: 40 ○ K6>12: 145 ○ binge drinking: 74				

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ illicit drug use: 93 • CSH >18: ○ Past year SI: 5237 ○ SI with plan: 2537 ○ SI with attempt: 756 ○ SI with hospitalization: 247 ○ K6>12: 3419 ○ binge drinking: 3214 ○ illicit drug use: 4455				
van der Miesen (2020)[124] [redacted] the Netherlands, between 2012 and 2015	**N = 450 TGNB adolescents referred to a specialized gender identity clinic** **Eligibility criteria**: Not clearly stated **Sampling method**: Transgender cohort: Adolescents who just started the diagnostic procedure were assessed during their first sessions at the VUmc. Adolescents diagnosed with GD were assessed before the start of GAH. During both assessments, parents and children completed several questionnaires during 2012 to 2015, 504 adolescents were seen in their gender identity service. 53 participants did not complete the assessment process and therefore, did not participate in this study. The	TGNB subjects who did not started any affirmative medical treatment yet: Mean age (SD) in years = 14.47 (2.18); 116 assigned boys at birth and 156 assigned girls at birth TGNB subjects receiving affirmative care and about to start GAH treatment: Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth	**Transgender group**: on puberty suppression and about to start unspecified CSH treatment (n = 178)	**Transgender group**: have not yet received any affirmative medical treatment (n = 272)	• Psychological functioning outcomes were measured using the Dutch version of the YSR to assess: ○ Self-harm/suicidality ○ Effect sizes Cohen's d: .80 or higher is a large effect size, .50-.79 a medium effect size, .20-.49 small, and effect sizes < .20 are negligible **Cross-sectional:** Exposures/outcomes measured at the same time	**Suicidality**: Mean scores (SD) on the Youth Self-Report for suicidality • The adolescents at referral had significantly higher scores than those using puberty suppression. ○ transgender adolescents receiving affirmative care: 0.17 (0.52) ○ transgender adolescents who did not receive any affirmative treatment: 0.41 (0.78) ○ Effect sizes Cohen's d between the groups was 0.36

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	reason for dropout was failure to complete the questionnaire or alternation of symptoms of GD. Of the adolescents diagnosed with GD, 179 were about to start GAH treatment. One participant did not complete the questionnaire and was thus excluded. **Subset:** Comparisons were made between TGNB adolescents receiving affirmative care and about to start GAH treatment: (N = 272) and TGNB adolescents at referral, that have not yet started affirmative care (n = 178)					
	Subset: Comparisons were made between TGNB adolescents that had received puberty suppression who were AMAB (n = 68) vs AFAB (n = 110).	Transgender subjects receiving affirmative care and about to start CSH treatment: Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth	**TGNB adolescents AMAB:** have been receiving puberty suppression, and getting ready to start CSH treatment (n = 68)	**TGNB adolescents AFAB:** have been receiving puberty suppression, and getting ready to start CSH treatment (n = 110)		• **Suicidality**: Mean scores (SD) on the Youth Self-Report for suicidality • Gender assigned at birth had negligible effect on suicidality, effect size Cohen's d of -0.04 ○ assigned boys: 0.16 (0.48) ○ assigned girls: 0.18 (0.54)
Vehmas (2022)[125] Adolescent gynecology clinic [redacted] (Finland)	Transgender adolescents desiring gender-affirming hormonal treatment (N = 124) **Eligibility:** Adolescents diagnosed with GD, referred to gender identity services at Helsinki University Hospital before 18 years of age for GD symptoms, and further referred to the adolescent gynecology clinic	• Assigned sex at birth: ○ AMAB: n = 20 ○ AFAB: n = 104 • Median age at the first contact with gender identity services (yr, range; N = 124): ○ 16.7 (12.1 to 18.0) • Median age at GD diagnosis (yr, range; N = 124):	Presence of comorbid psychiatric conditions in MTF adolescents (n = 20)	Presence of comorbid psychiatric conditions in FTM adolescents (n = 104)	The proportion of patients that also had a diagnosis for a psychiatric condition **Cross-sectional:** exposures/outcomes were measured at the same time	• Presence of psychiatric comorbidities (n, %): • Depression, *P* = NS: ○ MTF: 5 (25.0) ○ FTM: 31 (29.8) • Anxiety, *P* = NS: ○ MTF: 4 (20.0) ○ FTM: 20 (19.2) • Attention-deficit/hyperactivity disorder, *P* = .14:

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.1. Clinical studies with between-TGNB-group comparisons examining mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	for gender-affirming hormonal assessment **Sampling method**: Referred by gender identity services **Subset definition:** Comparisons were made between **MTF (n = 20)** and **FTM (n = 104)** transgender adolescents	○ 18.1 (14.8 to 20.1) • Median age at the time of assessment at the adolescent gynecology clinic (yr, range; N = 124): ○ 17.7 (14.6 to 19.8)				○ MTF: 2 (10.0) ○ FTM: 3 (2.9) • Eating disorder, *P* = NS: ○ MTF: 0 (0) ○ FTM: 2 (1.9) • Psychotic disorder, *P* = NS: ○ MTF: 0 (0) ○ FTM: 2 (1.9) • Autism, *P* = NS: ○ MTF: 1 (5.0) ○ FTM: 1 (1.0) • Antidepressant use, *P* = NS ○ MTF: 4 (22.2) ○ FTM: 27 (26.2)

[a] *Multivariate logistic regression adjusted for socioeconomic status, census region, age, sexual orientation, gender identity, race/ethnicity, parent support for gender identity, gender identity conversion efforts, gender identity-based victimization, and prior puberty blocker use (Green 2022)*

[b] *Multivariable logistic regression models were adjusted for demographic variables (eg, family support, education level, employment status, sexual orientation, total household income, age); the demographic variables that were adjusted varied based on the measured outcome (Turban 2020).*

[c] *Multivariable linear regression model used the following variables: Nonbinary identity, gender-affirming hormonal intervention use, and family and friends social support (Olsavsky, 2023).*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; aOR: adjusted odds ratio; BDI-(Y), Beck Depression Inventory (for Youth); CBCL, Child Behavior Checklist; CDC, Center for Disease Control and Prevention; CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CESD-R, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CSH, cross sex hormones; C-SSRS, Columbia suicide severity rating scale; DISC = IV, Diagnostic Interview Schedule for Children version IV; EMR, electronic medical record; FTM, female-to-male; GAD-7, Generalized Anxiety Disorder, 7-item; GAH, gender affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog; GWBS, General Well-Being Scale; K6, Kessler Psychological Distress Scale; LGBTQ, lesbian, gay, bisexual, transgender, queer; LSAS, Liebowitz Social Anxiety Scale; MDS, Modified Depression Scale; MSPSS, multi-dimensional scale of perceived social support; MRI, magnetic resonance imaging; MTF, male-to-female; N/A, not applicable; NIH, National Institutes of Health; N/R, not reported; NS, not significant; OASIS, Overall Anxiety Severity and Impairment Score; OR, odds ratio; PBs, puberty blockers; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RCMAS-2, Revised-Children's Manifest Anxiety Scale; SBQ-R, Suicide Behaviors Questionnaire-Revised; SCARED, Screen for Child Anxiety Related Disorders; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender/nonbinary; TPI, Spielberger's Trait Anger Scale; US, United States; WISC, Wechsler Intelligence Scale for Children; yr(s), year(s)

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Achille (2020)[55] A US [redacted] NY) pediatric endocrine gender dysphoria clinic	TGNB adolescents (N = 50) **Eligibility:** Participants were recruited at the clinic, and a vast majority consented/assented. **Sampling method:** Participants must have completed 3 waves of questionnaires at 6-month intervals, for a total of approximately 12 months of observation **Subset definition:** Comparisons were made between **treated and untreated MTF (n = 17)** and **FTM (n = 33)** adolescents	• Mean age (yr, SD): ○ MTF: 15.5 (1.6) ○ FTM: 16.6 (2.5) • Depressed in the prior year: ○ MTF: 12 (70.6) ○ FTM: 20 (60.6) • Reported suicidality: ○ MTF: 2 (11.8) ○ FTM: 3 (9.1) • Seeing a therapist: ○ MTF: 16 (94.1) ○ FTM: 29 (87.9) • Taking psychiatric medications: ○ MTF: 5 (29.4) ○ FTM: 17 (34.0)	• Puberty suppression using: ○ GnRH analogs and/or antiandrogens for MTF youth (n = 15) ○ GnRH analogs or medroxyprogesterone for FTM youth (n = 8) • Cross-sex hormones using: ○ Estrogen for MTF youth (n = 7) ○ Testosterone for FTM youth (n = 28)	• No puberty suppression ○ MTF: n = 2 ○ FTM: n = 25 • No cross-sex hormones ○ MTF: n = 10 ○ FTM: n = 5	Self-reported measures: • QLES-Q-SF questionnaire **Cohort:** outcomes were measured at 12 months (wave 3)	• Difference in change from baseline QLES-Q-SF: • No significant differences between groups was found • Puberty suppression vs. none: ○ MTF: Coefficient 1.26, *P* = NS, R^2 = 0.13 ○ FTM: Coefficient 0.71, *P* = NS, R^2 = 0.01 • Cross-sex hormones vs. none: ○ MTF: Coefficient 0.87, *P* = NS, R^2 = 0.08 ○ FTM: Coefficient 0.93, *P* = NS, R^2 = 0.11
Allen (2019)[56] [redacted]	**N = 47** TGNB adolescents • **Eligibility**: Adolescents and young adults (age range 13–20 years) who received services for GD at the clinic. Participants were included if they had pretest and final assessment data points and were treated with CSH for at least 3 months • **Sampling method**: A total of 47 eligible participants had pretest and final assessment data. The pretest for 23 participants occurred at their first contact with the clinic (the other participants' pretest assessment was completed at a subsequent visits to clinic but prior to starting CSH). Thirteen of the	• The age of the participants ranged from 13.73 to 19.04 years (mean = 16.59, SD = 1.19). • The range of treatment length was 113-1016 days (mean = 349, SD = 193). • For most of the sample (90%), the duration of treatment was at, or under, 600 days. • Assigned female at birth was n = 33 (70.2%) and assigned male at birth was n = 14 (29.8%). • The majority of participants were white N = 39 (83%).	**CSH** treatment	**CSH** with previous **GnRH analog treatment**	• The GWBS was used to measure psychological well-being (general well-being and general health) **Cohort:** outcomes are measured after the exposure has been measured (retrospective review)	Psychological well-being: • There were no significant differences in GWBS scores between the CSH-only group and GnRH analogs + CSH group at T0 and T1, *P* = NS • The estimated adjusted mean (standard error) of GWBS scores for CSH-only group was 62.75 (16.43) at T0 and 70.79 (13.46) at T1. The estimated adjusted mean (standard error) of GWBS scores for GnRH analogs + CSH group was 64.29 (8.32) at T0 and 69.2 (12.8) at T1.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	participants first presented to our clinic in 2015; 19 in 2016; 14 in 2017; and one in 2018. Patients are administered questionnaires and screeners at the beginning of their clinic visit, either at the time of the diagnostic evaluation or during a follow-up appointment with the multidisciplinary team. Responses are reviewed by the mental health professional prior to meeting with the patient. • **Subset definition**: Of the 47 participants, Comparisons were made between those that were administered GnRH analogs prior to beginning CSH (GnRH analogs + CSH subgroup) (n = 8) and those that were not received GnRH analogs prior to being administered CSH (CSH-only subgroup) (n = 39).					
	• **Subset definition:** Comparisons were made between youth AMAB (n = 33) and AMAB (n = 14)		**AMAB**	**AFAB**	Self-reported measures: • 5-item MDS questionnaire • 5-item OASIS questionnaire • Suicidal ideation and attempts were evaluated using the Canadian Community Health Survey **Cross-sectional:** exposures/outcomes were measured at the same time	Psychological well-being: • The predicted interaction effect of sex assigned at birth with regard to well-being scores was non-significant, F(1, 44) = 1.00, *P* = NS, partial η^2 = .02, demonstrating a small effect size. • The estimated adjusted mean (standard error) of GWBS scores for AFAB group was 64.95 (2.66) at T0 and 70.94 (2.35) at T1. The estimated adjusted mean (standard error) of GWBS scores for AMAB group was 58.44 (4.09) at T0 and 69.52 (3.62) at T1.
Arnoldussen (2020)[100] [redacted]	N = 1072 (404 natal males, 668 natal females)	Full cohort: for natal gender, 37.7% are natal males and 62.3% are natal females,	TGNB youth categorized by year of assessment from 2000-2016	TGNB youth categorized by year of assessment from 2000-2016	Psychological functioning measured by: • CBCL	**Psychological Functioning (CBCL and YSR analyses) plus adding time as a categorical variable from 2000-2016:** • A decreasing trend was found between 2000-2016 in the mean total T-score of the assessed adolescents on the CBCL

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
[redacted] the Netherlands	**Eligibility**: referred to the Center of Expertise on GD, potentially eligible for gender affirming therapies **Sampling method:** consecutively referred, from 2000-2016.	Mean (SD) age at assessment was 14.64 years (2.19); Parents' marital status, 54% were living with both biological parents, 41.9% were living with other, 4.1% had an unknown status; Parents' educational level, 54.2% were vocational education, 30% were higher vocational and academic educated, 15.8% had an unknown status; Mean (SD) full-scale IQ was 99.15 (16.08), In terms of diagnosis, 5.3% were not diagnosed with a form of GD, 84.7% were diagnosed with a form of GD, 10% were unknown			• YSR • Intensity of gender dysphoria measured by: • Utrecht Gender Dysphoria Scale • IQ Cohort study: Outcomes were measured over 16 years.	and the YSR and was still found by the analyses with time as a categorical variable. • There was no trend over time in the mean internalizing total T-scores on the CBCL and YSR • The mean externalizing T-score on the CBCL and YSR of the adolescents who applied in later years became significantly lower compared to the mean score of adolescents who applied in early years. The trend persisted through the analyses with time as a categorical variable. • Initial analyses showed a significant decrease for the clinical range total T-scores for the CBCL and YSR. The more detailed analyses with time as a categorical variable contradicted this trend and showed fluctuation over the years rather than a decrease. • The clinical range internalizing total T-scores of the adolescents on the CBCL and the YSR showed no trend over time • In the clinical range externalizing total T-scores, a decreasing trend was found on both parent and self-report. A similar trend was seen in the subsequent analyses with time as a categorical variable. • Initial regression analyses showed a decreasing trend in the Peer Relation Scale on the CBCL and the indicating that the quality of the peer relations of adolescents in more recent years was assessed better compared to the quality of the peer relations of adolescents in earlier years. Analyses with time as a categorical variable also showed this trend for the CBCL. On the YSR, however, this decreasing trend was less clear. • Initial regression analyses showed no trend in time in the score on the Suicidality Scale on the CBCL or the YSR • No interaction based on sex was found for any of the variables ○ CBCL T-score (mean) ▪ Total: β = -0.396, *P* < .001, 95% CI (-0.553, -0.240) ▪ Internalizing: β = -0.100, *P* = NS, 95% CI (-0.272, 0.071)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ Externalizing: β = -0.408, *P* < .001, 95% CI (-0.582, -0.234) ▪ Total-clinical: OR = 0.950, *P* = .002, 95% CI (0.919, 0.982) ▪ Internalizing- clinical: OR = 0.986, *P* = NS, 95% CI (0.954, 1.018) ▪ Externalizing- clinical: OR = 0.922, *P* < 0.001, 95% CI (0.892, 0.953) ▪ Peer Relation Scale: β = -0.017, *P* < .001, 95% CI (-0.024, -0.010) ▪ Suicidality Scale: β = 0.007, *P* = NS, 95% CI (-0.005, 0.019) ○ YSR T-score (mean) ▪ Total: β = -0.278, *P* < .001, 95% CI (-0.434, -0.122) ▪ Internalizing: β = -0.011, *P* = NS, 95% CI (-0.169, 0.192) ▪ Externalizing: β = -0.323, *P* < .001, 95% CI (-0.473, -0.173) ▪ Total- clinical: OR = 0.968, *P* = 0.041, 95% CI (0.937, 0.999) ▪ Internalizing-clinical: OR = 1.016, *P* = NS, 95% CI (0.985, 1.049) ▪ Externalizing- clinical: OR = 0.931, *P* < .001, 95% CI (0.897, 0.966) ▪ Peer Relation Scale: β = -0.009, *P* = 0.007, 95% CI (-0.016, -0.003) ▪ Suicidality Scale: β = 0.006, *P* = NS, 95% CI (-0.001, 0.013) ▪ **Gender Dysphoria changes over time from 2000-2016** • UGDS (mean) ○ The intensity of the feeling of dysphoria did not significantly change over time ▪ Natal male: β = 0.055, *P* = NS, 95% CI (-0.214, 0.323) ▪ Natal female: β = -0.015, *P* = NS, 95% CI (-0.159, 0.129)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						IQ changes over time from 2000-2016 • Initial analyses showed that mean Full-Scale IQ of the adolescents became higher over time (β 0.366, *P* = .004, 95% CI 0.116–0.617), however, when time was used as a categorical variable, it showed that the mean score remained within the average range each year and thus it did not change over time.
Arnoldussen (2022)[71] [redacted]	TGNB adolescents (N = 72) **Eligibility**: referred prior to 2010, met GD diagnostic criteria, started PS before the age of 17 years followed by cross-sex hormonal treatment and gender-affirming surgery **Sampling method:** 72 out of 119 eligible participated **Subset:** • transgender men (n = 45) • transgender women (n = 27)	Full cohort: • Gender ○ 62.5% are transgender males ○ 37.5% are transgender females • Adolescent living situation prior to treatment, ○ 72.2% lived with both biological parents, ○ 26.4% lived with other ○ 1.4% were unknown • mean (SD) age at baseline: 12.78 years (1.48) • Age, mean (SD) ○ at the start of puberty suppression: 13.77 years (1.46) ○ at the start of CSH: 16.22 years (0.82) ○ at the start of GAS: 18.70 years (0.77) ○ at the evaluation of educational achievement: 20.40 years (1.03) ○ between start puberty suppression and start of CSH was 2.40 years (1.08) • IQ, mean (SD) ○ total IQ: 100.29 (15.07)	Lower pre-treatment IQ score (total, verbal and performance IQ)	Higher pre-treatment IQ score (total, verbal and performance IQ)	IQ was measured using the WISC Educational achievement later in life after gender affirming treatment (PS, CSHT and gender-affirming surgery) was measured via survey question. Educational level was dichotomized into "vocational educated" and "higher vocational educated/academic educated" Cohort study: Outcomes were measured after a mean duration of 7.6 years of gender-affirming treatment	**Total IQ Score:** • For each increase of one point in total IQ score, the chance of being higher educated increased with 1.170 odds.[c] (β = 0.157, *P* < .001, 95% CI 1.074, 1.275) **Verbal IQ score:** • For each increase of one point in verbal IQ score, the chance of being higher educated increased with 1.164 odds [c] (β = 0.152, *P* = .001, 95% CI 1.068, 1.268) **Performance IQ score** • For each increase of one point in performance IQ score, the chance of being higher educated increased with 1.127 odds.[c] (β = 0.120, *P* < .001, 95% CI 1.054, 1.206) ○ Results similar to general population.
			Transgender men	Transgender women		• There was no significant difference in total, verbal or performance IQ scores between transgender men and transgender women, *P* = NS • There was no significant difference between educational levels achieved between transgender men and transgender women

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ verbal IQ: 99.53 (15.01) ○ performance IQ: 100.72 (14.26) ○ *P* = NS between trans men and trans women • Education level achieved ○ 37 were vocational educated (51.4%) ○ 35 were higher vocational educated (48.6%). ○ *P* = NS between trans men and trans women				
Becker-Hebly (2021)[72] [redacted]	TGNB adolescents (**N =** 75) **Eligibility**: confirmed diagnosis for GD; older than 11 years old and not previously treated; no significant psychiatric conditions **Sampling method**: 75 out of 204 patients (completed diagnostic criteria meeting inclusion criteria) agreed to participate	• Age mean (SD) • Full cohort (n = 75): ○ Baseline: 15.56 years (1.21), ○ follow-up age: 17.38 years (1.69) • Not receiving medical treatment (n = 21): ○ baseline: 15.50 years (1.19) ○ follow-up age was 16.67 years (1.54) • GnRH analogs (n = 11): ○ Baseline: 15.56 years (1.85) ○ follow-up age was 16.57 years (2.02) • CSH and GnRH analogs (n = 32): ○ Baseline: 15.47 years (1.04) ○ follow-up age was 17.51 years (1.24) • GA surgery and CSH (n = 11): ○ baseline was 15.96 years (1.02) ○ follow-up age was 19.17 years • Onset:	TGNB adolescents: • not receiving medical treatment • receiving GnRH analogs • receiving CSH and GnRH analogs • receiving GA surgery and CSH at baseline and follow-up	TGNB adolescents: • not receiving medical treatment • receiving GnRH analogs • receiving CSH and GnRH analogs • receiving GA surgery and CSH at baseline and follow-up	• Emotional and behavioral problems was assessed using YSR/ASR • Global functioning was assessed using the CGAS • Psychological and physical dimensions of quality of life were assessed using the Kidscreen-27 Cohort: Outcomes were measured after exposure	**Baseline Psychological Functioning** At baseline, there were no significant differences found between the treatment groups on any measure **YSR/ASR Total T-Score, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 64.29 (9.33), 95% CI (60.04, 68.53) ○ GnRH analogs (n = 11): 62.27 (8.96), 95% CI (56.26, 68.29) ○ CSH and GnRH analogs (n = 32): 61.56 (9.17), 95% CI (58.26, 64.87) ○ GA surgery and CSH (n = 11): 62.18 (8.78), 95% CI (56.28, 68.08) **YSR/ASR Internalizing T-Score, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 65.76 (9.68), 95% CI (61.36, 70.17) ○ GnRH analogs (n = 11): 63.64 (10.97), 95% CI (56.87, 70.40) ○ CSH and GnRH analogs (n = 32): 64.94 (11.18), 95% CI (60.91, 68.97) ○ GA surgery and CSH (n = 11): 65.73 (9.55), 95% CI (59.31, 72.14)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• Full cohort (n = 75): ○ 80% were early onset ○ 20% were late onset • Not receiving medical treatment (n = 21): ○ 62% were early onset ○ 38% were late onset • GnRH analogs (n = 11): ○ 91% were early onset ○ 9% were late onset • CSH and GnRH analogs (n = 32): ○ 84% were early onset ○ 16% were late onset • GA surgery and CSH (n = 11): ○ 91% were early onset ○ 9% were late onset ○ Gender: • Full cohort (n = 75): ○ 85.3% were trans-male, ○ 14.7% were trans-female • Not receiving medical treatment (n = 21): ○ 85.7% were trans-male ○ 14.3% were trans-female • GnRH analogs (n = 11): ○ 72.7% were trans-male ○ 27.3% were trans-female • CSH and GnRH analogs (n = 32): ○ 87.5% were trans-male ○ 12.5% were trans-female • GA surgery and CSH (n = 11):				**YSR/ASR Externalizing T-Score, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 57.81 (9.07), 95% CI (53.67, 61.95) ○ GnRH analogs (n = 11): 57.73 (10.05), 95% CI (50.98, 64.48) ○ CSH and GnRH analogs (n = 32): 54.13 (7.17), 95% CI (51.54, 56.71) ○ GA surgery and CSH (n = 11):54.09 (7.80), 95% CI (48.85, 59.33) **CGAS Global Functioning, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 68.10 (11.23), 95% CI (62.98, 73.21) ○ GnRH analogs (n = 11): 67.27 (11.91), 95% CI (59.27, 75.27) ○ CSH and GnRH analogs (n = 32): 73.13 (10.91), 95% CI (69.19, 77.06) ○ GA surgery and CSH (n = 11): 66.36 (14.33), 95% CI (56.73, 75.99) **Health-related quality of life-mental, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 34.86 (6.27), 95% CI (32.00, 37.71) ○ GnRH analogs (n = 11): 39.04 (9.25), 95% CI (32.82, 45.25) ○ CSH and GnRH analogs (n = 32):36.16 (6.78), 95% CI (33.72, 38.60) ○ GA surgery and CSH (n = 11):37.88 (6.53), 95% CI (33.49, 42.27) **Health-related quality of life-physical, mean (SD), 95% CI** • No significant differences between groups ○ No medical treatment (n = 21): 37.51 (8.27), 95% CI (33.74, 41.27)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ 90.9% were trans-male ○ 9.1% were trans-female • Additional psychotherapy • Full cohort (n = 75): ○ 79% had additional psychotherapy ○ 21% did not • Not receiving medical treatment (n = 21): ○ 71% had additional psychotherapy ○ 29% did not • GnRH analogs (n = 11): ○ 91% had additional psychotherapy ○ 9% did not • CSH and GnRH analogs (n = 32): ○ 81% had additional psychotherapy ○ 19% did not • GA surgery and CSH (n = 11): ○ 73% had additional psychotherapy ○ 27% did not				○ GnRH analogs (n = 11): 43.43 (8.61), 95% CI (37.65, 49.22) ○ CSH and GnRH analogs (n = 32): 39.12 (7.10), 95% CI (36.56, 41.68) ○ GA surgery and CSH (n = 11): 39.88 (8.49), 95% CI (34.17, 45.59) **Follow-up Psychological Functioning** • At follow-up, TGNB adolescents who had GA surgery and were on CSH had lower internalizing, externalizing, and total YSR T-scores, a higher CGAS score and higher health related quality of life scores than those not receiving medical treatment. • At follow-up, TGNB adolescents who were on CSH and GnRH analogs had lower internalizing, externalizing and total YSR T-scores and a higher CGAS score than those not receiving medical treatment. • At follow-up, TGNB adolescents who were on GnRH analogs had a higher CGAS score than those not receiving medical treatment. **YSR/ASR Total T-Score, mean (SD), 95% CI.** • TGNB adolescents on CSH and GnRH analogs, and having GA surgery and CSH had lower scores than those with no medical treatment ($P < .05$)[b] ○ No medical treatment (n = 21): 64.86 (9.68), 95% CI (60.45, 69.26) ○ GnRH analogs (n = 11): 61.91 (10.55), 95% CI (54.82, 69.00) ○ CSH and GnRH analogs (n = 32): 60.09 (9.67), 95% CI (56.61, 63.58) ○ GA surgery and CSH (n = 11): 58.27 (8.72), 95% CI (52.42, 64.13) **YSR/ASR Internalizing T-Score**, mean (SD), 95% CI. • TGNB adolescents on CSH and GnRH analogs, and having GA surgery and CSH have lower scores than those with no medical treatment ($P < .05$)[b]

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ No medical treatment (n = 21): 65.95 (8.26), 95% CI (62.19, 69.71) ○ GnRH analogs (n = 11): 61.55 (12.72), 95% CI (53.00, 70.09) ○ CSH and GnRH analogs (n = 32): 59.56 (10.34), 95% CI (55.83, 63.29) ○ GA surgery and CSH (n = 11): 55.36 (8.74), 95% CI (49.49, 61.24) **YSR/ASR Externalizing T-Score,** mean (SD), 95% CI. • TGNB adolescents on CSH and GnRH analogs, and having GA surgery and CSH have lower scores than those with no medical treatment ($P < .05$)[b] ○ No medical treatment (n = 21): 56.38 (13.6), 95% CI (59.19, 62.57) ○ GnRH analogs (n = 11): 54.82 (11.37), 95% CI (47.18, 62.45) ○ CSH and GnRH analogs (n = 32): 52.03 (8.43), 95% CI (48.99, 55.07) ○ GA surgery and CSH (n = 11): 45.27 (10.87), 95% CI (37.97, 52.58) **CGAS Global Functioning,** mean (SD), 95% CI. • TGNB adolescents on GnRH analogs, CSH and GnRH analogs, and having GA surgery and CSH have higher scores than those with no medical treatment ($P < .05$)[b] ○ No medical treatment (n = 21): 70.00 (12.25), 95% CI (64.43, 75.57) ○ GnRH analogs (n = 11): 81.82 (7.51), 95% CI (76.77, 86.86) ○ CSH and GnRH analogs (n = 32): 85.63 (9.14), 95% CI (82.33, 88.92) ○ GA surgery and CSH (n = 11): 83.64 (8.09), 95% CI (78.20, 89.07) **Health-related quality of life-mental, mean (SD), 95% CI.** • TGNB adolescents with GA surgery and CSH had higher scores than those without medical treatment, ($P < .05$)[b]

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ No medical treatment (n = 21): 36.37 (7.71), 95% CI (32.85, 39.88) ○ GnRH analogs (n = 11): 43.17 (10.20), 95% CI (36.31, 50.01) ○ CSH and GnRH analogs (n = 32):42.07 (10.74), 95% CI (38.20, 45.94) ○ GA surgery and CSH (n = 11): 43.44 (9.57), 95% CI (37.01, 49.87) **Health-related quality of life-physical, mean (SD), 95% CI.** • TGNB adolescents with GA surgery and CSH had higher scores than those without medical treatment, ($P < .05$)[b] ○ No medical treatment (n = 21): 42.51 (10.40), 95% CI (37.78, 47.25) ○ GnRH analogs (n = 11): 49.57 (11.64), 95% CI (41.75, 57.39) ○ CSH and GnRH analogs (n = 32): 49.36 (9.81), 95% CI (45.82, 52.90) ○ GA surgery and CSH (n = 11): 53.87 (6.15), 95% CI (49.74, 58.00)
Carmichael (2021) [73] UK [redacted]	TGNB adolescents (N = 44) • **Eligibility Criteria**: ○ Patients recruited from those referred to GIDS who were between 12-15 years and had commenced GnRH analog treatment. ○ Had been seen for at least 6 months and attended at least 4 interviews. ○ Psychological stability to withstand the stresses of medical treatment and ○ Displayed severe and persistent GD and actively	• **Full cohort**: • Median age was 13.6. • Tanner stage: ○ n = 19 (43%) stage 3 ○ n = 16 (36%) stage 4 ○ n = 9 (21%), stage 5 • spent a median of 31 months in study with a median age of 16.1 at end of pathway. • 89% of patients were of white ethnicity. • All participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical exam for birth-registered sex and	TGNB youth registered male at birth starting GnRH analogs (n = 25)	TGNB youth registered female at birth starting GnRH analogs (n = 19)	• Measures of Psychological functioning were measured using the YSR (self-report.) • Psychological and social functioning was assessed using the CGAS **Cohort study**: Outcomes were compared from baseline to 12 months on treatment	**YSR total T-score** • TGNB youth DFAB showed no significant difference in outcome at 12 months compared to TGNB youth DMAB with a difference or 2.1, 95% CI (-5.2, 9.4), P = NS **GCAS score** • TGNB youth DFAB showed no significant difference in outcome at 12 months compared to TGNB youth DMAB with a difference of -3.2, 95% CI (-10.0, 3.5), P = NS
			TGNB participants who were Tanner stage 4 at baseline (n = 16)	TGNB participants who were Tanner stage 3 (n = 19) or 5 (n = 9) at baseline		**YSR total t-score** • Pubertal stage at baseline showed no significant effect on outcome at 12 months. ○ Participants starting at Tanner stage 3 at baseline showed a difference of 0.2, 95% CI (-8.3,8.7), compared to those starting at Tanner stage 4, P = NS

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	requesting pubertal suppression ○ Able to give informed consent ○ Met physical/medical criteria of being in established puberty and having normal endocrine function and karyotype consistent with birth registered sex. • **Exclusions:** Inability to fully participate, BMI < 2nd percentile, serious psychiatric conditions, Inability to give consent, low spine or hip BMD • **Sampling Method:** Patients attending GIDS were provided with information and those wishing to find out more discussed with their clinician. Those likely deemed eligible were given detailed information and invited to a medical clinic for discussion. Young people needed to commit to regular medical and psychosocial follow up. Informed consent was obtained. 48 young people attended the clinics and 44 wished to participate. 8 young people were not yet eligible, but were able to enter the study when sufficiently advanced in puberty. **Subset Definition:** • Comparisons between birth registered male (N = 25) and	normal full blood count and liver and renal function. • **Birth registered male:** • Median age 13.4 • spent a median 37 months in study • **Birth registered female**: • Median age 13.9 • spent a median 29 months in study • All patients left study following their 16th birthday when they chose whether to pursue cross-sex hormone therapy.				○ Participants starting at Tanner stage 5 at baseline showed a difference of 0.4, 95% CI (-9.9, 10.8), compared to those starting at Tanner stage 4 *P* = NS **GCAS score** • Pubertal stage at baseline showed no significant effect on outcome at 12 months. ○ Participants starting at Tanner stage 3 at baseline showed a difference of 1.6, 95% CI (-5.5,8.8), compared to those starting at Tanner stage 4, *P* = NS. ○ Participants starting at Tanner stage 5 at baseline showed a difference of - 7.9, 95% CI (-17.6, 1.8), compared to those starting at Tanner stage 4, *P* = NS.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	birth registered female (N = 19) adolescents. • Comparisons between TGNB participants who were Tanner stage 4 at baseline (n = 16) and TGNB participants who were Tanner stage 3 (n = 19) or 5 (n = 9) at baseline					
Chen (2021)[104] Four pediatric academic medical centers in the US	Adolescents seeking GnRH analog therapy (N = 95) **Eligibility:** Patients aged 8 to 20 years old, diagnosed with GD, eligible to start GnRH analogs or CSH as deemed by the primary treatment team, proficient in English, and seeking care at one of the study clinic locations **Sampling method**: Patients presenting at one of the four medical centers between July 2016 and September 2018, desiring to start GnRH analog or CSH treatment for GD **Subset definition:** Comparisons were made between **AFAB (n = 46)** and **AMAB (n = 49)**	• Mean age (yr, SD), *P* = .002: ○ AFAB: 10.76 (1.43) ○ AMAB: 11.65 (1.36) • **Gender identity**, *P* = .000: • Transmasculine/Male: ○ AFAB: 40 (87) ○ AMAB: 1 (2) • Transfeminine/Female: ○ AFAB: 1 (2.2) ○ AMAB: 44 (89.8) • Non-binary: ○ AFAB: 5 (10.9) ○ AMAB: 4 (8.2)	AFAB patients seeking GnRH analog therapy (n = 46)	AMAB patients seeking GnRH analog therapy (n = 49)	Parent-reported measures: • NIH Toolbox Life Satisfaction **Cross-sectional:** exposures/outcomes were measured at the same time	• Mean NIH Toolbox Life Satisfaction T-score (n = 94) (SD) ○ There was no significant difference between groups (*P* = NS) ▪ AFAB: 45.97 (9.61) ▪ AMAB: 45.85 (12.64)
	Adolescents seeking CSH therapy (ie, testosterone or estrogen) (N = 316) **Eligibility:** Same as above **Sampling method**: Same as above **Subset definition:** Comparisons were made between **AFAB (n = 205)** and **AMAB (n = 111)**	• Mean age (yr, SD), *P* = 0 NS ○ AFAB: 15.87 (1.76) ○ AMAB: 16.23 (2.08) • **Gender identity**, *P* = .000: • Transmasculine/Male: ○ AFAB: 191 (93.72) ○ AMAB: 0 (0) • Transfeminine/Female:	AFAB patients seeking CSH therapy (n = 205)	AMAB patients seeking GnRH analog therapy (n = 111)	Self-reported measures: • NIH Toolbox Life Satisfaction **Cross-sectional:** exposures/outcomes were measured at the same time	• Mean NIH Toolbox Life Satisfaction T-score (n = 313) (SD) ○ There was no significant difference between groups (*P* = NS) ▪ AFAB: 40.37 (9.18) ▪ AMAB: 38.82 (13.47)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ AFAB: 1 (0.5) ○ AMAB: 105 (94.6) • Non-binary: ○ AFAB: 13 (6.3) ○ AMAB: 6 (5.4)				
Chen (2023)[67] USA- Gender clinics at [redacted] from July 2016 through June 2019	TGNB adolescents (N = 315) **Eligibility:** Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating GAH as part of their clinical care. For minors, parental consent was required to initiate treatment. **Sampling Method:** Youth were recruited from 4 different sites at the start of GAH therapy. They were enrolled if they met inclusion criteria **Subset definition:** • Comparisons were made between those designated female at birth(n = 204) and those designated male at birth (n = 111) • Comparisons were made between those who started GAH in early puberty (n = 24) and those who started in later puberty (n = 291)	• Participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) • Higher percentage of those designated female at birth (64.8%) then male. • Mostly Non-Latinx or non-Latin white (58.1%) Tanner stage at GAH initiation: no (%) • Early n = 24 ○ Stage 1: 2 (0.6) ○ Stage 2: 14 (14.1) ○ Stage 3: 9 (2.9) • Late n = 291 ○ Stage 4: 29 (9.2) ○ Stage 5: 262 (83.2)	TGNB youth starting GAH in early puberty (Tanner stages 1-3) (n = 24)	TGNB youth starting GAH in later puberty (Tanner stages 4-5) (n = 291)	**Positive Effect and Life Satisfaction** were assessed using measure from the NIH Toolbox—Emotion Battery. Cohort: outcomes were measured at baseline, 6, 12, 18 and 24 months of GAH therapy	Positive affect • Those that had initiated GAH in early puberty had a significantly higher score of 50.27 (12.08) compared to 42.47 (10.49) for those who initiated GAH in later puberty at baseline. *P* < .001 Life satisfaction • Those that had initiated GAH in early puberty had a higher score of 44.90 (14.13) compared to 39.35 (10.46) for those who initiated GAH in later puberty at baseline. *P* < .08
			TGNB youth DFAB (n = 204)	TGNB youth DMAB (n = 111)		Positive affect • No significant difference after 24 months of GAH among youth designated female at birth vs youth designated male at birth Life satisfaction • T scores increased over 24 months of GAH among youth designated female at birth but not among those designated male at birth with a time-invariant effect on slope of -1.86, 95% CI (-3.49 to -0.24)
Costa (2015)[77] [redacted] United Kingdom)	Adolescents with GD (N = 201) **Eligibility:** Diagnosis of GD **Sampling method**: Participants were referred to the Gender Identity Development Service between 2010 and 2014 and	• Mean age at baseline (yr, SD), *P* = NS ○ Natal males: 15.61 (1.70) ○ Natal females: 15.46 (1.22) • Mean age at start of GnRH analogs (yr, SD), *P* = NS	Immediately eligible adolescents for puberty suppression (n = 101) Received psychological support during the entire study duration (18 months) +	Delayed eligible adolescents for puberty suppression (n = 100) Received psychological support only during the study duration (18 months)	Physician-reported measure(s): • CGAS **Cohort:** outcomes were measured at baseline (T0), 6	**Mean CGAS score (SD):** • There was no significant difference between cohorts at any time point • Baseline (T0), *P* = NS: ○ Immediately eligible adolescents (N = 101): 58.72 (11.38)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	completed the 6-month diagnostic evaluation **Subset definition:** Comparisons were made between **immediately eligible (n = 101)** and **delayed eligible (n = 100)** adolescents for puberty suppression	○ Natal males: 16.64 (1.22) ○ Natal females: 16.39 (1.28) • Living in the role of the desired gender: • Completely, *P* < .001: ○ Natal males: 29 (42.6) ○ Natal females: 88 (73.9) • Mean CGAS at baseline (SD), *P* = .03: ○ Natal males: 55.4 (12.7) ○ Natal females: 59.2 (11.8)	12 months of puberty suppression		months (T1), 12 months (T2), and 18 months (T3)	○ Delayed eligible adolescents (N = 100): 56.63 (13.14) • After 6 months of psychological support in both groups (T1), *P* = NS ○ Immediately eligible adolescents (N = 101): 60.89 (12.17) ○ Delayed eligible adolescents (N = 100): 60.29 (12.81) • After 12 months of psychological support for delayed and immediately eligible adolescents, with 6 months of puberty suppression for immediately eligible adolescents only (T2), *P* = NS: ○ Immediately eligible adolescents (N = 60): 64.70 (13.34) ○ Delayed eligible adolescents (N = 61): 62.97 (14.10) • After 18 months of psychological support for delayed and immediately eligible adolescents, with 12 months of puberty suppression for immediately eligible adolescents only (T3), *P* = NS: ○ Immediately eligible adolescents (N = 35): 67.40 (13.93) ○ Delayed eligible adolescents (N = 36): 62.53 (13.54)
de Vries (2010)[78] [redacted]	N = 27 TGNB adolescents • **Eligibility**: not clearly stated • **Sampling method:** 140 of 196 consecutively referred adolescents were considered eligible for medical intervention between 2000 and 2008 at the clinic. Of this cohort, 29 adolescents who were age 16 years or older were prescribed CSH only, and 111 adolescents were prescribed GnRH analogs to suppress puberty. Subsequently, 70 of the 111 started CSH treatment between the years 2003 and 2009. The first 30 young adults who had become age 18 and had GRS between 2004 and 2009 were	**Full cohort (N = 27):** • Age, mean (SD) ○ assessment of pre-treatment: 13.5 (1.8) with a range of 11.2–17.0. ○ start of GnRH analogs: 14.6 (1.7) with a range of 11.5–17.9. ○ start of CSH: 16.6 (1.1) with a range of 13.9–18.6. ○ assessment of post treatment: 20.9 (1.0) with a range of 19.7–22.8. • The mean (SD) full-scale intelligence was 98.2 (15.0) with a range of 70–131. **MTFs group (N = 11):** • Age, mean (SD)	MTF TGNB adolescents	FTM TGNB adolescents	Quality of life was measured using the WHOQOL-Brief and SWLS Cohort: participants are followed over time to monitor the exposure status and the development of the outcome of interest (prospective review). Measured pre-treatment and post-treatment, at least one year after gender reassignment surgery.	Quality of life: • Significant gender differences were observed. In the Psychological domain of the WHOQOL-breve, MTFs reported their quality of life as better (M = 15.9, SD = 2.1) compared to FTMs (M = 13.9, SD = 2.2; U = 35.0, *P* < .01). • On the SWLS, MTFs were observed to be more satisfied than FTMs (M = 28.8, SD = 4.2 versus M = 22.9, SD = 6.7; U = 34.0, *P* < .01).

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	invited to participate at least one year after their last operation. GRS was vaginoplasty for MTFs and hysterectomy for FTMs, because after these surgeries transsexuals can legally change their gender. One person (MTF) refused to participate and two (one FTM and one MTF) failed to send back their questionnaires. This resulted in 27 participants, 11 MTFs and 16 FTMs. • **Subset definition:** Comparisons were made between MTF adolescents (n = 11) and FTM adolescents (n = 16)	○ assessment of pre-treatment: 13.9 (.8). ○ start of GnRH analogs: 15.0 (0.6). ○ start of CSH: 16.7 (1.4). ○ assessment of post treatment: 21.3 (1.1). • The mean (SD) full-scale intelligence was 94.4(12.3). **FTMs group (N = 16):** • Age, mean (SD) age ○ assessment of pre-treatment: 13.2 (1.8). ○ start of GnRH analogs: 14.4 (0.3). ○ start of CSH: 16.6 (0.9). ○ assessment of post treatment was 20.7 (0.8). • The mean (SD) full-scale intelligence was 103.5 (15.2).				
de Vries (2011)[57] [redacted]	Transgender adolescents (N = 70) **Eligibility:** N/R **Sampling method**: First 70 transgender adolescents who were referred for medical treatment (ie, puberty suppression) between 2000 and 2008 **Subset definition:** Comparisons were made between **natal males (n = 33)** and **natal females (n = 37)**	• Mean age at assessment (yr, SD), *P* = .028 ○ Natal males: 13.14 (1.55) ○ Natal females: 14.10 (1.99) • Mean age at start of GnRH analogs (yr, SD), *P* = 0.036 ○ Natal males: 14.25 (1.79) ○ Natal females: 15.21 (1.95) • Mean age at start of CSH (yr, SD), *P* = .008 ○ Natal males: 16.24 (1.21) ○ Natal females: 16.99 (1.07) • Mean time between start of GnRH analogs and CSH (yr, SD)*P* = NS	Natal males (n = 33)	Natal females (n = 37)	Physician-reported measure(s): • CGAS **Cohort:** outcomes were measured before (T0) and while on puberty suppression, before CSH (T1)	**Mean CGAS score (SD; N = 41)** • Compared with natal males, natal females had a significantly lower score on the global assessment of functioning scale at T0 and T1 • Before starting puberty suppression (T0): ○ Natal males: 73.10 (8.44) ○ Natal females: 67.25 (11.06) • While taking puberty suppression (T1): ○ Natal males: 77.33 (8.69) ○ Natal females: 70.30 (9.44) • Between-sex significance: 5.77, *P* = .021

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		○ Natal males: 1.99 (0.94) ○ Natal females: 1.78 (1.16)				
de Vries (2014)[79]  Netherlands)	Transgender adults who had received puberty suppression during adolescence, and completed gender reassignment surgery (N = 55) **Eligibility:** Prescribed puberty suppression at the clinic as an adolescent with GD, and received gender reassignment surgery between 2004 and 2011 **Sampling method**: This group of adolescents belonged to a larger group of adolescents (n = 196) who were referred for treatment between 2000 and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery **Subset definition:** Comparisons were made between **transgender women (n = 22)** and **transgender men (n = 33)**	• Mean age at assessment before treatment is started (yr, SD): ○ Transgender women: 13.6 (1.8) ○ Transgender men: 13.7 (2.0) • Mean age at start of GnRH analogs (yr, SD): ○ Transgender women: 14.8 (2.0) ○ Transgender men: 14.9 (1.9) • Mean age at start of CSH (yr, SD): ○ Transgender women: 16.5 (1.3) ○ Transgender men: 16.8 (1.0) • Mean age at gender reassignment surgery (yr, SD): ○ Transgender women: 19.6 (0.9) ○ Transgender men: 19.0 (0.8) • Mean age at assessment after gender reassignment surgery (yr, SD): ○ Transgender women: 21.0 (1.1) ○ Transgender men: 20.5 (0.8) • Mean pre-treatment CGAS (SD): ○ Transgender women: 74.33 (7.53) ○ Transgender men: 67.65 (11.87)	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Physician-reported measure(s): • CGAS **Cohort:** outcomes were measured before the start of puberty suppression (pre-treatment; T0), at the start of CSH (T1), and at least 1 year after gender reassignment surgery (T2)	**Mean CGAS score (SD):** • There was a significant difference in CGAS scores between natal males and females • At the start of CSH (T1): ○ Transgender women: 78.20 (9.56) ○ Transgender men: 70.65 (9.89) • At least 1 year after gender reassignment surgery (T2): ○ Transgender women: 82.40 (8.28) ○ Transgender men: 76.29 (14.48)
de Vries (2016)[107] 	TGNB adolescents (N = 316) **Eligibility:** All adolescents were seen at the clinics and met the DSM criteria for gender identity disorder. **Sampling method:** not specified **Subset definition:**	• Age (in years), mean (SD), *P* = NS ○ Amsterdam (n = 139): 15.69 (1.46) ○ Toronto (n = 177): 15.92 (1.27) • Natal gender, *P* = NS ○ Males (%) ▪ Amsterdam: 79 (56.8) ▪ Toronto: 94 (53.1)	TGNB youth at initial clinical assessment seen in Amsterdam + natal male gender (2 comparators-clinic + sex)	TGNB youth at initial clinical assessment seen in Toronto + natal female gender (2 comparators-clinic + sex)	• Ratings of psychological functioning was obtained at the time of assessment. • Behavioral and emotional problems were measured using the CBCL and YSR	**Behavioral and Emotional problems scored on CBCL/YSR** • For the CBCL Total Problem score, on average, the Toronto adolescents had more behavioral and emotional problems than Amsterdam adolescents, F(1, 253) = 24.63, *P* < .001, d = .64. ○ Toronto boys and girls had significantly higher Internalizing T scores than the Amsterdam boys and girls (respective *P* < .01 and < .03)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
[redacted]	• The Amsterdam sample of (n = 139) adolescents between the ages of 13–18 years referred and assessed between 1996 and 2008 and was compared to the Toronto sample, consisting of (n = 177) adolescents in the same age range referred and assessed between 1980 and 2010 • CBCL data were available for 112 (80.6 %) adolescents and YSR data were available for 106 (76.3 %) adolescents in the Amsterdam clinic. CBCL data were available for 142 (80.2 %) adolescents and YSR data were available for 138 (78.0 %) adolescents in the Toronto clinic. • Comparisons were made between natal genders (opposite gender within clinic and same gender between clinics) ○ Amsterdam males: n = 79 ○ Amsterdam females: n = 60 ○ Toronto males: n = 94 ○ Toronto females: n = 83	○ Females (%) ▪ Amsterdam: 60 (43.2) ▪ Toronto: 83 (46.9) • M:F ratio ○ Amsterdam: 1.31:1 ○ Toronto: 1.13:1 • Full-Scale IQ, mean (SD), *P* = NS ○ Amsterdam (n = 92): 95.79 (16.45) ○ Toronto (n = 163): 97.76 (19.08) • Social class, N (%), *P* = NS ○ I ▪ Amsterdam: 52 (49.5) ▪ Toronto: 90 (51.1) ○ II–III ▪ Amsterdam: 29 (27.6) ▪ Toronto: 49 (27.8) ○ IV-V ▪ Amsterdam: 24 (22.9) ▪ Toronto: 37 (21.0) • Parental marital status, N (%), *P* = NS ○ Both Parents ▪ Amsterdam: 57 (50.0) ▪ Toronto: 77 (43.5) ○ Other ▪ Amsterdam: 57 (50.0) ▪ Toronto: 100 (56.5)			• Peer Relations Scale was created from three CBCL items, item 25,38 and 48 • All data analyzed using a 2 (Sex) x 2 (Clinic) ANOVA **Cross sectional:** Exposure/outcome was measured at one point in time at time of participant's initial assessment at the clinic.	○ For the Externalizing T score, the Toronto boys had significantly higher scores than the Amsterdam boys (*P* < .001) whereas the Externalizing T scores of the Amsterdam and Toronto girls were comparable. ○ Post-hoc tests also showed that both the natal boys and girls from Toronto and the natal boys from Amsterdam had significantly higher Internalizing scores than Externalizing scores (all *P* < .001), but the two broad-band scores did not differ significantly for the natal girls from Amsterdam. • For the YSR Total Problem score, on average, the Toronto adolescents reported more behavioral and emotional problems than Amsterdam adolescents, F (1, 243) = 12.36, *P* = .001, d = .46. ○ Post-hoc tests showed that both the natal boys and natal girls had a significantly higher Internalizing score than Externalizing score (*P* < .001 and < .01, respectively). ○ The natal boys had a significantly higher Internalizing score than did the natal girls (*P* < .02) whereas the natal girls had a significantly higher Externalizing score than did the natal boys (*P* < .03). • Between clinics, a significantly greater percentage of adolescents scored in the clinical range in the Toronto clinic compared to the Amsterdam clinic on the CBCL Total Problem score, χ^2 (1) = 13.99, *P* < .001, the CBCL Internalizing T score, χ^2 (1) = 12.02, *P* = .001, but not on the CBCL Externalizing *T* score. • There were no significant differences on any of the YSR measures. **CBCL and YSR Clinical range scores (> 90% percentile)** • A significantly greater percentage of the Toronto girls had a score in the clinical range for the CBCL Total problem score, χ^2 (1) = 9.59, *P* = .002, compared to the Amsterdam girls, but not on any of the other five measures. • The percentage of boys scoring in the clinical range was significantly higher in the Toronto clinic than in the Amsterdam clinic for the CBCL Total problem score, χ^2

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						(1) = 4.99, *P* = .025, and the CBCL Internalizing T score, $\chi^2(1) = 10.99$, *P* = .001, but not for the CBCL Externalizing T score or any of the YSR problem scores. • Across both clinics, for the six measures of emotional and behavioral problems, a significantly greater percentage of boys scored in the clinical range compared to girls for the CBCL and YSR Internalizing T scores, $\chi^2(1) = 7.03$, *P* = .008 and $\chi^2(1) = 10.83$, *P* = .001, respectively, but not for the CBCL and YSR Total Problem scores and CBCL and YSR Externalizing T scores. • In the Amsterdam clinic, the percentage of boys scoring in the clinical range was significantly higher than for the girls for the CBCL and YSR Internalizing T scores, $\chi^2(1) = 7.67$, *P* = .006, and $\chi^2(1) = 6.97$, *P* = .002, but not for the Total Problem scores and the Externalizing T scores. • In the Toronto clinic, the percentage of boys scoring in the clinical range was significantly higher than for the girls for the CBCL Externalizing T score, $\chi^2(1) = 3.87$, *P* = .049 and for the YSR Internalizing T score, $\chi^2(1) = 4.03$, *P* = .038, but not for the other four measures. **CBCL, mean (SD), % in clinical range** • Total Problems Score ○ Amsterdam (n = 112): 45.59 (26.75), 55.4% ▪ Males (n = 63): 45.84 (26.00), 57.2% ▪ Females (n = 49): 45.27 (27.95), 53.1% ○ Toronto (n = 142): 64.47 (31.81), 77.5% ▪ Males (n = 75): 69.27 (32.35), 81.3% ▪ Females (n = 67): 59.10 (30.55), 73.1% • Internalizing T ○ Amsterdam (n = 112): 64.14 (10.89), 53.6% ▪ Males (n = 63): 65.11 (10.67), 65.1% ▪ Females (n = 49): 62.90 (11.17), 38.8% ○ Toronto (n = 142): 68.78 (9.83), 74.5% ▪ Males (n = 75): 69.95 (8.99), 78.7%

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ Females (n = 67): 67.48 (10.61), 69.7% • Externalizing T ○ Amsterdam (n = 112): 59.48 (11.62), 43.8% ▪ Males (n = 63): 58.14 (11.94), 39.7% ▪ Females (n = 49): 61.20 (11.09), 49.0% ○ Toronto (n = 142): 62.89 (10.82), 48.2% ▪ Males (n = 75): 64.79 (11.01), 56.0% ▪ Females (n = 67): 60.76 (10.28), 39.4% **YSR, mean (SD), % in clinical range** • Total Problems Score ○ Amsterdam (n = 106): 51.62 (24.81), 40.6% ▪ Males (n = 58): 50.16 (25.31), 41.4% ▪ Females (n = 48): 53.40 (24.33), 39.6% ○ Toronto (n = 138): 64.07 (28.29), 39.9% ▪ Males (n = 71): 66.14 (31.17), 42.3% ▪ Females (n = 67): 61.88 (24.92), 37.3% • Internalizing T ○ Amsterdam (n = 106): 61.53 (12.52), 45.3% ▪ Males (n = 58): 63.02 (12.95), 56.9% ▪ Females (n = 48): 59.73 (11.86), 31.2% ○ Toronto (n = 138): 62.41 (11.96), 46.4% ▪ Males (n = 71): 64.55 (13.03), 54.9% ▪ Females (n = 67): 60.15 (10.34), 37.3% • Externalizing T ○ Amsterdam (n = 106): 54.77 (11.72), 18.9% ▪ Males (n = 58): 51.72 (11.75), 13.8% ▪ Females (n = 48): 58.46 (10.67), 25.0% ○ Toronto (n = 138): 56.72 (10.89), 25.4% ▪ Males (n = 71): 56.49 (11.73), 22.5% ▪ Females (n = 67): 56.97 (9.99), 28.4%

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						Peer Relations Scale • On the CBCL, on average, adolescents in Toronto had poorer peer relations than those in Amsterdam, F (1, 253) = 16.68, *P* < .001, d = .76. and boys had poorer peer relations than girls, F (1, 253) = 11.23, *P* = .001, d = .39. • On the YSR, on average, adolescents in Toronto had poorer peer relations than those in Amsterdam, F(1, 243) = 11.50, *P* < .001, d = .59, and boys had poorer peer relations than girls, F(1, 243) = 11.75, *P* = .003, d = .35. • **CBCL**, mean (SD), ○ Amsterdam (n = 112): 1.52 (1.65) ▪ Males (n = 63): 1.83 (1.85) ▪ Females (n = 49): 1.12 (1.29) ○ Toronto (n = 142): 2.88 (1.88) ▪ Males (n = 75): 3.28 (1.72) ▪ Females (n = 67): 2.43 (1.96) • **YSR**, mean (SD) ○ Amsterdam (n = 106): 1.42 (1.56) ▪ Males (n = 58): 1.69 (1.67) ▪ Females (n = 48): 1.10 (1.37) ○ Toronto (n = 138): 2.41 (1.78) ▪ Males (n = 71): 2.75 (1.75) ▪ Females (n = 67): 2.06 (1.75)
	Same as above	Same as above	TGNB youth at initial clinical assessment compared using a variety of variables that would predict CBCL and YSR behavioral and emotional problems	TGNB youth at initial clinical assessment compared using a variety of variables that would not predict having CBCL and YSR behavioral and emotional problems	• A multiple linear regression analysis was conducted for the combined sample as well as separately for boys and girls. There were seven independent (predictor) variables: ○ clinic ○ age ○ Full-Scale IQ,	After a multiple linear regression analysis accounting for variables: • For both the CBCL and the YSR Total Problem score (collapsed across natal sex of the adolescents), the Peer Relations Scale was the strongest predictor. (CBCL, *B* = 8.26, *P* < .001; YSR, *B* = 8.09, *P* < .001) • For the CBCL Total Problem score, social class (*B* = 2.53, *P* = .012), Full-Scale IQ, (*B* = -2.66, *P* = .008), and Clinic (*B* = -2.28, *P* = .023), were also significant predictors. Adolescents with poorer peer relations, from a lower socioeconomic

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
					○ parents' social class ○ parents' marital status ○ the sum of the two CBCL/YSR gender items ○ the CBCL/ YSR Peer Relations Scale. • The dependent (criterion) variable was the CBCL/YSR Total Problem score **Cross sectional:** Exposure/outcome was measured at one point in time at time of participant's initial assessment at the clinic.	background, with a lower IQ, and from the Toronto clinic showed more behavioral and emotional problems. • For boys, peer relations (*B* = 5.86, *P* < .001), social class (*B* = 3.29, *P* = .001), and Clinic (*B* = -2.40, *P* = .018), were significant predictors . • For girls, peer relations (*B* = 5.77, *P* < .001), and Full-Scale IQ (*B* = -2.64, *P* = .009), was were significant predictors. • For the YSR and gender, only Poor peer relations was a significant predictor. (boys: *B* = 6.21, *P* < .001; girls: *B* = 25.25, *P* < .001)
Grannis (2021)[110] A gender developmental clinic at a children's hospital	FTM adolescents (N = 42) **Eligibility:** Diagnosis of GD, 9 to 21 yrs of age, and able to participate in MRI-based research **Sampling method**: Study sample was drawn from a larger study of transgender youth receiving gender affirming medical care (both puberty blockers and CSH). All participants were receiving gender affirming behavioral support and had not been prescribed PBs previously. **Subset definition:** Comparisons were made between **treated (n = 19)** and **untreated (n = 23)** FTM adolescents	• Mean age (yr, SD), *P* < .01: ○ Treated FTM: 17.0 (1.2) ○ Untreated FTM: 15.8 (1.5) • History of anxiolytics/anti-depressant use: ○ Treated FTM: 10 (52.6) ○ Untreated FTM: 18 (78.3) • Birth control use: ○ Treated FTM: 15 (79.0) ○ Untreated FTM: 15 (65.2) • Mean duration of testosterone use (months, SD): ○ Treated FTM: 13.1 (10.3) • Mean testosterone dosage (mg, SD): ○ Treated FTM: 242.1 (82.3)	Received intramuscular testosterone cypionate (n = 19)	Did not receive intramuscular testosterone cypionate (n = 23)	Amygdala activation using fMRI during a face processing task **Cross-sectional:** exposures/outcomes were measured at the same time	• There was a significant interaction effect between testosterone treatment and amygdala connectivity regarding generalized anxiety, but not depression or suicidality. • Participants receiving testosterone cypionate had higher activation in the left amygdala compared to untreated participants in response to threatening faces • A stronger connectivity in the ventromedial prefrontal cortex for the seed in the right amygdala was observed for treated participants compared to untreated participants, but the difference was not statistically significant • No significant relations were found between body image dissatisfaction or mental health, and brain measures
Mirabella (2022)[113] [redacted]	TGNB adolescents (N = 125)	Total cohort: • Center seen:	Natal male (n = 40)	Natal female (n = 85)	• The Gender Diversity Questionnaire (GDQ) was used to evaluate the ways in which gender variant people	**Gender fluidity** (chi^2, *P value*) • There were no statistically significant differences in gender fluidity between TGNB natal males and natal females

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
[redacted]	Eligibility: referred between April 2019 and June 2021, age between 11 and 18 years Sampling method: Adolescents had been consecutively referred. All who met inclusion criteria were included. Subset Definition: Comparisons were made between natal males (n = 40) and natal females (n = 85) Comparisons were made between trans-binary adolescents (n = 93) and non-binary adolescents (n = 23)	○ 94 were seen at SAIFIP ○ 31 were seen at the Gender Incongruence Unit of the Careggi Hospital in Florence • Sex assigned at birth: ○ 40 natal males ○ 85 natal females • Natal female: ○ center seen: ▪ 61 (71.8) were seen at SAIFIP ▪ 24 (28.2) were seen at the Gender Incongruence Unit ○ age group ▪ 19 (22.4) were in-between 11 to 14 YO and ▪ 66 (77.6) were in-between 15 to 18 YO ○ Gender identity ▪ 64 (75.30) Trans binary ▪ 21 (24.70) Nonbinary • Natal male: ○ Center seen: ▪ 33 (82.5) were seen at SAIFIP and ▪ 7 (17.5) were seen at the Gender Incongruence Unit ○ age group: ▪ 13 (32.5) were in-between 11 to 14 YO ▪ 27 (67.5) were in-between 15 to 18 YO ○ Gender identity			identify and express their gender **Cross-sectional:** exposures/outcomes were measured <u>at the same time</u>	○ Fixed gender identity- no time or context-based change: 3.058, *P* = NS ○ Fluid gender identity- context-based change: 0.178, *P* = NS ○ Fluid gender identity- time-based change: 2.269, *P* = NS ○ Currently exploring gender identity: 4.683, *P* = NS **Factors influencing gender identity** • No statistically significant differences in factors influencing gender identity between natal males and natal females ○ Body discomfort (B%), *P* = NS ▪ Natal male: 90% ▪ Natal female: 98.8% ○ Puberty (%), *P* = NS ▪ Natal male: 72.5% ▪ Natal female: 69.5% ○ Friends (%), *P* = NS ▪ Natal male: 45.1% ▪ Natal female: 27.5% ○ Family (%), *P* = NS ▪ Natal male: 10% ▪ Natal female: 26.8% ○ Social media (%), *P* = NS ▪ Natal male: 42.5% ▪ Natal female: 52.4% ○ Meeting trans people (%), *P* = NS ▪ Natal male: 30% ▪ Natal female: 35.4% ○ Television programs (%), *P* = NS ▪ Natal male: 17.5% ▪ Natal female: 20.7% **Desired medical interventions (chi^2, P value)** ○ Puberty blockers: 13.005, *P* < .001

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		▪ 29 (72.50) Trans binary ▪ 11 (27.50) Nonbinary A Chi squared test found no significant difference in the distribution of trans binary vs non-binary individuals between natal male and natal female participants				▪ Significantly more natal males than natal female participants reported that they desired puberty blockers (estimated from figure: > 70% vs 40%) ○ Breast/chest surgery: 36.427, *P* < .001 ▪ Significantly more natal females wanted breast/chest surgery than natal males [n = 81 (98.8%) vs. n = 23 (57.5%)] ○ Genital surgery: 4.750, *P* = NS ○ Cross-sex hormones: 0.967, *P* = NS ○ Other surgeries: 27.438, *P* = .037
			Trans binary adolescents (n = 93)	Non-binary adolescents (n = 23)	• The Gender Diversity Questionnaire (GDQ) was used to evaluate the ways in which gender variant people identify and express their gender **Cross-sectional:** exposures/outcomes were measured at the same	**Gender fluidity (chi^2, P value)** • Non-binary subjects appeared to have a more fluid and less stable gender-identity both over time and across contexts compared to trans binary adolescents. ○ Fixed gender identity- no time or context-based change: 23.487, *P* < .001 ○ Fluid gender identity- context-based change: 23.070, *P* < .001 ○ Fluid gender identity- time-based change: 27.942, *P* < .001 ○ Currently exploring gender identity: 16.945, *P* < .001 **Factors influencing gender identity** • No statistically significant differences in factors influencing gender identity between natal males and natal females ○ Body discomfort, *P* = NS ▪ Trans-binary: 95.7% ▪ Non-binary: 96.7% ○ Puberty, *P* = NS ▪ Trans-binary: 69.6% ▪ Non-binary: 73.3% ○ Friends, *P* = NS ▪ Trans-binary: exact number not reported, < 40% based on figure

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ Non-binary: exact number not reported, ~ 50% based on figure ○ Family, *P* = NS ▪ Trans-binary: exact number not reported, < 20% based on figure ▪ Non-binary: exact number not reported, ~ 30% based on figure ○ Social media, *P* = NS ▪ Trans-binary: exact number not reported, ~ 50% based on figure ▪ Non-binary: exact number not reported, ~ 50% based on figure ○ Meeting trans people, *P* = NS ▪ Trans-binary: 30.4% ▪ Non-binary: 43.3% ○ Television programs, *P* = NS ▪ Trans-binary: exact number not reported, < 20% based on figure ▪ Non-binary: exact number not reported, ~ 20% based on figure ○ Other, *P* = NS ▪ Trans-binary: exact number not reported, < 5% based on figure ▪ Non-binary: exact number not reported, < 5% based on figure • **Desired medical interventions** (chi^2, P value) ○ No significant differences emerged for desired medical interventions between non-binary and trans binary subjects (significance determined by authors) ▪ Puberty blockers: 1.114, *P* = NS ▪ Breast/chest surgery: 0.116, *P* = NS ▪ Genital surgery: 0.939, *P* = NS ▪ Cross-sex hormones: 6.169, *P* = .013

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ Other surgeries: 21.857, *P* = NS
Morningstar (2023)[114] A gender development clinic at an academic pediatric center located in the US	FTM TGNB adolescents (N = 44) **Eligibility:** Participants were excluded if they had prior use of PBs, diagnosis of Turner's syndrome, lack a caregiver able to provide stimuli, brain resection after a tumor, or unable to complete the MRI scan **Sampling method**: A total of 53 FTM adolescents were recruited, but after excluding 9 ineligible participants, 44 were included in the study population **Subset definition:** Comparisons were made between **treated (n = 19)** and **untreated (n = 25)** FTM adolescents	• Mean age (yr, SD), *P* = .04: ○ Treated FTM: 16.2 (1.1) ○ Untreated FTM: 15.3 (1.5) • History of using PBs: ○ Treated FTM: 0 (0) ○ Untreated FTM: 0 (0) • Mean age at starting testosterone (yr, range): ○ Treated FTM: 15.8 (13 to 18) • Mean duration of testosterone use (yr, range): ○ Treated FTM: 1.1 (1 month to 2.8 years) • Testosterone dosage range (mg/week): ○ Treated FTM: 12.5 to 60	FTM adolescents treated with exogenous testosterone (n = 19)	FTM adolescent who did not receive exogenous testosterone (n = 25)	Self-reported measures: • NRI questionnaire • Whether testosterone influences neural processing of emotional (vocal) stimuli by the patient's caregiver (eg, parent) compared to an unknown teenage peer, based on fMRI **Cross-sectional:** exposures/outcomes were measured at the same time	• NRI questionnaire responses of those who received testosterone compared to those who did not: ○ There was no significant difference between treated and untreated FTM adolescents on self-reported NRI responses for the length of friendships and the type of parental relationships (*P* = NS) • Neural responses of those who received testosterone compared to those who did not: ○ In response to their caregiver's angry voice, treated FTM had a significantly less anterior cingulate cortex response compared to untreated FTM (*P* < .05) ○ Nonsignificant differences were observed between treated and untreated FTM patients for anterior cingulate cortex response to an unknown teenager's angry and happy voice, and their caregiver's happy voice • Relative closeness to peers vs. parents of those who received testosterone compared to those who did not: ○ Treated and untreated patients did not have significant differences for relative closeness to peers over parents (*P* = NS), closeness to peers (P value = 0.88), or closeness to parents (*P* = NS)
Sorbara (2020)[118] Transgender youth clinic in [redacted] Canada	**TGNB youth (N = 300)** **Eligibility**: Diagnosis of gender dysphoria and seen by clinic staff. Exclusion criteria was if they were not seeking CSH or had previously been on hormone blockers or CSH. **Sampling method**: patients that were eligible from clinic **Subset definition**: Younger presenting youth (YPY) were < 15 years old at presentation to clinic (n = 116) were compared to older presenting youths (OPY) were > 15	**YPY (n = 116):** • Age: 13.9 (range 12.9 to 14.5) • AFAB: 87 (75.0) • Tanner stage < 3 (early puberty): 24 (20.7) • Tanner stage > 4 (late puberty): 82 (70.7) • Tanner Stage not reported: 10 (8.6) • Socially transitioned: 76 (65.5) **OPY (n = 184):** • Age = 16.3 (range 15.6 to 16.8)	Younger presenting youth to clinic (n = 116)	Older presenting youth to clinic (n = 184)	• Youth or caregiver reports were extracted from initial visit documentation.	• The median age of recognition of gender incongruence was significantly younger among YPY than OPY (5.8 years [IQR 3.0–11.0] vs 9.0 years [IQR 5.0–13.0]; *P* < .001). • YPY reported coming out about their gender identity at younger ages (12.0 years [IQR 11.0–13.0] vs 15.0 years [IQR 13.0–15.0]; *P* < .001). • Social transition occurred earlier for YPY than for OPY (13.0 years [IQR 12.0–13.4] vs 15.0 years [IQR 14.0–16.0]; *P* < .001 • The time from recognition of gender incongruence to first TYC visit was similar between YPY and OPY (7.4 years [IQR 3.1–10.4] vs 6.8 years [IQR 3.5–11.9]; *P* = NS)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	years when presented to clinic (n = 184).	• AFAB: 142 (77.2) • Tanner Stage < 3 (early puberty): 2 (1.1) • Tanner Stage > 4 (late puberty): 166 (90.2) • Tanner Stage not reported: 16 (8.7) • Socially transitioned: 149 (81.0)				• The time from recognition of gender incongruence to first TYC visit was similar between YPY and OPY (7.4 years [IQR 3.1–10.4] vs 6.8 years [IQR 3.5–11.9]; *P* = NS) • The time between coming out and the first TYC visit was similar between YPY and OPY (1.3 years [IQR 0.9–2.0] vs 1.7 years [IQR 1.1–2.3]; *P* = NS • The rate of autism spectrum disorder was similar between YPY and OPY (7 [6.0%] vs. 11 [6.0 %]; *P* = NS)
Staphorsius (2015)[119] [redacted] Netherlands)	Adolescents with GD (N = 41[a]) **Eligibility:** Diagnosed with GD (per DSM-IV-TR), and adolescent age. To receive a GnRH analog, patients must be at least 12 years of age, and have breast development of Tanner stage B2 (natal girls) or genital development of Tanner stage G2 to G3 (natal boys). Exclusion criteria included uncontrolled endocrine disorders, neurological or psychiatric conditions that could alter study results, contraindication for MRI scan, psychotropic medication use, lack sufficient communication of Dutch language **Sampling method**: Participants were recruited from the VU University Medical Center in Amsterdam **Subset definition:** Comparisons were made between treated and untreated **MTF (n = 18)** and **FTM (n = 22)** adolescents	• Mean age (yr, SD): ○ MTF (n = 18): 15.1 (2.4) ▪ Treated MTF (n = 8): 15.4 (0.7) ▪ Untreated MTF (n = 10): 14.6 (3.2) ○ FTM (n = 22): 15.8 (1.9) ▪ Treated FTM (n = 12): 16.1 (1.7) ▪ Untreated FTM (n = 10): 15.4 (2.3) • Mean IQ (SD): ○ MTF (n = 18): 102.6 (18.5) ▪ Treated MTF (n = 8): 94.0 (10.3) ▪ Untreated MTF (n = 10): 109.4 (21.2) ○ FTM (n = 22): 97.1 (15.4) ▪ Treated FTM (n = 12): 95.8 (15.6) ▪ Untreated FTM (n = 10): 98.5 (15.9) • Mean Tanner stage (SD): ○ MTF (n = 18): 3.9 (1.1) ▪ Treated MTF (n = 8): 4.1 (1.0) ▪ Untreated MTF (n = 10): 3.8 (1.1) ○ FTM (n = 22): 4.5 (0.9)	Puberty suppression using a GnRH analog (SubQ or IV triptorelin 3.75 mg every 4 weeks) • MTF: n = 8 • FTM: n = 12	No puberty suppression (untreated): • MTF: n = 10 • FTM: n = 10	• TOL performance, an executive functioning task, and brain activation using fMRI **Cross-sectional:** exposures/outcomes were measured at the same time	• TOL performance: • Mean percentage of correct trials (accuracy) (SD): ○ Treated MTF had significantly reduced mean accuracy scores than untreated FTM (*P* = .04) ○ MTF (n = 18): 79.1 (10.3) ▪ Treated MTF (n = 8): 73.9 (9.1) ▪ Untreated MTF (n = 10): 83.4 (9.5) ○ FTM (n = 22): 87.1 (10.0) ▪ Treated FTM (n = 12): 85.7 (10.5) ▪ Untreated FTM (n = 10): 88.8 (9.7) • Mean reaction time in seconds (SD): ○ No significant differences existed between groups ○ MTF (n = 18): 10.4 (3.5) ▪ Treated MTF (n = 8): 10.9 (4.1) ▪ Untreated MTF (n = 10): 9.9 (3.1) ○ FTM (n = 22): 10.0 (2.6) ▪ Treated FTM (n = 12): 9.9 (3.1) ▪ Untreated FTM (n = 10): 10.0 (2.0) • Brain activation: ○ There were no significant group differences based on the whole-brain analyses for task load ○ ROI analyses showed treated MTF showed more activation in the bilateral precuneus, right and left DLPFC, and bilateral RLPFC compared to treated FTM

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		▪ Treated FTM (n = 12): 4.1 (1.1) ▪ Untreated FTM (n = 10): 4.9 (0.3) • Mean duration of triptorelin (Decapeptyl-CR) use (yr, SD): ○ Treated MTF: 1.8 (0.8) ○ Treated FTM: 1.4 (1.1)				○ Compared to untreated MTF, untreated FTM showed a modest increase in right DLPFC activation ($P < .10$) ○ Treated MTF showed more activation in the left RLPFC and left DLPFC than untreated MTF ○ Untreated FTM demonstrated greater activation of the bilateral precuneus compared to treated FTM
Tollit (2023)[120] [redacted] gender clinic in Australia.	TGNB youth (N = 359) **Eligibility**: First appointment with clinic from January 1, 2007 to December 31, 2016, and had a self-reported gender identity which differed from their gender at birth or sough clinical guidance on their gender identity. **Sampling method:** Patients were selected if they met criteria and were a patient of the clinic. **Subset definition:** Comparisons were made between assigned males at birth (n = 166) vs assigned females at birth (n = 193)	AMAB (n = 166): • Gender: ○ 139 were transgender, ○ 14 were non binary, ○ 4 were cisgender and 9 weren't sure. • Age: ○ Average age was 12.4 years. at GD diagnosis • Treatment: ○ 126. 39 were on puberty blockers, ○ 7 were on antiandrogens ○ 19 were on gender affirming hormones. • AFAB (n = 193): ○ Gender: ▪ 174 were transgender, ▪ 12 were nonbinary, ▪ 2 were cisgender and 5 were not sure. ○ Age: ▪ Average age was 14.8 years. ○ Treatment: ▪ 15 were on puberty blockers	Trans females presenting at RCHGS. (n = 166)	Trans males presenting at RCHGS. (n = 193)	Data extracted from clinician-recorded notes collected at clinic appointments for: • Neurodevelopmental disorders including presences of ADHD or ASD • School related difficulties including peer bullying, history of school refusal or dropping out of school. **Cross-sectional:** exposures/outcomes were measured <u>at the same time</u>	ADHD: • There was no significant difference between trans males and trans females with ADHD ○ TM = 6 ○ TF = 3 ASD: • There were significantly more trans males with ASD then trans females, $P < .05$. ○ TM = 37 ○ TF = 21 • Peer bullying: • There was no significant difference between trans males and trans females who had experienced peer bullying ○ TM: 60 ○ TF = 56 • History of school refusal: • Trans females were significantly more likely to have a history of school refusal than trans males, $P < .05$ ○ TM = 20 ○ TF = 39 • Dropped out of school: • There was no significant difference between trans males and trans females who had dropped out of school. (P = NS) ○ TM = 17

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		▪ 57 were on menses suppression ▪ 29 were on gender affirming hormones.				○ TF = 19
van der Miesen (2020)[124] [redacted] the Netherlands, between 2012 and 2015	N = 450 TGNB adolescents referred to a specialized gender identity clinic **Eligibility criteria:** Not clearly stated **Sampling method:** Transgender cohort: Adolescents who just started the diagnostic procedure were assessed during their first sessions at the VUmc. Adolescents diagnosed with GD were assessed before the start of GAH. During both assessments, parents and children completed several questionnaires during 2012 to 2015, 504 adolescents were seen in their gender identity service. 53 participants did not complete the assessment process and therefore, did not participate in this study. The reason for dropout was failure to complete the questionnaire or alternation of symptoms of GD. Of the adolescents diagnosed with GD, 179 were about to start GAH treatment. One participant did not complete the questionnaire and was thus excluded. **Subset:** Comparisons were made between TGNB adolescents receiving affirmative care and about to start GAH treatment: (N = 272) and TGNB adolescents at referral, that have not yet started affirmative care (n = 178). Comparisons were made between	• Transgender subjects who did not started any affirmative medical treatment yet: • Mean age (SD) in years = 14.47 (2.18); 116 assigned boys at birth and 156 assigned girls at birth • Transgender subjects receiving affirmative care and about to start GAH treatment: • Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth	**Transgender group**: on puberty suppression and about to start unspecified GAH treatment (n = 178)	**Transgender group**: have not yet received any affirmative medical treatment (n = 272)	Psychological functioning outcomes were measured using the Dutch version of the YSR to assess: • Internalizing and externalizing problems Poor peer relations • Effect sizes Cohen's d: .80 or higher is a large effect size, .50-.79 a medium effect size, .20-.49 small, and effect sizes < .20 are negligible **Cross-Sectional**: Exposures / Outcomes were assessed at the same time.	**Internalizing**: Mean scores (SD) on the Youth Self-Report • the adolescents at referral had significantly higher scores than the adolescents using suppression. ○ transgender adolescents receiving affirmative care: 7.76 (6.68) ○ transgender adolescents who did not receive any affirmative treatment: 11.67 (8.38 ▪ effect sizes Cohen's d between the 2 groups was 0.52 **Externalizing:** Mean scores (SD) on the Youth Self-Report • There was no significant difference between groups. ○ transgender adolescents receiving affirmative care: 9.82 (5.79) ○ transgender adolescents who did not receive any affirmative treatment: 10.19 (6.33) ▪ effect sizes Cohen's d between the 2 groups was 0.06. **Peer relations:** Mean scores (SD) on the Youth Self-Report • The adolescents at referral had significantly higher scores than those using puberty suppression. ○ transgender adolescents receiving affirmative care: 0.70 (1.06) ○ transgender adolescents who did not receive any affirmative treatment: 1.08 (1.31) ▪ Effect sizes Cohen's d between the 2 groups was 0.32

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	TGNB adolescents that had received puberty suppression who were AMAB vs AFAB.					
	Subset: Comparisons were made between TGNB adolescents that had received puberty suppression who were AMAB vs AFAB.	• Transgender subjects receiving affirmative care and about to start GAH treatment: • Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth	**TGNB adolescents AMAB:** have been receiving puberty suppression, and getting ready to start GAH treatment (n = 68)	**TGNB adolescents AFAB:** have been receiving puberty suppression, and getting ready to start GAH treatment (n = 110)		**Psychological functioning:** • Gender assigned at birth had negligible effect on psychological functioning • **Internalizing**: Mean scores (SD) on the Youth Self-Report ○ assigned boys: 7.79 (6.76) ○ assigned girls: 7.74 (6.66) ▪ effect size Cohen's d of 0.01. • **Externalizing:** Mean scores (SD) on the Youth Self-Report ○ assigned boys: 10.32 (6.26) ○ assigned girls: 9.51 (5.31) ▪ effect size Cohen's d of 0.14. • **Peer relations:** Mean scores (SD) on the Youth Self-Report ○ assigned boys:0.91 (1.18) ○ assigned girls: 0.57 (0.95) ▪ effect size Cohen's d of 0.32.
Vrouenraets (2021)[126] [redacted] the Netherlands, between January 1, 2016, and December 31, 2017 or [redacted]	TGNB adolescents (N = 74) **Eligibility criteria**: All adolescents visiting the clinics were eligible for study participation; there was no selection process. Not speaking Dutch and being cisgender were exclusion criteria. **Sampling method**: The researchers identified the adolescents who were about to start PS through the medical files, and the adolescents and their parents were invited by the involved clinician to participate. **Subset:** Comparisons were made between birth-assigned boys:	• Birth-assigned boys (n = 16, 21.6%): • Mean age (range) in years at the IC session = 14.02 (12.02–17.11); mean total IQ (range) = 99.47 (82–131); mean duration of diagnostic trajectory (range) in month = 9.25 (4–18) • Birth-assigned girls (n = 58, 78.4%): • Mean age (range) in years at the IC session = 14.87 (10.63–18.34); mean total IQ (range) = 100.42 (66–144); mean duration of diagnostic trajectory (range) in month = 8.69 (2–26)	Birth-assigned boys starting puberty suppression (n = 16)	Birth-assigned girls starting puberty suppression (n = 58)	• Behavioral outcomes: CBCL was used to assess behavioral and emotional difficulties. The total-problem T-score was calculated as age-standardized measure of total behavioral and emotional difficulties. **Cross-Sectional**: Exposures/Outcomes measured at the same time.	**CBCL** • The mean CBCL total-problem T score (range) in birth-assigned boys group, 60.62 (44–72) was similar to the mean score of the birth-assigned girls group 60.94 (42–77), *P* = NS. • The percentage in clinical range of CBCL total-problem T score in birth-assigned boys group, 38.5% was similar to the birth-assigned girls group, 43.7%, *P* = NS.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
[redacted] the Netherlands, between March 1, 2017, and December 31, 2017.	(n = 16) and birth-assigned girls: (n = 58)					
Zucker (2010)[65] [redacted] Ontario, Canada	**N = 109 TGNB Adolescents** • **Eligibility**: TGNB youth referred to the clinic with gender identity disorder between 2000 and 2009. • **Sampling Method:** Participants were consecutively referred to, and then assessed in the Gender Identity Service. Referrals were initiated either by the youth or by parents or professionals. Youth were excluded if they were referred for other reasons than gender identity disorder. • **Subset definition:** Comparisons were made between TGNB youth in which hormonal therapy was recommended (n = 66) vs. those where hormonal therapy was not recommended (n = 43). Of the total sample, n = 54 were natal males, and n = 55 were natal females	N/R	TGNB youth at initial clinical assessment compared using a variety of variable that would predict recommendation to start HT	TGNB youth at initial clinical assessment compared using a variety of variable that would predict not getting a recommendation to start HT	• Whether youth was recommended for hormonal blocker therapy was ascertained and then compared with demographic, behavioral and psychosocial variables • Youth and their families or a guardian, such as a child protection agency worker) were seen for a diagnostic assessment that typically involved a family interview, interviews with parents, and an interview with the youth. Parents were not involved in the assessment if either the youth did not wish to have them participate or the youth was in-care (e.g., in residential treatment) or living independently and the parents were not available to be seen. As part of the assessment, the youth were seen for psychological testing, which consisted of a battery of tests and tasks, including cognitive testing, projective testing, and gender-specific measures. • Eight demographic variables were coded for the present study:	Univariable test examining the association between baseline characteristics and HT recommendation: • For the eight demographic variables, the only significant difference as a function of hormonal treatment recommendation was that biological females were significantly more likely to receive a recommendation for hormonal suppression than biological males. • There was no significant difference on the CBCL mean sum score as a function of hormonal treatment recommendation, but youth not recommended for hormonal therapy had a significantly higher YSR mean score than youth who were recommended. • All of the psychosexual variables examined in the current study showed significant differences as a function of recommendation for hormonal therapy. Youth who were recommended for hormonal therapy were more likely to draw an opposite sex person first on the DAP, had, on average, a more extreme mean score on the parent-report GIQ-Ad measure of concurrent cross-sex-typed behavior, self-reported more gender dysphoria on the GIDYQ, recalled more cross-gender behavior during childhood on the RCGI, and were more likely to be classified as homosexual (on both the EROS and the SHQ) than as non-homosexual. • **Age**, mean (SD), t = 1.23, P = NS ○ HT recommended (n = 66): 17.01 (1.74) years ○ HT not recommended (n = 43): 16.59 (1.74) years • **Sex**, n (%), c^2 = 7.95, P = .005 ○ Male: ▪ HT recommended:25 (46.3) ▪ HT not recommended: 29 (53.7) ○ Female:

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
					○ (1) the patient's biological sex, ○ (2) age at assessment, ○ (3) year of assessment (YOA), ○ (4) Full-Scale IQ on an age-appropriate Wechsler Intelligence Scale, ○ (5) parents' social class (Hollingshead, 1975), ○ (6) parents' marital status, ○ (7) race/ethnicity, and ○ (8) whether or not the youth was in-care (e.g., via a child protection society and living in a group home, residential treatment, a foster family). • Behavior Problems were assessed through the CBCL and YSR • Psychosexual variables were assessed through the GIQ-Ad, GIDYQ, RCGI, EROS and SHQ **Cross sectional**: Exposure/outcome was measured at one point of time- whether patient was recommended for hormonal blocker therapy or not was assessed at initial clinical assessment	▪ HT recommended: 41 (74.5) ▪ HT not recommended: 14 (25.5) • **Year of Assessment**, mean (SD), $t < 1$, P = NS ○ HT recommended (n = 66): 2005.83 (2.70) ○ HT not recommended: (n = 43) 2005.63 (2.45) • **Full-Scale IQ**, mean (SD), $t < 1$, P = NS ○ HT recommended (n = 65): 104.23 (17.91) ○ HT not recommended (n = 42): 101.60 (18.60) • **Social Class**, n(%), $c^2 = 4.04$, P = NS ○ I-II ▪ HT recommended: 38 (69.1) ▪ HT not recommended: 17 (30.9) ○ III ▪ HT recommended: 17 (56.7) ▪ HT not recommended: 13 (43.3) ○ IV-V ▪ HT recommended: 11 (45.8) ▪ HT not recommended: 13 (54.2) • **Parent's Marital Status,** n (%), c2 < 1, P = NS ○ Both Parents ▪ HT recommended: 33 (64.7) ▪ HT not recommended: 18 (35.3) ○ Other ▪ HT recommended: 33 (56.9) ▪ HT not recommended: 25 (43.1) • **Ethnicity**, n (%), c2 = 2.45, P = NS ○ Caucasian ▪ HT recommended: 47 (56.0) ▪ HT not recommended: 37 (44.0) ○ Other

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ HT recommended: 19 (76.0) ▪ HT not recommended: 6 (24.0) • **In Care**, n (%), c2 = 3.11, *P* = NS ○ Yes ▪ HT recommended: 6 (37.5) ▪ HT not recommended: 10 (62.5) ○ No ▪ HT recommended: 60 (64.5) ▪ HT not recommended: 33 (35.5) **Behavior Problems** • **CBCL: Sum Items,** mean (SD), *t* < 1, *P* = NS ○ HT recommended (n = 62): 61.02 (27.17), 83.9% clinical range ○ HT not recommended (n = 39): 63.59 (32.55), 69.2% clinical range • **YSR: Sum Items**, mean (SD), *t* = 2.78, *P* = .006 ○ HT recommended (n = 65): 60.95 (24), 40.0% clinical range ○ HT not recommended (n = 42): 75.17 (28), 42.9% clinical range **Psychosexual Measures** • **Draw-a-Person**, n (%), c^2 = 3.43, *P* = NS ○ Cross-Sex Drawn First ▪ HT recommended: 47 (69.1) ▪ HT not recommended: 21 (30.8) ○ Same-Sex Drawn First ▪ HT recommended: 18 (48.6) ▪ HT not recommended: 19 (51.3) • **GIQ-Ad**, mean (SD), *t* = 5.06, *P* < .001 ○ HT recommended (n = 60): 2.17 (0.74) ○ HT not recommended (n = 37): 2.94 (0.70) • **GIDYQ,** mean (SD), *t* = 4.74, *P* < .001

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ HT recommended (n = 60): 2.21 (035) ○ HT not recommended (n = 39): 2.61 (0.47) • **RCGI,** mean (SD), *t* = 5.48, *P* < .001 ○ HT recommended (n = 65): 2.05 (0.67) ○ HT not recommended (n = 42): 2.84 (0.79) • **Sexual Orientation (in fantasy)**, n (%), c^2 = 7.51, *P* = .006 ○ Homosexual ▪ HT recommended: 45 (72.6) ▪ HT not recommended: 17 (28.4) ○ Non-Homosexual ▪ HT recommended: 20 (44.4) ▪ HT not recommended: 25 (55.6) • **Sexual Orientation (in behavior)**, n (%), c2 = 12.96, *P* < .001 ○ Homosexual ▪ HT recommended: 43 (78.2) ▪ HT not recommended:12 (21.8) ○ Non-Homosexual ▪ HT recommended: 22 (42.3) ▪ HT not recommended:30 (57.7) **Logistical Regression Predicting Hormonal Therapy Recommendations:** • When controlling for all other covariates, of the 16 predictor variables, 5 were significant at *P* < .10 (per author), with *P* values ranging from .016 to .096: ethnicity, the GIDYQ, the GIQ-Ad, the RCGI, and the YSR sum score. A recommendation for hormonal blockers was more likely to be made when the patients were of a visible minority ethnicity, when parent-report indicated more concurrent cross-gender behavior, when the patients self-reported more concurrent gender dysphoria, recalled more cross-gender behavior in childhood, and had a lower YSR behavior problem sum score. At *P* < .05, YSR sum scores would be excluded. ○ GIQ-Ad: β = 1.63, SE = 0.67, *P* = .016

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.2. Clinical studies with between-TGNB-group comparisons examining psychosocial functioning

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ GIQAA: β = 2.79, SE = 1.23, *P* = .025 ○ RCGI: β = 1.17, SE = 0.58, P .045 ○ Ethnicity: β = 1.91, SE = 0.95, *P* = .047 ○ YSR Sum: β = −0.02, SE = 0.01, *P* = .096 ○ Sex: β = 0.01, SE = 0.79, *P* = NS ○ Age at assessment: β = 0.22, SE = 0.22, *P* = NS ○ YOA: β = −0.08, SE = 0.13, *P* = NS ○ Full-Scale IQ: β = 0.03, SE = 0.03, *P* = NS ○ Parent's Marital Status: β = −0.53, SE = 0.76, *P* = NS ○ Social Class: β = −0.76, SE = 0.49, *P* = NS ○ In-Care: β = 0.13, SE = 1.19, *P* = NS ○ CBCL Sum: β = −0.01, SE = 0.01, *P* = NS ○ Draw-a-Person: β = −1.20, SE = 0.91, *P* = NS ○ EROS: β = −0.18, SE = 0.82, *P* = NS

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
Bauer (2021)[102] 10 Canadian medical clinics located across Canada (eg, [redacted] All clinics had ≥ 1 pediatric specialist, and resources to mental health physicians	Pubertal and post-pubertal youth (N = 174) **Eligibility:** GD diagnosis, < 16 yrs of age, no previous use of estrogen, testosterone, or GnRH analogs (except contraceptives), and referred for hormone use **Sampling method:** Recruitment processes differed due to the site location and requirements set by the Research Ethics Board. Potential eligible participants were invited to contact the research investigator prior to their first visit **Subset definition:** Comparisons were made between **transfeminine (n = 37)** and **transmasculine (n = 137)** participants	• **Assigned sex at birth:** ○ AMAB: 37 (21.3) ○ AFAB: 137 (78.7) • **Age**, *P* = NS • 10–13 yrs old: ○ Transfeminine: 14 (40.6) ○ Transmasculine: 40 (28.7) • 14–15 yrs old: ○ Transfeminine: 23 (59.4) ○ Transmasculine 97 (71.3) • **Gender identity**, *P* = < 0.001 • Male or primarily a boy: ○ Transfeminine: 1 (2.4) ○ Transmasculine: 125 (92.2) • Female or primarily a girl: ○ Transfeminine: 32 (87.1) ○ Transmasculine: 0 (0) • Nonbinary: ○ Transfeminine: 3 (10.5) ○ Transmasculine: 11 (7.8) • Living in their identified gender, *P* < .001 • All the time: ○ Transfeminine: 24 (58.1) ○ Transmasculine: 122 (90.1) • Some of the time: ○ Transfeminine: 11 (37.8) ○ Transmasculine: 13 (9.9) • Not at all: ○ Transfeminine: 2 (4.1)	Pubertal and post-pubertal transfeminine youth (n = 37)	Pubertal and post-pubertal transmasculine youth (n = 137)	• Weight z-scores • Height z-scores • BMI z-scores **Cross-sectional:** exposures/outcomes were measured at the same time	• **Weighted mean for growth parameters, for sex at birth** (based on *WHO Growth Charts for Canada*, 2014 revision; SD): • There was no significant difference in height, weight or BMI z-scores between the transfeminine and transmasculine cohort based on sex assigned at birth. • Height-for-age z-score, *P* = NS: ○ Transfeminine: 0.49 (0.69) ○ Transmasculine: 0.31 (0.81) • BMI-for-age z-score, *P* = NS: ○ Transfeminine: 0.45 (1.01) ○ Transmasculine: 0.71 (2.00) • Weight-for-age z-score, *P* = NS: ○ Transfeminine: 0.57 (0.88) ○ Transmasculine: 0.66 (1.16) • Weighted mean for growth parameters, for gender (SD): • There was a significant difference in height and BMI z-scores based on gender • Height-for-age z-score, *P* < .001: ○ Transfeminine: 1.40 (0.85) ○ Transmasculine: −0.41 (0.93) • BMI-for-age z-score, *P* = .02: ○ Transfeminine: 0.29 (0.96) ○ Transmasculine: 0.89 (1.25) • Weight-for-age z-score, *P* = NS: ○ Transfeminine: 0.84 (0.88) ○ Transmasculine: 0.43 (1.22)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ Transmasculine: 0 (0) • Other providers whom the adolescent and family had met with to discuss gender with prior to the clinic visit: • Family physician, *P* = NS: ○ Transfeminine: 23 (68.2) ○ Transmasculine: 85 (68.6) • Pediatrician or adolescent medicine, *P* = NS: ○ Transfeminine: 13 (33.4) ○ Transmasculine: 39 (30.5) • Psychologist or psychiatrist, *P* = NS: ○ Transfeminine: 18 (46.2) ○ Transmasculine: 64 (45.4) • Counselor, elder, religious leader, *P* = NS: ○ Transfeminine: 17 (50.7) ○ Transmasculine: 64 (45.6)				
Boogers (2022)[66] [redacted] The Netherlands)	Transgender girls (N = 161) **Eligibility:** Started GnRH analog treatment before 18 years old, received estrogen therapy, and had reached adult height **Sampling method:** Out of the 8,831 individuals in the data set, 5,350 were AMAB. 176 subjects met the inclusion criteria, but 15 were excluded for various reasons (eg, missing data). 161 individuals were included in the study, and assigned to a pubertal (BA < 16 years; n = 88) or post-pubertal group (almost or completely finished linear growth; n = 73)	• Median age at start of puberty suppression (yr, range): ○ Regular dose: 13.5 (13.2 to 14.5) ○ High dose: 13.1 (12.1 to 13.6) ○ Ethinyl estradiol: 12.4 (12.1 to 14.0) • Tanner stage at start of puberty suppression: • G2: ○ Regular dose: 7 (16) ○ High dose: 9 (41) ○ Ethinyl estradiol: 6 (55) • G3:	Transgender girls who received **high dose** 17β-estradiol: 6 mg per day (n = 22)	Transgender girls who received **regular dose** 17β-estradiol: 2 mg per day (n = 47)	• Growth • Adult height • Predicted adult height • Target height **Cohort:** outcomes were measured at the start of puberty suppression and then every 3 to 6 months	• Compared to regular dose treatment, high dose estradiol resulted in a non-significant reduction in adult height compared to PAH of 0.9 cm (95% CI, -0.9 cm to 2.8 cm) • Duration of puberty suppression (yrs, 95% CI): 0.0 (−0.4 to 0.4) • Bone age at start of CSHT (yrs, 95% CI): −0.7 (−1.1 to −0.3) • Predicted adult height at start of CSHT (cm, 95% CI): 5.9 (2.1 to 9.8) • Height (cm, 95% CI): ○ Start of puberty suppression: −2.5 (−6.5 to 1.6) ○ Start of CSHT: 1.1 (−2.3 to 4.5) ○ Adult height: 4.8 (4.2 to 5.5) • Male height SD score (95% CI): ○ Start of puberty suppression: 0.38 (−0.09 to 0.85)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Subset definition: Comparisons were made between pubertal transgender girls who received **high-dose estradiol (6 mg per day; n = 22)** and **regular-dose estradiol (2 mg per day; n = 47)**	○ Regular dose: 14 (31) ○ High dose: 11 (50) ○ Ethinyl estradiol: 3 (27) • G4: ○ Regular dose: 9 (19) ○ High dose: 1 (5) ○ Ethinyl estradiol: 1 (9) • G5: ○ Regular dose: 17 (36) ○ High dose: 1 (5) ○ Ethinyl estradiol: 1 (9) • Mean height at start of puberty suppression (cm, SD): ○ Regular dose: 165.8 (8.4) ○ High dose: 163.4 (7.2) ○ Ethinyl estradiol: 160.8 (6.3) • Median BA at start of puberty suppression (yrs, range): ○ Regular dose: 13.5 (13.0 to 14.0) ○ High dose: 13.0 (12.5 to 13.5) ○ Ethinyl estradiol: 13.0 (12.0 to 13.5) • Median predicted adult height at start of puberty suppression (cm, range): ○ Regular dose: 182.9 (177.0 to 186.7) ○ High dose: 184.2 (180.7 to 188.6) ○ Ethinyl estradiol: 185.2 (180.4 to 197.5) • Median target height (cm, range):				○ Start of CSHT: 0.59 (0.12 to 1.05) ○ Adult height: 0.69 (0.28 to 1.10) ○ Target height: 0.68 (0.60 to 0.77)
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between pubertal transgender girls who received **ethinyl estradiol (100 or 200 ug per day; n = 11)** and **regular-dose estradiol (2 mg per day; n = 47)**		Transgender girls who received **ethinyl estradiol** (100 or 200 ug per day; n = 11)	Transgender girls who received **regular dose** 17β-estradiol: 2 mg per day (n = 47)	• Growth • Adult height • Predicted adult height • Target height **Cohort:** outcomes were measured at the start of puberty suppression and then every 3 to 6 months	• Compared to regular dose treatment, EE treatment resulted in a significant reduction in adult height compared to PAH of 3.0 cm (95% CI, 0.2 cm to 5.8 cm) • Duration of puberty suppression (yrs, 95% CI): 0.2 (−0.3 to 0.7) • Bone age at start of CSHT (yrs, 95% CI): −0.8 (−1.3 to −0.2) • Predicted adult height at start of CSHT (cm, 95% CI): 4.2 (−1.6 to 10.0) • Height (cm, 95% CI): ○ Start of puberty suppression: −5.0 (−10.2 to 0.2) ○ Start of CSHT: −1.9 (−6.3 to 2.4) ○ Adult height: 0.3 (−0.8 to 1.3) • Male height SD score (95% CI): ○ Start of puberty suppression: 0.06 (−0.55 to 0.67) ○ Start of CSHT: 0.04 (−0.55 to 0.64) ○ Adult height: 0.05 (−0.58 to 0.47) ○ Target height: 0.28 (0.12 to 0.44)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ Regular dose: 180.0 (176.5 to 184.0) ▪ Missing: 5 (11) ○ High dose: 184.0 (181.0 to 189.5) ▪ Missing: 1 (5) ○ Ethinyl estradiol: 180.3 (178.5 to 186.3) ▪ Missing: 3 (27)				
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between pubertal transgender girls who started CSHT at a lower BA vs those who started at a higher BA		Started CSHT at a lower BA	Started CSHT at a higher bone age		• Height vs PAH • Individuals who started CSHT at a lower BA reached an adult height that was 1.6 cm/year (95% CI, 0.6 to 2.7) further below PAH at the start of CSHT
Eitel (2023)[80] [redacted]	TGNB subjects with 1-hour post injection hormone levels who self-reported clinical puberty suppression (N = 55) **Eligibility:** Diagnosed with GD and receiving leuprolide (either Lupron or Eligard, both dosed at 22.5 mg every 3 months, intramuscularly or subcutaneously, respectively) between January 2016 and December 2021 **Sampling method:** 48 patients, with 55 incidents of 1-hour post injection levels were included in the study. Patients were excluded if they were missing post-injection LH and sex steroid hormone levels **Subset definition:** Comparisons were made between TGNB subjects with 1-hour post-injection hormone	• Mean age at first gender clinic visit (yrs, SD): ○ Eligard: ▪ AFAB (n = 16): 12.0 (1.0) ▪ AMAB (n = 26): 13.8 (2.0) ○ Lupron: ▪ AFAB (n = 1): 11.4 (0) ▪ AMAB (n = 12): 14.0 (1.9) • Mean age at first injection (yrs, SD): ○ Eligard: ▪ AFAB (n = 16): 12.2 (1.0) ▪ AMAB (n = 26): 14.5 (2.0) ○ Lupron: ▪ AFAB (n = 1): 11.5 (0) ▪ AMAB (n = 12): 14.7 (1.9)	TGNB subjects with 1-hour post-injection hormone levels taking Eligard (n = 42)	TGNB subjects with 1-hour post-injection hormone levels taking Lupron (n = 13)	• Self-reported clinical suppression (defined as no puberty progression) • Biochemical suppression as measured by 1-hour post-injection levels of LH < 4 mIU/mL, estradiol < 20 pg/mL, or total testosterone < 30 ng/dL **Cross-sectional:** exposures/outcomes were measured at the same time	• Achieved self-reported clinical suppression (n, %): ○ Eligard: 42 (100) ○ Lupron: 13 (100) • Achieved biochemical suppression (n, %), P NS: ○ Eligard: 38 (90) ○ Lupron: 9 (69)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	levels **taking Eligard (n = 42)** and those **taking Lupron (n = 13)**	• Tanner stage on examination in the 6 months before starting leuprolide (N = 55): ○ II: 12 (22) ○ III: 8 (14.5) ○ IV: 10 (18) ○ V: 8 (14.5) ○ Unknown: 17 (31) • Receiving concurrent CSHT: ○ Eligard: ▪ AFAB (n = 16): 2 (12.5) ▪ AMAB (n = 26): 18 (69.2) ○ Lupron: ▪ AFAB (n = 1): 0 (0) ▪ AMAB (n = 12): 8 (66.7) • Median baseline LH level obtained in the 6 months before starting leuprolide (mIU/mL, range): ○ Eligard: ▪ AFAB (n = 16): 6.3 (4.3 to 5.3) ▪ AMAB (n = 26): 1.7 (0.7 to 3.8) ○ Lupron: ▪ AFAB (n = 1): N/R ▪ AMAB (n = 12): 2.1 (0.7 to 4.6) • Median baseline estradiol level obtained in the 6 months prior to starting leuprolide (pg/mL, range): ○ Eligard: ▪ AFAB (n = 16): 34.9 (7.2 to 39.8) ▪ AMAB (n = 26): N/R ○ Lupron: ▪ AFAB (n = 1): 16.1 (N/R)				

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		▪ AMAB (n = 12): N/R • Median baseline total testosterone level obtained in the 6 months prior to starting leuprolide (ng/dL, range): ○ Eligard: ▪ AFAB (n = 16): N/R ▪ AMAB (n = 26): 319 (16 to 704) ○ Lupron: ▪ AFAB (n = 1): N/R ▪ AMAB (n = 12): 350 (37 to 616)				
Grimstad (2021)[81] [redacted]	Gender diverse adolescents or young adults taking testosterone for > 1 year for menstrual suppression (N = 232) **Eligibility:** AFAB or intersex with intact and functional uterus and ovaries at the time of starting testosterone, seen in clinic between 2010 and 2020, and taking testosterone for > 1 year **Sampling method:** 367 transgender and gender diverse natal females were taking testosterone for gender-affirming care. After excluding those who were taking testosterone for ≤ 1 year, those with no documentation of uterine bleeding, among other reasons, 232 subjects were included in the study **Subset definition:** Comparisons were made between those **with no breakthrough bleeding (n = 174)** and those **with breakthrough bleeding (n = 58)**	• Mean age at starting testosterone (yrs, SD), *P* = NS: ○ No breakthrough bleeding: 16.3 (1.8) ○ Breakthrough bleeding: 16.3 (2.2) • Testosterone duration (months, SD), *P* < .001 ○ No breakthrough bleeding: 28.5 (14.6) ○ Breakthrough bleeding: 37.3 (16.9) • Testosterone formulation, *P* = 0.936 • Injectable: ○ No breakthrough bleeding: 170 (97.7) ○ Breakthrough bleeding: 51 (87.9) • Topical gel: ○ No breakthrough bleeding: 1 (0.6) ○ Breakthrough bleeding: 0 (0) • Injectable to subcutaneous pellets: ○ No breakthrough bleeding: 1 (0.6) ○ Breakthrough bleeding: 3 (5.2) • Topical gel to injectable:	Subjects taking testosterone for more than 1 year who *did not* experience breakthrough bleeding (n = 174)	Subjects taking testosterone for more than 1 year *who did* experience breakthrough bleeding (n = 58)	• Demographic characteristics **Cross-sectional:** exposures/outcomes were measured at the same time	• Mean testosterone duration time was significantly longer for patients who had at least one episode of breakthrough bleeding compared to patients who did not experience any breakthrough bleeding (*P* < .001) • Endometriosis, confirmed by laparoscopy, was more common in patients who had breakthrough bleeding than those who did not (*P* = .049) • No significant differences were found between groups for mean age at starting testosterone, BMI, testosterone formulation used, and other menstrual suppression agents (started before testosterone or used concomitantly with testosterone)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ No breakthrough bleeding: 1 (0.6) ○ Breakthrough bleeding: 1 (1.7) • Injectable to topical gel to subcutaneous pellets: ○ No breakthrough bleeding: 1 (0.6) ○ Breakthrough bleeding: 0 (0) • Injectable to topical gel: ○ No breakthrough bleeding: 0 (0) ○ Breakthrough bleeding: 3 (5.2) • Mean BMI (kg/m², SD), *P* = NS: ○ No breakthrough bleeding: 27.2 (7.1) ○ Breakthrough bleeding: 26.2 (6.9) • Comorbid endometriosis, *P* = .04: ○ No breakthrough bleeding: 1 (0.6) ○ Breakthrough bleeding: 3 (5.2) • Using a GnRH analog (ie, Depo Lupron or Histrelin implant), *P* = NS ○ No breakthrough bleeding: 15 (8.6) ○ Breakthrough bleeding: 1 (1.7) • GnRH analog and testosterone overlap (months, SD), *P* = NS: ○ No breakthrough bleeding: 19.1 (14.5) ○ Breakthrough bleeding: 1 (N/R) • **Hysterectomy**, *P* = .047**:** ○ No breakthrough bleeding: 10 (5.9) ○ Breakthrough bleeding: 8 (13.8)				
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between subjects **who**	N/R	Subjects who experienced breakthrough bleeding while consistently on testosterone (n = 36)	Subjects who experienced breakthrough bleeding while consistently on testosterone + menstrual suppression (n = 10)	• Demographic characteristics **Cross-sectional:** exposures/outcomes were measured <u>at the same time</u>	**Demographics at time of breakthrough bleeding:** • Mean age (yr, SD), *P* = NS: ○ Testosterone: 16.4 (2.6)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	experienced breakthrough bleeding while consistently on testosterone (n = 36) and those **consistently on testosterone and menstrual suppression (n = 10)**					○ Testosterone + menstrual suppression: 15.5 (0.7) • Testosterone duration (months, SD), *P* = NS ○ Testosterone: 37.7 (18.9) ○ Testosterone + menstrual suppression: 30.6 (8.8) • Mean BMI (kg/m², SD), *P* = NS ○ Testosterone: 25.8 (7.8) ○ Testosterone + menstrual suppression: 25.9 (4.6) • Estradiol (pg/mL, SD), *P* = .01 ○ The testosterone group that had breakthrough bleeding had higher estradiol than the group with consistent menstrual suppression. ○ Testosterone: 44.3 (28.4) ○ Testosterone + menstrual suppression: 24.6 (7.2) • Testosterone (ng/dL, SD), *P* = NS ○ Testosterone: 467.8 (169.5) ○ Testosterone + menstrual suppression: 433.0 (130.8) • Overlap on menstrual suppression (months, SD), *P* < .001 ○ Testosterone (n = 15): 8.9 (10.3) ○ Testosterone + menstrual suppression: 26.2 (9.2)
Karakilic Ozturan (2023)[112] A tertiary pediatric endocrinology clinic in Turkey.	TGNB adolescents (N = 28) **Eligibility**: Participants must have been diagnosed with GD based on DSM-5 diagnostic criteria by a mental health professional after at least six months of psychiatric follow-up, and must have been referred to the GD outpatient clinic. They could not start hormone treatment without informed consent from both themselves and their legal guardians. They must have stayed below the age of 18 during the follow-up period of the study (3-6 months).	**Age,** median (IQR), years: • MTF starting GnRH analogs: 16.7 (1.2) • FTM starting GnRH analogs: 16.7 (1.0), *P* = NS	MTF adolescents that started GnRH analogs (n = 9)	FTM adolescents that started GnRH analogs (n = 13)	• Physical examination done by the same examiner each visit. Height and weight were measured, and BMI calculated. • Standard deviation scores (SDS) were calculated according to natal sex Cross Sectional: Exposures/Outcomes were measured at one point in time at the onset of GnRH analogs	**Height,** Median (IQR) • There was a significant difference in height between the MTF cohort at 176.1 (3.0) cm. vs. 160.8 (5) cm. in the FTM cohort, *P* < .001 **Height SDS**, Median (IQR) • There was no significant difference in the height SDS of the MTF cohort of 0.6 (0.9) vs.: -0.2 (1.5) in the FTM cohort, *P* = NS **BMI**, median (IQR) • There was no significant difference in the BMI of the MTF cohort of 24.8 (5.8) kg/m² vs. 23.1 (4.5) kg/m²) in the FTM cohort, *P* = NS **BMI SDS**, median (IQR)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Sampling Method: Authors retrospectively examined the medical records of all adolescents diagnosed with GD after at least 6 months of psychiatric follow-up and that were referred to their GD outpatient clinic between 2016 and 2022. **Subset Definition:** There were n = 13 MTF participants and n = 15 FTM participants. From this group, comparisons were made between: • MTF starting GnRH analogs (n = 6) vs FTM starting GnRH analogs (n = 13) • MTF who took GnRH analogs and then started CSH (n = 6) vs MTF who took combined androgen receptor blocker and then started CSH (n = 6) • MTF participants who were starting CSH (combined group whose previous treatment was GnRH analogs and combined androgen receptor blocker) (n = 12) vs. FTM starting CSH (n = 9)					• There was no significant difference in the BMI SDS of the MTF cohort of 0.7 (1.5) vs. 0.7 (1.5) in the FTM cohort, *P* = NS
		Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1) • MTF with combined androgen receptor blocker treatment 17.5 (1.3), *P* = NS	MTF adolescents that used GnRH analogs before starting CSH (n = 6)	MTF adolescents that used combined androgen receptor blockers before starting CSH (n = 6)	• Physical examination done by the same examiner each visit. Height and weight were measured and BMI calculated. • Standard deviation scores (SDS) were calculated according to natal sex **Cross-sectional:** Outcomes were measured at one point of time before participants started CSH	**Height,** median (IQR) • There was no significant difference in the median height of the GnRH analogs group, 177.9 (2.0) cm vs. 169.4 (3.3) in the combined androgen receptor blocker group, *P* = NS **Height SDS**, median (IQR) • There was no significant difference in the SDS of the GnRH analogs group of 0.3 (0.5) vs. 0.4 (1.3) in the combined androgen receptor blocker group, *P* = NS **BMI**, median (IQR) • There was no significant difference in the BMI of the GnRH analog group of 20.1 (0.7) kg/m² vs. 19.8 (5.9) kg/m² in the combined androgen receptor blocker group, *P* = NS **BMI SDS**, median (IQR) • There was no significant difference in the BMI SDS of the GnRH analog group of -1.2 (0.7) vs. -0.9 (2.1) in the combined androgen receptor blocker group, *P* = NS
		Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1) • MTF with combined androgen receptor blocker treatment: 17.5 (1.3) • FTM: 17.8 (0.4), *P* = NS	MTF adolescents that used either GnRH analogs or combined androgen receptor blockers before starting CSH (n = 12)	FTM adolescents that used GnRH analogs before starting CSH (n = 9)	• Physical examination done by the same examiner each visit. Height and weight were measured and BMI calculated. • Standard deviation scores (SDS) were calculated according to natal sex **Cross-sectional:** Outcomes and measures were taken at one point in time at the start of CSH	**Height,** median (IQR) • There was a significant difference in the height of the MTF cohort [177.9 (2.0) cm and 169.4 (3.3)] compared to the FTM cohort at 164.9 (7.4) cm, *P* = 0.019 **Height SDS**, Median (IQR) • There was a no significant difference in the height SDS of the MTF cohort [0.3 (0.5) and 0.4 (1.3)] compared to the FTM cohort at -0.4 (1.4), *P* = NS **BMI**, median (IQR) • There was a no significant difference in the BMI of the MTF cohort [20.1 (0.7) kg/m² and 19.8 (5.9) kg/m²] compared to the FTM cohort at 24.5 (6.9) kg/m², *P* = NS **BMI SDS**, Median, IQR

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• There was a no significant difference in the BMI SDS of the MTF cohort [1.2 (0.7) and -0.9 (2.1)] compared to the FTM cohort at 1.1 (2.9), *P* = NS
Klaver (2018)[83] [redacted] the Netherlands	**TGNB adolescents (N = 192)** **Eligibility:** Patients must have started hormonal treatment (either GnRH analogs or cross-sex hormones (CHT)) before the age of 18, started the Dutch treatment protocol, underwent whole-body dual-energy x-ray absorptiometry (DXA) during their treatment, and had medical checkups in young adulthood (when they were over 20.5 years old). **Sampling Method:** Authors reviewed the medical records of all adolescents seen between 1998-2014 diagnosed with gender dysphoria according to the DSM-4 at the VU University Medical Center and collected data from three time points: when they started GnRH analogs, when they added CHT, and at 22 years of age (range 20.5-23.5 years). **Subset Definition:** Comparisons were made between trans women that started treatment in early puberty (n = 16), mid-puberty (n = 21) and late puberty (n = 34). Comparisons were made between trans men starting treatment in early to mid-puberty (n = 11) and late puberty (n = 110)	**FTM:** • Mean age (SD) at the start of GnRH analog treatment was 15.3 (2.0), and at the start of CHT was 16.9 (0.9). • 94% were Caucasian • 84% had experienced menarche (but data on menarche was missing for 8% of the sample). **MTF:** • Mean age (SD) at the start of GnRH analog treatment was 14.5 (1.8), and at the start of CHT was 16.4 (1.1). • 98% were Caucasian.	TGNB women who started hormone therapy in early puberty (n = 16)	TGNB women who started hormone therapy in mid-puberty (n = 21) or late puberty (n = 34)	• waist-to-hip ratio (WHR): Waist circumference was defined as the smallest abdominal circumference. Hip circumference was measured at the level of the trochanter major. • total body fat (%): Measured using DXA. • lean body mass (LBM) (%): Measured using DXA. • BMI (kg/m^2): Body height and weight were measured at each visit. • Cohort Study: • Outcomes were measured when participants started GnRH analogs, started CHT, and at 22 years of age.	**Body Composition** early puberty vs. mid-puberty, Mean difference • There were no significant differences in body composition at 22 years of age between TGNB women who started hormone therapy in early puberty and those that started in mid puberty. ○ waist-to-hip ratio (WHR): 0.00 (95% CI = -0.07, 0.07) ○ total body fat (%): 3 (95% CI = -4, 10) ○ lean body mass (LBM) (%): -3 (95% CI = -10, 4) ○ BMI (kg/m^2): 2.9 (95% CI = -0.3, 6) **Body Composition** early puberty vs. late puberty, Mean difference • There were no significant differences in body composition at 22 years of age between TGNB women who started hormone therapy in early puberty and those that started in late puberty. ○ waist-to-hip ratio (WHR): -0.03 (95% CI = -0.08, 0.02) ○ total body fat (%): -1 (95% CI = -6, 4) ○ lean body mass (LBM) (%): +1 (95% CI = -4, 6) ○ BMI (kg/m^2): -0.4 (95% CI = -3.1, 2.3)
			TGNB men who started hormone therapy in early-mid puberty (n = 11)	TGNB men who started hormone therapy in late puberty (n = 110)		• **Body Composition,** Mean difference • There was a significant difference in WHR at 22 years of age between TGNB men who started on hormone therapy in early to mid-puberty and those who started in late puberty. • There was no significant difference in total body fat, lean body mass or BMI at 22 years of age between TGNB men who started on hormone therapy in early to mid-puberty and those who started in late puberty. ○ waist-to-hip ratio (WHR): 0.06 (95% CI = 0.02, 0.12) ○ total body fat (%): -1 (95% CI = -6, 4)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						○ lean body mass (LBM) (%): +1 (95% CI = -4, 6) ○ BMI (kg/m^2): -1.4 (95% CI = -4.2, 1.4)
Laurenzano (2021)[84] A US gender/endocrine (doesn't specify) clinic at [redacted] California	**N = 119 TM/GD individuals** **Eligibility**: Younger than 21 years when starting T and received T for a minimum of 6 months, assessed by mental health professional to make sure they were ready to start T and met diagnostic criteria for GD. **Sampling method**: Patients were selected if they met criteria and were a patient of the clinic.	• Average age at presentation to clinic was 16 (10.1-19.8) years. • Average age of starting SC-T was 16.5 (13-19.9) years. • N = 110 patients were trans male, n = 3 were nonbinary, n = 6 patients were classified as "other." • 99 patients had no menstrual suppression before starting T, • 12 used GnRH analogs and 8 used contraceptive. • Average BMI was 24.85 (SD 7.26)	Subcutaneous testosterone injections starting at 50 mg	Subcutaneous testosterone injections starting at 50 mg	• Timing to cessation of menses. **Cohort**: After exposure, outcome was measured as time to event	• Timing to cessation of menses was significantly shorter with the higher starting dose of testosterone. It was 5.4 (SD 2.9) months with the starting dose of 50 mg and 3.9 (SD 3.0) months with the starting dose of 100 mg (*P* = .025).
Navabi (2021)[92] Endocrine diversity clinic [redacted] Ontario	Transgender youth with GD (N = 170) **Eligibility:** Patients < 18 yrs of age with a clinic visit between January 2006 to April 2017, and at least 1 DXA measurement **Sampling method:** Reviewed 198 medical records, with 172 meeting eligibility criteria **Subset definition:** Comparisons were made between **transgender males (n = 119)** and **transgender females (n = 51)**	• Mean LBM (kg, SD), *P* = .005 ○ Transgender males: 36.24 (56.14) ○ Transgender females: 45.74 (9.98) • Mean LBM z-score (SD), *P* = NS ○ Transgender males: −1.03 (1.22) ○ Transgender females: −1.19 (1.45) • Mean TBF percentage (SD), *P* < .001 ○ Transgender males: 37.14 (10.46) ○ Transgender females: 24.45 (12.48) • Mean TBF z-score percentage (SD), *P* = NS ○ Transgender males: 1.68 (0.96) ○ Transgender females: 1.42 (1.02) • Mean BMI (SD), *P* = NS ○ Transgender males: 24.04 (5.17) ○ Transgender females: 23.22 (6.33) • Mean BMI z-score (SD), *P* = NS	Transgender males (n = 119)	Transgender females (n = 51)	• Demographic characteristics for baseline body composition **Cross-sectional:** exposures/outcomes were measured at the same time	• There were no significant differences between transgender males and transgender females for LBM z-score, TBF z-score percentage, and BMI z-score • Transgender females had significantly higher LBM and lower TBF percentage compared to transgender males

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ Transgender males: 0.89 (1.25) ○ Transgender females: 0.62 (1.67)				
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between patients with a **BMI ≤ 85 percentile (n = 71)** and those with a **BMI > 85 percentile (n = 47)**	N/R	Baseline BMI percentile *below* the obesity risk threshold (≤ 85; n = 71)	Baseline BMI percentile *above* the obesity risk threshold (> 85; n = 47)	• GnRH analog-induced body composition changes **Cross-sectional:** exposures/outcomes were measured at the same time	• Mean change in BMI z-score (SD): ○ BMI ≤ 85 percentile: 0.11 (0.62) ○ BMI > 85 percentile: 0.00 (0.79) ▪ Difference (95% CI): 0.11 (−0.14 to 0.37), *P* = NS • Mean change in TBF z-score percentage (SD): ○ BMI ≤ 85 percentile: 0.58 (0.91) ○ BMI > 85 percentile: 0.19 (0.44) ▪ Difference (95% CI): 0.39 (0.11 to 0.67), *P* = NS • Mean change in LBM z-score (SD): ○ BMI ≤ 85 percentile: −0.31 (0.66) ○ BMI > 85 percentile: −0.15 (0.81) ▪ Difference (95% CI): −0.15 (−0.42 to 0.11), *P* = NS
Olson-Kennedy (2021)[93] Preexisting patients at [redacted] as well as patients enrolled in the Trans Youth Care study, which was a multisite observational study conduct at major hospitals in Southern California, [redacted]	N = 66 participants **Eligibility**: histrelin implant at Tanner stage 2 or 3 used to treat gender dysphoria. They had to have hormone levels measured before implantation. **Sampling method:** data was taken from patient charts of eligible patients from CHLA clinic and Trans Youth Care study. **Subset definition:** Patients who used Supprelin implant (n = 45) were compared to those that used the Vantas implant (n = 20)	• Average age is 11.3 years. • There were 51 (77.3%) participants in Tanner stage 2, and 15 participants (22.7%) in Tanner stage 3. • 46 (69.7%) participants had a Supprelin implant and 20 (30.3%) had a Vantas implant. • 32 (48%) were transfeminine and 32(52%) were transmasculine.	Patients who received the SupprelinLA at the follow up period T1 (n = 45).	Patients who received Vantas implant at T1 (n = 20).	• LH and FSH were measured at baseline and at follow up appointment • Difference in testosterone and estradiol levels were measured respective to gender identity **Cohort:** direct in time is forward. Comparison is drawn at the final follow up time, comparing baseline (T0) to 2-12 months following implantation (T1)	**Hormone comparison between implants** • Mann-Whitney test indicated no significant difference between change in LH (*P* = NS), and FSH (*P* = NS) between the two implants. • In transfeminine participants, there was no significant difference in testosterone between the two implants (*P* = NS). • In transmasculine patients there was no difference in estradiol between the two implants (*P* = NS).
	Subset definition: Comparisons were made between transfeminine patients (n = 32) and transmasculine patients (n = 34)	Same as above	Transfeminine patients treated with a histrelin implant (n = 32)	Transmasculine patients treated with a histrelin implant (n = 34).	Same as above	**LH** • The median LH level was not significantly different between transmasculine and transfeminine patients (*P* = NS) at baseline.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• At T1, LH was significantly higher in transfeminine patients. **FSH** • At baseline, there was no significant difference in FSH (*P* = NS) between transmasculine and transfeminine patients, • There was a significant difference at T1 (*P* < .001), with transmasculine patients having higher levels.
	Subset definition: Comparisons were made between Participants that received histrelin implant at Tanner stage 2 (n = 47) and Participants that received histrelin implant at Tanner stage 3 (n = 14)	Same as above	Participants that received histrelin implant at Tanner stage 2 (n = 47)	Participants that received histrelin implant at Tanner stage 3 (n = 14)	Same as above	**LH and FSH** • At baseline, median LH (*P* < .001) and median FSH (*P* < .005) was significantly higher in Tanner 3 patients. • At T1, LH was not significantly different (*P* = NS), while FSH was higher in Tanner 3 patients (*P* = .006). **Testosterone and Estradiol** • In transfeminine patients, testosterone was higher at T0 in Tanner 3 patients (*P* = 0.006), at T1 testosterone was still higher in Tanner 3 patients (*P* = .026). • In transmasculine patients, median estradiol was higher in Tanner 3 patients at T0 (*P* = .002) and T1 (*P* = .016). • All levels were prepubertal to early pubertal range.
Schagen (2018)[147] [redacted] between 1998 and 2009.	TGNB adolescents (n = 70) from larger study of 127 TGNB adolescents **Eligibility:** adolescents with DSM-IV criteria for gender identity disorder and met the criteria for treatment according to the Endocrine Society. **Sampling method:** there was no exclusion criteria. Since it is a prospective study, it can be assumed that those that met the inclusion criteria were included. **Subset**: 1 subgroup started treatment at 12-14 years and the other at 14 to 16 years.	Trans girls: mean ± SD (range) • Mean age at start of GnRH analogs: 14 ±1.6 (11.6-17.9) years • Weight- 57.4 ±12.7kg • BMI- 20.2 ± 2.2 • Tanner stage- 4 (2-5) • length of GnRH analog treatment- 22.8 ±11.8 mo Trans boys: (mean) • Mean age at GnRH analogs start- 14.3 ± 2.0 (11.5-18.6) years • weight- 56.8 kg ±14.3 • BMI- 21 ± 3.8 kg	TGNB males and females, who had been treated for 2 years of intramuscular injections of GnRH analog triptorelin (3.75 mg) at 0, 2 and 4 weeks followed by injections every 4 weeks. (n = 37)	TGNB males and females (age 14-16) at baseline before treatment. (n = 32)	Measurement: • Mean DHEAS • androstenedione levels Cohort: Outcomes were measured after 2 years of treatment.	**DHEAS** • Trans boys: ○ 2 years of treatment in the 12–14-year-old age group was comparable to the baseline of those aged 14-16 years: 4.65 ± 1.92 µmol/L vs 3.94 ± 1.66 µmol/L, *P* = NS • Trans girls: ○ after 2 years of treatment, treated girls had significantly higher levels than untreated girls: 5.41 ± 1.86 µmol/L vs 4.14 ± 1.98 µmol/L, *P* = .047 **Androstenedione** • Trans boys ○ Those that were treated had significantly lowered levels than the baseline of those aged 14-16 years: 4.76 ± 1.76 nmol/L vs 6.86 ± 2.96 nmol/L, *P* = .016

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	• Trans boys 12-14 (n = 17), untreated trans boys 14-16 (n = 18). • Trans girls 12-14 (n = 20), untreated trans girls 14-16 years (n = 14) TGNB youth that started treatment at 12-14 years were compared after 2 years of treatment to group of 14-16 yo TGNB youth who had not yet began treatment.	• Tanner stage 5 (2-5) • length of GnRH analog treatment- 24.5 ± 15.3 mo				• Trans girls: ○ the treated group had levels that were comparable to the untreated individuals: 3.86 ± 1.52 nmol/L vs 3.96 ± 1.33 nmol/L, *P* = NS
Schagen (2020)[94] Setting: N/R	Adolescents diagnosed with GD, eligible for hormonal treatment (N = 121) **Eligibility:** Diagnosed with GD (per DSM-IV-TR), eligible for treatment according to guidelines, had DXA scans available at the start of GnRH analog treatment, and were seen from 1998 to 2009 **Sampling method:** N/R **Subset definition:** Comparisons were made between **transgender females (n = 51)** and **transgender males (n = 70)**	• Mean age at the start of GnRH analogs (yrs, SD), *P* = NS: ○ Transgender females: 14.1 (1.7) ○ Transgender males: 14.5 (2.0) • Mean height at the start of GnRH analogs (cm, SD), *P* < .001 ○ Transgender females: 169.0 (8.9) ○ Transgender males: 162.2 (8.8) • Mean weight at the start of GnRH analogs (kg, SD), *P* = NS: ○ Transgender females: 57.9 (12.9) ○ Transgender males: 56.2 (14.7) • Mean BMI at the start of GnRH analogs (kg/m^2, SD), *P* = NS ○ Transgender females: 20.1 (3.3) ○ Transgender males: 21.3 (4.2) • Mean age at the start of CSH (yrs, SD), *P* = .005 ○ Transgender females: 16.2 (1.2) ○ Transgender males: 16.9 (1.1) • Duration of GnRH analogs use before starting CSH (yrs, SD), *P* = NS:	Transgender females starting GnRH analogs (n = 51)	Transgender males starting GnRH analogs (n = 70)	• Demographic characteristics **Cross-sectional:** exposures/outcomes were measured at the start of GnRH analog and CSH treatment	• Transgender males were significantly older at the start of CSH compared to transgender females • At the start of GnRH analogs and CSH, transgender females were significantly taller than transgender males • There were no significant differences between transgender females and transgender males at the start of GnRH analogs or CSH for weight and BMI

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ Transgender females: 2.0 (0.94) ○ Transgender males: 1.8 (1.11) • Mean height at the start of CSH (cm, SD), *P* = .005 ○ Transgender females: 176.5 (7.3) ○ Transgender males: 167.1 (7.4) • Mean weight at the start of CSH (kg, SD), *P* = NS: ○ Transgender females: 66.7 (11.9) ○ Transgender males: 63.5 (11.5) • Mean BMI at the start of CSH (kg/m², SD), *P* = NS: ○ Transgender females: 21.1 (3.2) ○ Transgender males: 22.8 (4.0)				
Schulmeister (2022)[95] Four gender specialty clinics in the US [redacted]	TGNB youth starting GnRH analog treatment for puberty suppression (N = 55) **Eligibility:** Adolescents seen at one of four gender specialty clinics between July 2016 and September 2018, and eligible to start a GnRH analog for puberty suppression. Participants were excluded if they had previously received a GnRH analog, had severe psychiatric symptoms, had precocious puberty, or could not read or comprehend English **Sampling method:** A total of 92 participants were enrolled, but 37 were excluded due to various reasons (eg, missing height measurements, started CSH prior to 12 months of GnRH analog use).	• **Mean age at starting GnRH analogs** (yrs, range), *P* = .01: ○ DMAB: 11.9 (10.2 to 14.5) ○ DFAB: 11.1 (9.0 to 13.9) • Identified gender: ○ Female: ▪ DMAB: 10 (38) ▪ DFAB: 0 (0) ○ Male: ▪ DMAB: 0 (0) ▪ DFAB: 15 (52) ○ Transgender female: ▪ DMAB: 14 (54) ▪ DFAB: 0 (0) ○ Transgender male: ▪ DMAB: 0 (0) ▪ DFAB: 13 (45)	Participants DMAB taking a GnRH analog (n = 26)	Participants DFAB taking a GnRH analog (n = 29)	• Height velocity during the first year of GnRH analog treatment **Cohort:** outcomes were measured at the start of GnRH analog treatment and at the 12-month visit	• DMAB participants were significantly older at the start of GnRH analog therapy compared to DFAB participants (*P* = .01) • There were no significant differences between DMAB and DFAB participants for height velocity during GnRH analog treatment (5.4 cm/yr vs. 4.8 cm/yr, respectively; *P* = NS), including when controlling for Tanner stage. ○ Median height velocity by Tanner stage at baseline (cm/yr, interquartile range): ○ Tanner stage II: ▪ DMAB: 5.6 (4.7 to 5.7) ▪ DFAB: 5.0 (4.2 to 5.4) ○ Tanner stage III: ▪ DMAB: 4.2 (2.3 to 6.4) ▪ DFAB: 4.4 (4.0 to 5.5) ○ Tanner stage IV: ▪ DMAB: 1.5 (1.4 to 1.6) ▪ DFAB: 2.9 (1.5 to 3.5)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Therefore, 55 participants were included in the study **Subset definition:** Comparisons were made between participants **DMAB (n = 26)** and **DFAB (n = 29)**	○ Nonbinary: ▪ DMAB: 2 (8) ▪ DFAB: 1 (3) • Tanner stage at start of GnRH analogs: ○ II: ▪ DMAB: 21 (81) ▪ DFAB: 13 (45) ○ III: ▪ DMAB: 3 (12) ▪ DFAB: 13 (45) ○ IV: ▪ DMAB: 2 (8) ▪ DFAB: 3 (10) • Mean BMI z-score *at baseline* (SD): ○ DMAB: 0.56 (0.84) ○ DFAB: 0.38 (0.94) • Mean BMI z-score at 12-month *follow-up* (SD): ○ DMAB: 0.68 (1.00) ○ DFAB: 0.63 (0.95)				• There were no significant differences between DMAB compared to DFAB participants for BMI z-scores at baseline or 12-month follow-up • There was no significant difference in height velocity between the 12 participants (9 DMAB, 3 DFAB) with ineffective blockage and those with suppressed gonadotropins (5.2 cm/yr vs. 5.1 cm/yr, respectively) • Participants concomitantly treated for ADHD (4 DMAB, 3 DFAB) had significantly lower BMI z-scores compared to those not being treated for ADHD (−0.29 vs. 0.59, respectively; *P* = .009), but height velocity was comparable between groups (*P* = NS)
van der Grift (2020)[123] [redacted]	N = 300 TGNB participants **Eligibility:** Participants were included if a gender dysphoria diagnosis was confirmed, they were at least 18 when data was collected (i.e. during follow-up), they were < 18 when starting PS, they initiated and continued PS treatment, and were not lost to follow-up. **Sampling Method:** All adolescents that applied for gender-affirming	• Gender, n (%) ○ Total: *P* < .001 ▪ Transgender man: 184 (61.3) ▪ Transgender woman: 116 (38.7) ○ Tanner 2/3: ▪ Transgender man: 17 (39.5) ▪ Transgender woman: 26 (60.5) ○ Tanner 4/5: ▪ Transgender man: 117 (63.6) ▪ Transgender woman: 40 (34.5)	TGNB FTM that started PS at Tanner 2/3 (n = 17), FTM that started PS at Tanner 4/5 (n = 117)	TGNB FTM controls not treated with PS (n = 50)	• Routine physical examinations that determined height, weight, and Tanner staging of breasts and genitals were performed by trained pediatric endocrinologists according to clinical guidelines. Preoperative physical exams were performed by trained specialists and included the examination of breasts in FTM and genitals in MTF. Physical	• Mean (SD) height in meters: *P* = NS ○ FTM, Tanner 2/3: 1.73 (0.08) ○ FTM, Tanner 4/5: 1.68 (0.07) ○ FTM control: 1.68 (0.07) • Mean (SD) weight in kg: *P* = NS ○ FTM, Tanner 2/3: 67 (7.6) ○ FTM, Tanner 4/5: 66 (11.5) ○ FTM control: 71 (13.6) • Mean (SD) BMI: *P* = 0.04 ○ FTM, Tanner 2/3: 22.4 (2.1)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	medical interventions at the single center between 2006-2013 were screened for eligibility using local registries. A random sample of clinical controls (TGNB that did not take PS) was identified with hospital records. **Subset Definition:** Comparisons were made between FTM that started PS in Tanner stages 2/3 (n = 17) vs. Tanner stages 4/5 (n = 117) vs. Matched TGNB FTM controls who did not take PS (n = 50)	○ Controls: ▪ Transgender man: 50 (50) ▪ Transgender woman: 50 (50) • Age at initial assessment, median (IQR), *P* < .001 ○ Total: 16 (12-18) ○ Tanner 2/3: 10 (9-11) ○ Tanner 4/5: 15 (12.5-16) ○ Controls: 19 (18-21) • Age at study follow-up, mean (SD), *P* < .001 ○ Total: ○ Tanner 2/3: 20 (0.3) ○ Tanner 4/5: 22 (0.2) ○ Controls: 25 (0.2) • Age at start of PS, mean (SD), *P* < .001 ○ Total: 15 (2.0) ○ Tanner 2/3: 12 (0.1) ○ Tanner 4/5: 15 (0.1) ○ Controls: N/! • Age at start of CSH, mean (SD), *P* < .001 ○ Total: 18 (2.9) ○ Tanner 2/3: 15 (0.5) ○ Tanner 4/5: 17 (1.0) ○ Controls: 21 (2.4) • Age at first surgery, median (IQR), *P* < .001 ○ Total: 19 (18-21) ○ FTM Tanner 2/3: 18 (18-18 ○ FTM Tanner 4/5: 18 (18-19)			examination of the breasts included visual assessment of the breast cup and visual and manual assessment of breast ptosis . **Cross-sectional**: Exposures/Outcomes were measured at a single point in time, immediately before participants had gender-affirming surgery. The *P* values calculated also incorporated the results of the controls, which did not take PS.	○ FTM, Tanner 4/5: 23.5 (3.6) ○ FTM control: 24.8 (4.5) • Breasts cup size, N (%): *P* < .001 ○ FTM, Tanner 2/3: ▪ AA, A: 7 (87.5) ▪ greater than or equal to B: 1 (12.5) ○ FTM, Tanner 4/5: ▪ AA, A: 35 (41.2) ▪ greater than or equal to B: 50 (58.8) ○ FTM control: ▪ AA, A: 3 (9.1) ▪ greater than or equal to B: 30 (90.9) • Elasticity, N (%): *P* = 0.04 ○ FTM, Tanner 2/3: ▪ poor, moderate: 0 (0) ▪ good: 8 (100) ○ FTM, Tanner 4/5: ▪ poor, moderate: 18 (30) ▪ good: 42 (70) ○ FTM control: ▪ poor, moderate: 13 (46.4) ▪ good: 25(53.6) • Mean (SD) chest circumference in cm, *P* = NS ○ FTM, Tanner 2/3: 84 (1.5) ○ FTM, Tanner 4/5: 81 (1.4) ○ FTM control: 83 (1.5) • Mastectomy, N (%): *P* < .001 ○ Increased likelihood of no mastectomy required among Tanner 2/3 and Tanner 4/5 vs. controls ○ Decreased likelihood of IMF mastectomy required among Tanner 2/3 and Tanner 4/5 vs. vs controls.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		○ FTM Controls: 23 (21-25) • Age at first surgery, mean (SD), *P* < .001 ○ Total: 21 (2.5) ○ MTF Tanner 2/3: 18 (0.8) ○ MTF Tanner 4/5: 19 (1.3) ○ MTF Controls: 23 (2.2)				○ FTM, Tanner 2/3: ▪ none required: 9 (52.9) ▪ periarteriolar, semicircular resection: 8 (47.1) ▪ IMF resection: 0 (0) ○ FTM, Tanner 4/5: ▪ none required: 1 (1.0) ▪ periarteriolar, semicircular resection: 76 (72.4) ▪ IMF resection: 28 (26.7) ○ FTM control: ▪ none required: 0 (0) ▪ periarteriolar, semicircular resection: 18 (48.6) ▪ IMF resection: 19 (51.4) • Mastectomy, mean (SD) *P* = .006 ○ FTM, Tanner 2/3: ▪ total weight resected in g: 144 (33) ▪ Total volume resected 540 g less than FTM control group, Cohen's *d* (95% CI) = -2.12 (-3.09 to -1.15) ○ FTM, Tanner 4/5: ▪ total weight resected in g: 474 (43) ▪ Total volume resected 209 g less than FTM control group, Cohen's *d* (95%CI) = -0.45 (-0.89to -0.02) ○ FTM Control: ▪ total weight resected in g: 684 (91) • Ptosis, N (%): *P* = NS ○ FTM, Tanner 2/3: ▪ Grade 1, 2: 6 (100) ▪ Grade 3, 4: 0 (0) ○ FTM, Tanner 4/5: ▪ Grade 1, 2: 44 (74.6) ▪ Grade 3, 4: 15 (25.4) ○ FTM Control:

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						▪ Grade 1, 2: 20 (64.5) ▪ Grade 3, 4: 11 (35.5) • Genital surgery, N (%): *P* = NS ○ FTM, Tanner 2/3: ▪ metoidioplasty: 0 (0) ▪ phalloplasty: 1 (5.9) ▪ surgical removal of uterus and ovaries: 11 (64.7) ▪ colpectomy: 6 (35.3) ○ FTM, Tanner 4/5: ▪ metoidioplasty: 1 (0.9) ▪ phalloplasty: 13 (11.1) ▪ surgical removal of uterus and ovaries: 91 (77.8) ▪ colpectomy: 29 (24.8) ○ FTM controls: ▪ metoidioplasty: 2 (4.0) ▪ phalloplasty: 8 (16.0) ▪ surgical removal of uterus and ovaries: 37 (74.0) ▪ colpectomy: 16 (32.0)
	Same except for subset definition **Subset Definition:** Comparisons were made between MTF that started PS in Tanner 2/3 (n = 26) vs. Tanner 4/5 (n = 40) vs. matched TGNB MTF controls who did not take PS (n = 50)		MTF that started PS at Tanner 2/3, MTF that started PS at Tanner 4/5	TGNB MTF controls not treated with PS		• Mean (SD) height in meters: *P* = NS ○ MTF, Tanner 2/3: 1.81 (0.01) ○ MTF, Tanner 4/5: 1.80 (0.00) ○ MTF controls: 1.79 (0.01) • Mean (SD) weight in kg: *P* = NS ○ MTF, Tanner 2/3: 68 (1.8) ○ MTF, Tanner 4/5: 70 (2.2) ○ MTF controls: 74 (1.9) • Mean (SD) BMI: *P* = 0.03 ○ MTF, Tanner 2/3: 20.7 (0.6) ○ MTF, Tanner 4/5: 21.9 (0.6) ○ MTF controls: 22.9 (0.5)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• Mean (SD) penile length in cm (n = 103): *P* = < 0.001 ○ MTF, Tanner 2/3: 7.9 (0.6) ▪ Penile length 4.8 cm shorter than control, Cohen's *d* (95% CI) = -1.73 (-2.30 to -1.15) ○ MTF, Tanner 4/5: 10.7 (0.5) ▪ Penile length 2.1 cm shorter than control, Cohen's *d* (95% CI) = -0.83 (-1.29 to -0.37) ○ MTF controls: 12.8 (0.3) • Testes descended, N (%): *P* = NS ○ MTF, Tanner 2/3: 21 (91.3) ○ MTF, Tanner 4/5: 31 (100) ○ MTF controls: 422 (100) • Vaginoplasty, n (% of those who underwent surgery): *P* < .001 ○ MTF, Tanner 2/3: ▪ intestinal vaginoplasty: 13 (68.4) • Increased likelihood compared to control, OR (95% CI) 84 (9.29 to 768.82) ▪ penis inversion with FTG: 2 (10.5) ▪ penis inversion: 4 (21.2) ▪ not executed yet: 7 ○ MTF, Tanner 4/5: ▪ intestinal vaginoplasty: 6 (20) • Increased likelihood compared to control, OR (95% CI: 9.8 (1.11 to 86.01) ▪ penis inversion with FTG: 2 (6.7) ▪ penis inversion: 22 (73.3) ▪ not executed yet: 10 ○ MTF controls: ▪ intestinal vaginoplasty: 1 (2.5) ▪ penis inversion with FTG: 5 (12.5) ▪ penis inversion: 34 (85)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						▪ not executed yet: 8
Vehmas (2022)[125] Adolescent gynecology clinic in [redacted] (Finland)	Transgender adolescents desiring gender-affirming hormonal treatment (N = 124) **Eligibility:** Adolescents diagnosed with GD, referred to gender identity services at Helsinki University Hospital before 18 years of age for GD symptoms, and further referred to the adolescent gynecology clinic for gender-affirming hormonal assessment **Sampling method**: Referred by gender identity services **Subset definition:** Comparisons were made between **MTF (n = 20)** and **FTM (n = 104)** transgender adolescents	• Assigned sex at birth: ○ AMAB: n = 20 ○ AFAB: n = 104 • Median age at the first contact with gender identity services (yr, range; N = 124): ○ 16.7 (12.1 to 18.0) • Median age at GD diagnosis (yr, range; N = 124): ○ 18.1 (14.8 to 20.1) • Median age at the time of assessment at the adolescent gynecology clinic (yr, range; N = 124): ○ 17.7 (14.6 to 19.8)	FTM (n = 104)	MTF (n = 20)	• BMI **Cross-sectional:** exposures/ outcomes were measured at the beginning of the identity diagnostic process	• Median BMI (kg/m², range), *P* < .001: ○ FTM: 23.1 (17.2 to 39.0) ○ MTF: 19.5 (16.4 to 29.9) • Proportion of participants classified as overweight (BMI ≥ 25 kg/m², but ≤ 30 kg/m²; n, %), *P* = NS ○ FTM: 22 (25.3) ○ MTF: 3 (15.8) • Proportion of participants classified as obese (BMI > 30 kg/m²; n, %), *P* = NS ○ FTM: 10 (11.5) ○ MTF: 0 (0)
Willemsen (2023)[127] [redacted]	**N = 146 FTM** treated with GnRH analogs and testosterone that reached adult height • **Eligibility:** FTM individuals were eligible if they started PS before 16 years of age, received testosterone therapy for at least 6 months, and had reached the age of 18 at the time that the study was conducted. They were excluded if they had not reached adult height (defined as skeletal age of 14 years or older, or had a growth velocity of less than 2 centimeters per year). • **Sampling Method:** Data was retrospectively collected as part of the Amsterdam Cohort of Gender Dysphoria (ACOG)	• Pubertal group: n = 61 ○ Mean age was 12.7 ± 1.0 years at the start of PS. ○ BA was 12.4 ± 1.0 years at the start of PS. ○ Height at start of PS: 157.3 ± 8.5 cm ○ PAH at start of PS: 168.1 ± 6.2 cm • Postpubertal group: n = 85 ○ Mean age was 15.1 ± 0.9 years at the start of PS. ○ BA was 15.7 ± 1.1 years at the start of PS. ○ Height at start of PS: 166.4 ± 6.7 ○ PAH at start of PS: 167.3 ± 6.8	Pubertal group: BA of 14 years or less	Postpubertal group: BA older than 14 years	• Height and weight were assessed every 3-6 months from the start of PS • Height SDS was calculated according to Dutch reference data for females • Midparental height was calculated using (paternal height + maternal height)/2 - 6.5 • BA was determined by evaluating X-rays of the left hand Cohort: Outcomes were measured after exposure at start of PS, at start of CSHT and at adulthood.	**Height** (cm): The pubertal group was significantly taller at the start of PS and at adulthood. • at start of PS: 8.0 (95% CI = 5.5, 10.6) • at start of CSHT: 0.6 (95% CI = -1.7, 2.9) • at adulthood (adult height): 3.0 (95% CI = 0.7, 5.2) **Female height** SDS: While there was no difference at start of PS or CSHT, the pubertal group did have a higher SDS at adulthood compared to the pubertal group • at start of PS: 0.1 (95% CI = -0.3, 0.6) • at start of CSHT: 0.0 (95% CI = -0.3, 0.4) • at adulthood (adult height): 0.5 (95% CI = 0.1, 0.8) • PAH (cm) at start of CSHT: 3.5 (95% CI = 0.0, 7.0) **Adult height - PAH** (cm): While not significant and start of PS, at start of CSHT, the pubertal group had a larger difference between adult height and PAH

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	study, and includes the complete population of patients seen at the clinic. It was gathered from 1972 - December 2018. • **Subset Definition:** Participants were divided into two groups based on growth potential, based on bone age (BA). ○ Pubertal group: Participants had a BA of 14 years or less at the start of PS, or had menarche for less than 1 year before the start of PS. ○ Post pubertal group: Participants had a BA of older than 14 years or menarche for 1 year or more before the start of PS.					• at start of PS: 1.2 (95% CI = -0.1, 2.4) • at start of CSHT: 1.2 (95% CI = 0.2, 2.1) **Adult height - midparental** height (cm): The difference between adult height and midparental height was not significantly different between the groups • 0.9 (95% CI = -1.0, 2.9) **BA -CA** (cm): There was a significant difference between the comparison of BA to CA comparing the pubertal and post pubertal group • at start of PS: 1.2 (95% CI = 0.8, 1.6) • at start of CSHT: 2.4 (95% CI = 1.8, 2.9)
	N = 61 FTM treated with GnRH analogs and CSHT with growth potential (BA of 14 or less; or menarche for less than 1 year before start of PS) **Setting, eligibility, and sampling method:** same as above Subset Definition: Pubertal youth who had a bone age < 12 were compared with pubertal youth who had a bone age > 12	• Mean age was 12.7 ± 1.0 years at the start of PS. • BA was 12.4 ± 1.0 years at the start of PS. • Height at start of PS: 157.3 ± 8.5 cm • BA was 12.4 ± 1.0 years at the start of PS.	FTM with BA over 12 years	FTM with BA 12 years or less		**Height SDS:** • Transgender boys with BA > 12 years at start PS declined more in height SDS during PS compared with transgender boys with BA ≤ 12 years (difference between groups −0.6; 95% CI, −0.7 to −0.4), but height SDS at start of CSHT did not differ between the groups (difference 0.3; 95% CI, −0.3 to 0.9). **BA - CA (years):** • At the beginning of PS, comparing BA to CA, there was a difference among those with BA ≤ 12 at start PS compared with those with BA > 12 years (difference, 0.7 years; 95% CI, 0.2-1.2).
	Same as above. **Subset Definition:** Participants were split into two groups depending on length of time it took for them to reach the adult	• Mean age was 12.7 ± 1.0 years at the start of PS. • BA was 12.4 ± 1.0 years at the start of PS.	FTM that reached adult dose of testosterone within 1 year	FTM that reached adult dose of testosterone after 1 year		**Adult height (cm):** Adult height did not differ between the 2 dosing regimens • 0.8 (95% CI = -3.0, 4.6) **Height SDS at adulthood (adult height):** no difference (statistics not listed)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.3. Clinical studies with between-TGNB-group comparisons examining body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	testosterone dose (125 mg every 2 weeks or 250 mg every 3-4 weeks). Youth who reached adult dose within 1 year (n = 21) were compared to youth who reached adult dose after 1 year (n = 39	• Adult dose within 1 year: median 10.8 (IQR = 9.5, 11.6) months to reach adult dose. • Adult dose after 1 year: median 13.6 (IQR = 12.8, 15.9) months to reach adult dose.				**Adult height - PAH:** • at start of PS: no difference (statistics not listed) • at start of CSHT: no difference (statistics not listed) **Mean testosterone levels in first year of CSHT (nmol/L):** Levels were not significantly higher in subjects who reached adult dose within 12 months compared with > 12 months (95% CI = -18.2, 18.5) **IGF levels during CSHT:** no difference (statistics not listed)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ADHD, attention deficit hyperactivity disorder; AFAB, assigned female at birth; AMAB, assigned male at birth; BA, bone age; BMI, body mass index; cm, centimeter; CA, chronological age; DFAB, designated female at birth; dL, deciliter; DMAB, designated male at birth; DXA, dual-energy radiograph absorptiometry; FTM, female transitioning to male; FSH, follicle stimulating hormone; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; LBM, lean body mass; LH, luteinizing hormone; m, meters; mIU, milli-international units; mL, milliliter; ng, nanograms; MTF, male transitioning to female; N/R, not reported; N/S, not significant; PAH, predicted adult height; pg, picograms; SD, standard deviation; SDS, standard deviation score; SWLS, Satisfaction With Life Scale; TBF, total body fat; TGNB, transgender/nonbinary TF, transgender female; TM, transgender male; ; ug, microgram; WHO-QOL-Brief, World Health Organization Quality of Life Brief Version; WHR, waist hip ratio

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Avila (2019)[101] Academic multidisciplinary gender clinic	TGNB patients who completed the EDE-Q survey (N = 106) **Eligibility:** Transgender males, transgender females, and nonbinary patients ages 13 to 22 presenting at the clinic for transgender care between January 2018 to January 2019 **Sampling method**: Patients were invited to complete the survey during their clinic visit. Out of 107 invited participants, 106 agreed **Subset definition:** N/A	• Gender identity: ○ Transmasculine: 64 (61) ○ Transfeminine: 30 (28) ○ Nonbinary: 12 (11) • Mean age (yr, SD): ○ Transmasculine: 16.3 (1.9) ○ Transfeminine: 16.9 (2.2) ○ Nonbinary: 16.5 (2.3) • Mean percentage of mBMI based on assigned sex at birth (SD): ○ Transmasculine: 125.7 (31.9) ○ Transfeminine: 109.9 (32.2) ○ Nonbinary: 113.4 (35.7) • Taking hormonal treatment: ○ Transmasculine: ▪ GnRH analogs: 4 (6) ▪ Testosterone: 22 (34) ▪ Estrogen: 0 (0) ○ Transfeminine: ▪ GnRH analogs: 1 (3) ▪ Testosterone: 0 (0) ▪ Estrogen: 8 (27) ○ Nonbinary: ▪ GnRH analogs: 0 (0) ▪ Testosterone: 2 (17) ▪ Estrogen: 0 (0)	Treated participants who received hormonal treatments at the time of the survey (n = 34)[a]: • Unspecified GnRH analogs: n = 5 • Testosterone: n = 24 • Estrogen: n = 8	Participants who were untreated at the time of the survey (n = 72)	• EDE-Q scores • Intentional weight manipulation behaviors for the purposes of aligning with their preferred gender **Cross-sectional:** exposures/outcomes were measured <u>at the same time</u>	• EDE-Q scores: ○ There was no significant difference between treated and untreated participants (P value NS) who had elevated global EDE-Q scores (n = 16). Effect size: N/R • Intentional weight manipulation: ○ Out of the 101 participants that answered the question, 64 (63%) reported intentional weight manipulation for the purposes of aligning their body with their gender identity; no difference was observed based on hormonal therapy status (P value NS). Effect size: N/R
	TGNB survey respondents who answered the question about the frequency of intentional weight manipulation (n = 101) **Eligibility:** same as above **Sampling method**: same as above	N/R	Treated participants who received GnRH analogs, testosterone, or estrogen at the time of the survey (n, N/R)	Participants who did NOT receive GnRH analogs, testosterone, or estrogen (n, N/R)		

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	Subset definition: Out of all 106 survey respondents that agreed to participation, 101 answered this item (95%)					
Becker (2018)[103] Four specialized departments in Germany serving TGNB people. Adolescent sample came from [redacted]	N = 202 TGNB participants (82 adolescents, 120 adults) Setting: Adult sample came from a multicenter study of German transgender clinics led by the Max Planck Institute of Psychiatry in Munich. Recruited between September 2013 - December 2015. **Eligibility:** Patients were 14 years old or older, had to fulfill the diagnostic criteria for gender dysphoria/gender identity disorder according to the ICD-10 in all centers and the DSM-5 according to specialized clinicians, must have had a current or former application for any type of mental health service, medical intervention, or counseling for gender problems at one of the participating departments, and must be of German nationality. **Sampling Method:** Participation was a voluntary part of the diagnostic assessment of TGNB applying for gender-affirming care. **Subset Definition:** Comparisons between TGNB adolescents (N = 82) vs. TGNB adults (N = 120), were made using FBeK scores.	• FTM adolescents: (n = 62) • Mean age (SD) was 16.9 (1.96). • 34 (54.8%) had not had any medical interventions • 16 (25.8%) had taken hormones (either GnRH analogs or CSHT) • 12 (19.4%) had taken hormones and had surgery. • MTF adolescents: (n = 20) • Mean age (SD) was 16.55 (1.79). • 10 (50%) had not had any medical interventions • 8 (40%) had taken hormones (either GnRH analogs or CSHT) • 2 (10%) had taken hormones and had surgery. • FTM adults: (n = 50) • Mean age (SD) was 35.36 (10.72). • 6 (12%) had not had any medical interventions • 21 (42%) had taken hormones (either GnRH analogs or CSHT) • 23 (46%) had taken hormones and had surgery • MTF adults: (n = 70) • Mean age (SD) was 43.91 (11.91). • 9 (12.9%) had not had any medical interventions • 34 (48.6%) had taken hormones (either GnRH analogs or CSHT)	TGNB Adolescent (N = 120)	TGNB Adult (N = 82)	• Body image was assessed using the FBeK. **Cross-sectional:** exposures/outcomes were measured at the same time	Body Image: • There were no significant differences in any body image scale between TGNB adolescents and TGNB adults FBeK Scale 1: Attractiveness/Self-Confidence, Mean (SD) • TGNB adolescents had a non-significantly lower T score of 29.48 (7.94) vs 38.23 (11.91) in the TGNB adult cohort. (F = 0.40, *P* = NS) • FBeK Scale 2: Accentuation of Body Appearance, Mean (SD) • TGNB adolescents had a non-significantly lower T-score of 45.89 (9.99) vs. 55.15(9.84) in the TGNB adult cohort, (F = 2.66, *P* = NS) • FBeK Scale 3: Insecurity/Concern • TGNB adolescents had a non-significantly higher T-score of 55.30 (9.66) vs. 52.29 (9.42) in the TGNB adult cohort F = 0.45, *P* = NS • FBeK Scale 4: Sexual-Physical Discomfort • TGNB adolescents had a non-significantly higher T-score of 59.55 (9.30) vs. 58.62(11.10) in the TGNB adult cohort F = 3.70, *P* = NS

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
		• 27 (38.6%) had taken hormones and had surgery.				
Chen (2021)[104] Four pediatric academic medical centers in the US	Adolescents seeking GnRH analog therapy (N = 95) **Eligibility:** Patients aged 8 to 20 years old, diagnosed with GD, eligible to start GnRH analogs or CSH as deemed by the primary treatment team, proficient in English, and seeking care at one of the study clinic locations **Sampling method**: Patients presenting at one of the four medical centers between July 2016 and September 2018, desiring to start GnRH analogs or CSH treatment for GD **Subset definition:** Comparisons were made between **AFAB (n = 46)** and **AMAB (n = 49)**	• Mean age (yr, SD), *P* = .002: ○ AFAB: 10.76 (1.43) ○ AMAB: 11.65 (1.36) • **Gender identity**, *P* = .000: • Transmasculine/Male: ○ AFAB: 40 (87) ○ AMAB: 1 (2) • Transfeminine/Female: ○ AFAB: 1 (2.2) ○ AMAB: 44 (89.8) • Non-binary: ○ AFAB: 5 (10.9) ○ AMAB: 4 (8.2)	AFAB patients seeking GnRH analog therapy (n = 46)	AMAB patients seeking GnRH analog therapy (n = 49)	Self-reported measures: • BES **Cross-sectional:** exposures/outcomes were measured at the same time	• **Mean BES score** (n = 91; SD), *P* = NS: ○ There was no significant difference between the AFAB score of 45.53 (11.74), and the AMAB score of: 46.01 (9.97)
	Adolescents seeking CSH therapy (ie, testosterone or estrogen) (N = 316) **Eligibility:** same as above **Sampling method**: same as above **Subset definition:** Comparisons were made between **AFAB (n = 205)** and **AMAB (n = 111)**	• Mean age (yr, SD), *P* = NS ○ AFAB: 15.87 (1.76) ○ AMAB: 16.23 (2.08) • **Gender identity**, *P* = 0.000: • Transmasculine/Male: ○ AFAB: 191 (93.72) ○ AMAB: 0 (0) • Transfeminine/Female: ○ AFAB: 1 (0.5) ○ AMAB: 105 (94.6) • Non-binary: ○ AFAB: 13 (6.3) ○ AMAB: 6 (5.4)	AFAB patients seeking CSH therapy (n = 205)	AMAB patients seeking CSH therapy (n = 111)	Self-reported measures: • BES • BIS • TCS • GMSR-A **Cross-sectional:** exposures/ outcomes were measured at the same time	• There were no significant differences in BES and TCS scores by designated sex at birth, but there were significant differences on some BIS and GMSR-A subscales. Specifically, youth designated male at birth were significantly more dissatisfied with "neutral" body parts compared to youth designated female at birth, *P* = .001. • Youth designated female at birth experienced more non-affirmation of gender identity compared to youth designated male at birth, *P* = .02. • Regarding resilience, youth designated male at birth expressed more identity-related pride than youth designated female at birth, *P* = .002. There were no differences in overall satisfaction with primary or secondary sexual characteristics, internalized transphobia, negative expectations for the future or community connectedness by designated sex at birth. **Mean BES score** (n, N/R; SD), *P* = NS: ○ AFAB: 35.88 (8.19)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ AMAB: 36.23 (10.71) **Mean BIS** (n, N/R; SD): • Total scale score, *P* = NS: ○ AFAB: 3.19 (0.72) ○ AMAB: 3.33 (0.93) • Primary sexual characteristics, *P* = NS: ○ AFAB: 4.39 (0.72) ○ AMAB: 4.53 (0.74) • Secondary sexual characteristics, *P* = NS: ○ AFAB: 3.09 (0.77) ○ AMAB: 3.12 (0.97) • Neutral (hormonally unresponsive), *P* = .001: ○ AFAB: 2.60 (0.70) ○ AMAB: 2.93 (0.90) **Mean TCS** (n, N/R; SD): • Total scale score, *P* = NS: ○ AFAB: 2.85 (0.68) ○ AMAB: 2.78 (0.85) • Appearance congruence subscale, *P* = NS: ○ AFAB: 2.42 (0.78) ○ AMAB: 2.27 (1.03) • Identity acceptance subscale, *P* = NS: ○ AFAB: 4.14 (0.87) ○ AMAB: 4.30 (0.85) **Mean GMSR-A** (n, N/R: SD): • Non-affirmation of gender identity, *P* = .020: ○ AFAB: 15.78 (5.86) ○ AMAB: 14.07 (6.60) • Internalized transphobia, *P* = NS: ○ AFAB: 13.49 (8.23) ○ AMAB: 12.77 (8.97) • Negative expectations for the future, *P* = NS

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ AFAB: 19.41 (8.09) ○ AMAB: 18.49 (8.98) • Non-disclosure, *P* = .000: ○ AFAB: 14.66 (4.51) ○ AMAB: 11.97 (5.41) • Pride, P value = 0.002: ○ AFAB: 16.43 (8.05) ○ AMAB: 19.43 (7.72) • Community connectedness, *P* = NS: ○ AFAB: 13.58 (3.93) ○ AMAB: 13.39 (4.12)
Chen (2023)[67] USA gender clinics at the [redacted] from July 2016 through June 2019	TGNB adolescents (N = 315) **Eligibility:** Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating GAH as part of their clinical care. For minors, parental consent was required to initiate treatment. **Sampling Method:** Youth were recruited from 4 different sites at the start of GAH therapy. They were enrolled if they met inclusion criteria **Subset definition:** • Comparisons were made between those designated female at birth(n = 204) and those designated male at birth (n = 111) • Comparisons were made between those who started GAH in early puberty (n = 24) and those who started in later puberty (n = 291)	• participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) • Higher percentage of those designated female at birth (64.8%) then male. • Mostly Non-Latinx or non-Latin white (58.1%) Tanner stage at GAH initiation: no (%) • Early n = 24 ○ Stage 1: 2 (0.6) ○ Stage 2: 14 (14.1) ○ Stage 3: 9 (2.9) • Late n = 291 ○ Stage 4: 29 (9.2) ○ Stage 5: 262 (83.2)	TGNB youth starting GAH in early puberty (Tanner stages 1-3) (n = 24)	TGNB youth starting GAH in later puberty (Tanner stages 4-5) (n = 291)	**Appearance congruence** was captured through the 9-item appearance congruence subscale of the Transgender Congruence Scale. **Cohort:** outcomes were measured at baseline, 6, 12, 18 and 24 months of GAH treatment	Appearance congruence: mean (SD) • Those that had initiated GAH in early puberty had a significantly higher score of 3.08 (0.95) compared to 2.31 (0.85) for those who initiated GAH in later puberty at baseline, *P* < .001 • Youth initiating GAH in later puberty had greater improvements in appearance congruence over 24 months than those initiating GAH in early puberty with a time-invariant effect on slope of -0.42, 95% CI (-0.66 to -0.19)
			TGNB youth DFAB (n = 204)	TGNB youth DMAB (n = 111)		Appearance congruence: mean difference (SD) • There was no significant difference in scores between those DFAB and those DMAB: 0.03, 95% CI (-0.09-0.15)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Costa (2015)[77] [redacted] United Kingdom)	Adolescents with GD (N = 201) **Eligibility:** Diagnosis of GD **Sampling method**: Participants were referred to the Gender Identity Development Service between 2010 and 2014 and completed the 6-month diagnostic evaluation **Subset definition:** Comparisons were made between **natal males (n = N/R)** and **natal females (n = N/R)** adolescents for puberty suppression	• Mean age at baseline (yr, SD), *P* = NS ○ Natal males: 15.61 (1.70) ○ Natal females: 15.46 (1.22) • Mean age at start of GnRH analogs (yr, SD), *P* = NS ○ Natal males: 16.64 (1.22) ○ Natal females: 16.39 (1.28) • Living in the role of the desired gender: • Completely, *P* < .001: ○ Natal males: 29 (42.6) ○ Natal females: 88 (73.9)	Natal males	Natal females	Self-reported measures: • UGDS questionnaire Cross-sectional: exposures/outcomes were measured at the same time	• Mean UGDS score (SD), *P* < .001 • Natal females scored significantly higher than natal males ○ Natal males (n = 50): 51.6 (9.7) ○ Natal females (n = 110): 56.1 (4.3)
de Vries (2010)[78] [redacted]	N = 27 TGNB adolescents • Eligibility: not clearly stated • Sampling method: 140 of 196 consecutively referred adolescents were considered eligible for medical intervention between 2000 and 2008 at the clinic. Of this cohort, 29 adolescents who were age 16 years or older were prescribed CSH only, and 111 adolescents were prescribed GnRH analogs to suppress puberty. Subsequently, 70 of the 111 started CSH treatment between the years 2003 and 2009. The first 30 young adults who had become age 18 and had GRS between 2004 and 2009 were invited to participate at least one year after their last operation. GRS was vaginoplasty for MTFs and hysterectomy for FTMs, because after these surgeries transsexuals can legally change their gender. One	Full cohort (N = 27): • Age, mean (SD) ○ assessment of pre-treatment: 13.5 (1.8) with a range of 11.2–17.0. ○ start of GnRH analogs: 14.6 (1.7) with a range of 11.5–17.9. ○ start of CSH: 16.6 (1.1) with a range of 13.9–18.6. ○ assessment of post treatment: 20.9 (1.0) with a range of 19.7–22.8. • The mean (SD) full-scale intelligence was 98.2 (15.0) with a range of 70–131. MTFs group (N = 11): • Age, mean (SD) ○ assessment of pre-treatment: 13.9 (.8). ○ start of GnRH analogs: 15.0 (0.6). ○ start of CSH: 16.7 (1.4). ○ assessment of post treatment: 21.3 (1.1).	MTF TGNB adolescents	FTM TGNB adolescents	• Body satisfaction was measured with the BIS • Gender Dysphoria was measured using the UGDS **Cohort:** participants are followed over time to monitor the exposure status and the development of the outcome of interest (prospective review). Measured pre-treatment and post-treatment, at least one year after gender reassignment surgery.	Body satisfaction: • There were no significant gender differences on overall body satisfaction scores either Pre-treatment or Post treatment (*P* = NS). • The gender effect F(df) of the BIS primary sex characteristics, secondary sex characteristics and neutral body characteristics were 0.9 (1,20), 0.2 (1,20) and 4.2 (1,20). • There were significant interaction effects between gender and the changes of BIS between Pre-treatment and Post treatment (F(df)) of primary sex characteristics, secondary sex characteristics and neutral body characteristics were 14.0 (1,20), 6.0 (1,20) and 13.9 (1,20), respectively; • MTFs showed more improvement in their satisfaction with primary (*P* < 0.001) and secondary sex characteristics (*P* < 0.05) compared to FTMs. • With their neutral body characteristics, MTFs became more satisfied whereas FTMs became less satisfied between Pre-treatment and Post treatment (*P* < 0.001). Gender dysphoria: • There were no significant gender differences on the gender dysphoria either Pre-treatment or Post treatment (*P* = NS). • The gender effect (F(df)) of the UGDS score was 4.2 (1,19).

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	person (MTF) refused to participate and two (one FTM and one MTF) failed to send back their questionnaires. This resulted in 27 participants, 11 MTFs and 16 FTMs. • Subset definition: Comparisons were made between MTF adolescents (n = 11) and FTM adolescents (n = 16)	• The mean (SD) full-scale intelligence was 94.4(12.3). FTMs group (N = 16): • Age, mean (SD) age ○ assessment of pre-treatment: 13.2 (1.8). ○ start of GnRH analogs: 14.4 (0.3). ○ start of CSH: 16.6 (0.9). ○ assessment of post treatment was 20.7 (0.8). • The mean (SD) full-scale intelligence was 103.5 (15.2).				• The interaction effects between gender and the changes of gender dysphoria between Pre-treatment and post treatment was not statistically significant (*P* = NS).
de Vries (2011)[57] [redacted]	Transgender adolescents (N = 70) **Eligibility:** N/R **Sampling method**: First 70 transgender adolescents who were referred for medical treatment (ie, puberty suppression) between 2000 and 2008 **Subset definition:** Comparisons were made between **natal males (n = 33)** and **natal females (n = 37)**	• Mean age at assessment (yr, SD), *P* = .028 ○ Natal males: 13.14 (1.55) ○ Natal females: 14.10 (1.99) • Mean age at start of GnRH analogs (yr, SD), *P* = .036 ○ Natal males: 14.25 (1.79) ○ Natal females: 15.21 (1.95) • Mean age at start of CSH (yr, SD), *P* = .008 ○ Natal males: 16.24 (1.21) ○ Natal females: 16.99 (1.07) • Mean time between start of GnRH analogs and CSH (yr, SD), *P* = .NS ○ Natal males: 1.99 (0.94) ○ Natal females: 1.78 (1.16)	Natal males (n = 33)	Natal females (n = 37)	Self-reported measures: • UGDS questionnaire • BIS **Cohort:** outcomes were measured before (T0) and while on puberty suppression, before CSH (T1)	• Body image scores • Compared with natal males, natal females reported significantly more gender dysphoria and were more dissatisfied with their primary and secondary sex characteristics both at T0 and T1. There was a significant interaction effect between natal sex and the changes of gender dysphoria between T0 and T1; natal females became more dissatisfied with their secondary (F[1,55] = 14.59, *P* < 0.001) and neutral (F[1,55] = 15.26, *P* < 0.001) sex characteristics compared with natal males. • Mean UGDS score (SD; N = 41): • Before starting puberty suppression (T0): ○ Natal males: 47.95 (9.70) ○ Natal females: 56.57 (3.89) • While taking puberty suppression (T1): ○ Natal males: 49.67 (9.47) ○ Natal females: 56.62 (4.00) • Between-sex significance: 15.98, *P* < .001 • Mean BIS score (SD; N = 57): • Primary sex characteristics: ○ Before starting puberty suppression (T0): ▪ Natal males: 4.02 (0.61)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						▪ Natal females: 4.16 (0.52) ○ While taking puberty suppression (T1): ▪ Natal males: 3.74 (0.78) ▪ Natal females: 4.17 (0.58) ○ Between-sex significance: 4.11, *P* = .047 • Secondary sex characteristics: ○ Before starting puberty suppression (T0): ▪ Natal males: 2.66 (0.50) ▪ Natal females: 2.81 (0.76) ○ While taking puberty suppression (T1): ▪ Natal males: 2.39 (0.69) ▪ Natal females: 3.18 (0.42) ○ Between-sex significance: 11.57, *P* = .001 • Neutral characteristics: ○ Before starting puberty suppression (T0): ▪ Natal males: 2.60 (0.58) ▪ Natal females: 2.24 (0.62) ○ While taking puberty suppression (T1): ▪ Natal males: 2.32 (0.59) ▪ Natal females: 2.61 (0.50) ○ Between-sex significance: 0.081, *P* = NS
de Vries (2014)[79] [redacted] the Netherlands)	Transgender adults who had received puberty suppression during adolescence, and completed gender reassignment surgery (N = 55) **Eligibility:** Prescribed puberty suppression at the clinic as an adolescent with GD, and received gender reassignment surgery between 2004 and 2011 **Sampling method**: This group of adolescents belonged to a larger group of adolescents (n = 196) who	• Mean age at assessment before treatment is started (yr, SD): ○ Transgender women: 13.6 (1.8) ○ Transgender men: 13.7 (2.0) • Mean age at start of GnRH analogs (yr, SD): ○ Transgender women: 14.8 (2.0) ○ Transgender men: 14.9 (1.9) • Mean age at start of CSH (yr, SD): ○ Transgender women: 16.5 (1.3) ○ Transgender men: 16.8 (1.0)	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Self-reported measures: • UGDS questionnaire • BIS **Cohort:** outcomes were measured before the start of puberty suppression (pre-treatment; T0), at the start of CSH (T1), and at least 1 year after gender reassignment surgery (T2)	**Body satisfaction:** Trans women reported more satisfaction over time with primary sex characteristics than trans men and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Trans men reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. • Mean UGDS score (SD): ○ At the start of CSH (T1): ▪ Transgender women: 48.95 (10.80) ▪ Transgender men: 57.11 (3.40) ○ At least 1 year after gender reassignment surgery (T2): ▪ Transgender women: 17.27 (2.57)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	were referred for treatment between 2000 and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery **Subset definition:** Comparisons were made between **transgender women (n = 22)** and **transgender men (n = 33)**	• Mean age at gender reassignment surgery (yr, SD): ○ Transgender women: 19.6 (0.9) ○ Transgender men: 19.0 (0.8) • Mean age at assessment after gender reassignment surgery (yr, SD): ○ Transgender women: 21.0 (1.1) ○ Transgender men: 20.5 (0.8) • Mean pre-treatment UGDS (SD): ○ Transgender women (n = 11): 47.07 (11.05) ○ Transgender men (n = 22): 56.74 (3.74) • Mean pre-treatment BIS (SD): • Primary sex characteristics: ○ Transgender women (n = 17): 4.03 (0.68) ○ Transgender men (n = 28): 4.18 (0.53) • Secondary sex characteristics: ○ Transgender women (n = 17): 2.63 (0.60) ○ Transgender men (n = 28): 2.80 (0.72) • Neutral body characteristics: ○ Transgender women (n = 17): 2.57 (0.70) ○ Transgender men (n = 28): 2.21 (0.64)				▪ Transgender men: 15.08 (2.64) • Mean BIS score (SD): ○ Primary sex characteristics at the start of CSH (T1): ▪ Transgender women: 3.82 (0.56) ▪ Transgender men: 4.13 (0.60) ○ Primary sex characteristics at least 1 year after gender reassignment surgery (T2): ▪ Transgender women: 2.07 (0.74) ▪ Transgender men: 2.89 (0.71) ○ Secondary sex characteristics at the start of CSH (T1): ▪ Transgender women: 2.34 (0.68) ▪ Transgender men: 3.18 (0.43) ○ Secondary sex characteristics at least 1 year after gender reassignment surgery (T2): ▪ Transgender women: 1.93 (0.63) ▪ Transgender men: 2.48 (0.40) ○ Neutral body characteristics at the start of CSH (T1): ▪ Transgender women: 2.29 (0.50) ▪ Transgender men: 2.61 (0.52) ○ Neutral body characteristics at least 1 year after gender reassignment surgery (T2): ▪ Transgender women: 2.09 (0.56) ▪ Transgender men: 2.32 (0.44)
Grannis (2021)[110] A gender developmental clinic at a children's hospital	FTM adolescents (N = 42) **Eligibility:** Diagnosis of GD, 9 to 21 yrs of age, and able to participate in MRI-based research **Sampling method**: Study sample was drawn from a larger study of	• Mean age (yr, SD), $P < .01$: ○ Treated FTM: 17.0 (1.2) ○ Untreated FTM: 15.8 (1.5) • History of anxiolytics/anti-depressant use:	Received intramuscular testosterone cypionate (n = 19)	Did not receive intramuscular testosterone cypionate (n = 23)	Self-reported measures: • BIS Cross-sectional: exposures/outcomes were measured at the same time	• Participants who received testosterone cypionate reported significantly lower body image dissatisfaction compared to those who did not receive testosterone cypionate ($P < .01$, $\eta^2 = 0.21$) • Mean composite score (SD): ○ Treated FTM: 91.16 (19.67)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.4. Clinical studies with between-TGNB-group comparisons examining body image outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	transgender youth receiving gender affirming medical care (both PBs and CSH). All participants were receiving gender affirming behavioral support and had not been prescribed PBs previously. **Subset definition:** Comparisons were made between **treated (n = 19)** and **untreated (n = 23)** FTM adolescents	○ Treated FTM: 10 (52.6) ○ Untreated FTM: 18 (78.3) • Birth control use: ○ Treated FTM: 15 (79.0) ○ Untreated FTM: 15 (65.2) • Mean duration of testosterone use (months, SD): ○ Treated FTM: 13.1 (10.3) • Mean testosterone dosage (mg, SD): ○ Treated FTM: 242.1 (82.3)				○ Untreated FTM: 108.09 (13.32) • There was a significant direct relationship between self-reported body image dissatisfaction and depression (P value < 0.01) and suicidality within the previous year (P value < 0.10). The relationship between testosterone and depression and suicidality was non-significant after controlling for body image dissatisfaction • No direct effects were found between body image dissatisfaction and anxiety

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CHS, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog/analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s)

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Carmichael (2021)[73] UK [redacted]	N = 44 TGNB adolescents **Eligibility Criteria:** Patients recruited from those referred to GIDS who were between 12-15 years and had commenced GnRH analog treatment. • Had been seen for at least 6 months and attended at least 4 interviews. • Psychological stability to withstand the stresses of medical treatment and • Displayed severe and persistent GD and actively requesting pubertal suppression • Able to give informed consent • Met physical/medical criteria of being in established puberty and having normal endocrine function and karyotype consistent with birth registered sex. **Exclusions**: Inability to fully participate, BMI < 2nd percentile, serious psychiatric conditions, Inability to give consent, low spine or hip BMD **Sampling Method**: Patients attending GIDS were provided with information and those wishing to find out more discussed with their clinician. Those likely deemed eligible were given detailed information and invited to a medical clinic for discussion. Young people needed to commit to regular medical and psychosocial follow up. Informed consent was obtained. 48 young people attended the clinics and 44 wished to participate. 8 young people were	Full cohort: All participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical exam for birth-registered sex and normal full blood count and liver and renal function. All patients left study following their 16th birthday when they chose whether to pursue cross-sex hormone therapy. • Median age was 13.6. • Tanner stage: ○ n = 19 (43%) stage 3 ○ n = 16 (36%) stage 4 ○ n = 9 (21%), stage 5 • spent a median of 31 months in study with a median age of 16.1 at end of pathway. • 89% of patients were of white ethnicity. • Birth registered male: ○ Median age 13.4 ○ spent a median 37 months in study • Birth registered female: ○ Median age 13.9 ○ spent a median 29 months in study	TGNB youth registered male at birth starting GnRH analogs (n = 25)	TGNB youth registered female at birth starting GnRH analogs (n = 19)	Bone mineral density (BMD) in the lumbar (L1-L4) spine and hip was measured by dual energy X-ray absorptiometry (DEXA) scans. Cohort study-data was compared from baseline to 12 months on treatment	BMD at lumbar spine: • TGNB youth DFAB showed no significant difference in outcome at 12 months compared to TGNB youth DMAB with a difference of -0.02, 95% CI (-0.05,0.01) *P* = NS
			TGNB participants who were Tanner stage 4 at baseline (n = 16)	TGNB participants who were Tanner stage 3 (n = 19) or 5 (n = 9) at baseline		BMD at lumbar spine: • Participants starting at Tanner stage 3 at baseline showed a difference of 0.008, 95% CI (-0.03,0.04), *P* = NS compared to those starting at Tanner stage 4. • Participants starting at Tanner stage 5 at baseline showed a difference of -0.009, 95% CI (-0.05,0.03), *P* = NS compared to those starting at Tanner stage 4. • Pubertal stage at baseline showed no significant effect on outcome at 12 months.

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	not yet eligible, but were able to enter the study when sufficiently advanced in puberty. Subset Definition: • Comparisons between birth registered male (n = 25) and birth registered female (n = 19) adolescents. • Comparisons between TGNB participants who were Tanner stage 4 at baseline (n = 16) and TGNB participants who were Tanner stage 3 (n = 19) or 5 (n = 9) at baseline					
Karakilic Ozturan (2023)[112] A tertiary pediatric endocrinology clinic in Turkey.	TGNB adolescents (N = 28) **Eligibility**: Participants must have been diagnosed with GD based on DSM-5 diagnostic criteria by a mental health professional after at least six months of psychiatric follow-up, and must have been referred to the GD outpatient clinic. They could not start hormone treatment without informed consent from both themselves and their legal guardians. They must have stayed below the age of 18 during the follow-up period of the study (3-6 months). **Sampling Method**: Authors retrospectively examined the medical records of all adolescents diagnosed with GD after at least 6 months of psychiatric follow-up and that were referred to their GD outpatient clinic between 2016 and 2022. **Subset Definition**: BMD z-scores were compared between the entire cohort, between MTF individuals	Baseline characteristics are only given for the entire screened cohort (N = 53). • FTM: Median age was 16.4 years (IQR = 1.74) at the time of referral to the clinic adolescents. • MTF: Median age was 16.3 years (IQR = 1.53) at the time of referral	TGNB youth with low BMI receiving medical interventions	TGNB youth with normal - high BMI receiving medical interventions	• L1-L4 bone mineral density (BMD) z-scores: This value compares bone density to the average values for participants' age and natal sex. It was measured using dual-energy X-ray absorptiometry. **Cross sectional:** Outcomes and measures were measured at the same time.	BMD z-score: The median L1-L4 spine BMD z-score was lower in those with low BMI, *P* = .0006, R2 = .4 • In MTF subjects, there was a stronger correlation between BMD z-score and low BMI, *P* = .0135, R2 = .5 • In FTM subjects, the correlation was weaker, *P* = .02, R2 = .4 • The basal median L1-L4 spine BMD z-score of MTF and FTM adolescents was -1.1 (IQR 3.4) and 0.4 (IQR 1.9), respectively, no statistical difference was detected (*P* = NS)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	(n = 13), and between FTM (n = 15) individuals.					
	Subset Definition: Comparisons were made between MTF starting GnRH analogs (n = 6) vs FTM starting GnRH analogs (n = 13)	• **Age,** median (IQR), years: • MTF starting GnRH analogs: 16.7 (1.2) • FTM starting GnRH analogs: 16.7 (1.0) • *P* = NS	MTF adolescents that started GnRH analogs (n = 9)	FTM adolescents that started GnRH analogs (n = 13)	• L1-L4 bone mineral density (BMD) z-scores: This value compares bone density to the average values for participants' age and natal sex. It was measured using dual-energy X-ray absorptiometry. • 25-hydroxyvitamine levels were collected at the third and sixth month of treatment and every 6 months thereafter. **Cross Sectional:** Exposures/ Outcomes were measured at one point in time at the onset of GnRH analogs	25-hydroxyvitamine, Median (IQR): • Levels were significantly higher in the MTF cohort at 26.8 (10.6) ng/mL vs. 15.7 (6.9) ng/mL in the FTM cohort, *P* = .009 L1-L4 bone mineral density (BMD) z-score, Median (IQR): • There was no significant difference in the BMD z-score between the MTF cohort at -1.0 (3.3) vs. 0.4 (1.9) in the FTM cohort, *P* = NS
	Subset Definition: Comparisons were made between MTF who took GnRH analogs and then started CSH (n = 6) vs MTF who took combined androgen receptor blocker and then started CSH (n = 6)	Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1) • MTF with combined androgen receptor blocker treatment 17.5 (1.3) • *P* = NS	MTF adolescents that used GnRH analogs before starting CSH (n = 6)	MTF adolescents that used combined androgen receptor blockers before starting CSH (n = 6)	• L1-L4 bone mineral density (BMD) z-scores: This value compares bone density to the average values for participants' age and natal sex. It was measured using dual-energy X-ray absorptiometry. • 25-hydroxyvitamine levels were collected at the third and sixth month of treatment and every 6 months thereafter. **Cross-sectional:** exposures/ outcomes were measured at the same time before participants started CSH	25-hydroxyvitamine, Median (IQR) • There was no significant difference in levels between the GnRH analog cohort at 16.7 (3.4) ng/mL vs. 15.9 (2.3) ng/mL in the combined androgen receptor blocker cohort, *P* = NS L1-L4 bone mineral density (BMD) z-score, Median (IQR) • There was no significant difference in BMD z-score between the GnRH analog cohort at -0.91 (3.1) vs. -1.2 (2.3) in the combined androgen receptor blocker cohort, *P* = NS
	Subset Definition: Comparisons were made between MTF participants who were starting CSH (combined group whose previous treatment was GnRH analogs and	Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1)	MTF adolescents that used either GnRH analogs or combined androgen receptor blockers before starting CSH (n = 12)	FTM adolescents that used GnRH analogs before starting CSH (n = 9)	• L1-L4 bone mineral density (BMD) z-scores: This value compares bone density to the average values for participants' age and natal	25-hydroxyvitamine, Median (IQR) • There was no significant difference between the MTF cohort at 16.7 (3.4) ng/mL and 15.9 (2.3) ng/mL vs. 21.9 (17.9) ng/mL in the FTM cohort, *P* = NS

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	combined androgen receptor blocker) (n = 12) vs. FTM starting CSH (n = 9)	• MTF with combined androgen receptor blocker treatment: 17.5 (1.3) • FTM: 17.8 (0.4) • *P* = NS			sex. It was measured using dual-energy X-ray absorptiometry. • 25-hydroxyvitamine levels were collected at the third and sixth month of treatment and every 6 months thereafter. **Cross-sectional:** exposures/ outcomes were measured at the same time at the start of CSH	L1-L4 bone mineral density (BMD) z-score, Median (IQR) • There was no significant difference between the BMD z-scores in the MTF cohort at -0.91 (3.1) and -1.2 (2.3) vs. -0.9 (1.0) in the FTM cohort, *P* = NS
Lee (2020)[85] Four Children's hospitals [redacted]	N = 63 early pubertal TGNB youth initiating GnRH analogs • Eligibility: Tanner stage 2-3, initiation GnRH analogs • Sampling method: those meeting criteria with a DXA at an appropriate time • Subset: ○ Comparisons were made between TGNB youth with low BMD, (n = 14) vs TGNB youth with normal BMD, (n = 49) ○ Comparisons were made between TGNB natal males (n = 33) and natal females (n = 30) ○ Comparisons were made using the following predictors: 1. Natal female 2. PAQ-C score 3. BMI Z-score 4. Tanner stage 5. Age at blocker placement	• Assigned gender at birth: ○ 33 (52.4%) male ○ 30 (47.6%) female • Gender identity ○ 58 (92.1%) Binary ○ 5 (7.9%) Non binary • Mostly non-Hispanic white (55.6%) and Hispanic (19.1%) • Tanner Stage ○ 40 (63.5%) stage 2 ○ 23 (36.5%) stage 3	TGNB youth with normal BMD (n = 49)	TGNB youth with low BMD (n = 14)	• aBMD and vBMD were assessed by DXA and quantitative computed tomography measuring TBLH, LS, TH and FN. • Physical activity was assessed using the PAQ-C • Serum 25-hydroxyvitamin D was measured by standard clinical assays **Cross-sectional:** exposures/ outcomes were measured at the same time	Age at GnRH analog start, mean (SD) • There was no significant difference between those with normal BMD: 12.0 (1.7), compared to those with low BMD: 11.5 (1.4), *P* = NS Tanner stage, mean (SD) • There was no significant difference between those with normal BMD: 2.43 (0.50), compared to those with low BMD: 2.30 (0.47), *P* = NS PAQ-C, mean (SD) • Those with normal BMD had a significantly lower PAQ-C of 2.32 (0.71) vs. 2.76 (0.61) of those with low BMD, *P* = .01 Serum 25-hydroxyvitamin D, mean (SD) • There was no significant difference between those with normal BMD: 28.7 (0.8) compared to those with low BMD: 28.8 (9.3), *P* = NS Daily calcium intake, mean (SD) • There was no significant difference between those with normal BMD: 520 (106) compared to those with low BMD: 637 (334)), *P* = NS BMI Z-score, mean (SD), • There was no significant difference between those with normal BMD: 0.08 (1.57) compared to those with low BMD: 0.40 (0.99), *P* = NS Height Z-score, mean (SD)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	6. Daily calcium intake 7. Serum 25-OH D					• There was no significant difference between those with normal BMD: -0.27 (1.02) compared to those with low BMD: 0.22 (1.12), *P* = NS
			TGNB natal male (n = 33)	TGNB natal female (n = 30)		• Frequency of low vs normal BMD, percent (95% CI) o A low aBMD or vBMD Z-score, defined as < -2, was observed in more natal males: 30% (10/33, 95% confidence interval [CI], 15.6-48.7) compared to natal females: 13% (4/30, 95% CI, 3.8-30.7), *P* = NS • Areal BMD measurements o Natal males had significantly lower TH BMD scores than natal females, no other significant differences were observed • TBLH BMD Z-score, mean (SD), *P* = NS o Natal male (n = 18): -0.96 (1.10) o Natal female (n = 18): -0.65 (1.22) • LS BMD Z-score, mean (SD), *P* = NS o Natal male (n = 23): -0.37 (1.02) o Natal female (n = 21): -0.12 (1.25) • TH BMD Z-score, mean (SD), *P* = .003 o Natal male (n = 14): -0.69 (0.71) o Natal female (n = 10): 0.55 (1.10) • FN BMD Z-score, mean (SD), *P* = .01 o Natal male (n = 13): -0.78 (0.93) o Natal female (n = 9): 0.30 (0.92) • Volumetric BMD measurements o Natal males had significantly lower Cortical BMD z-scores than natal females. There was no significant difference in trabecular BMD z-scores • Trabecular BMD Z-score, mean (SD), *P* = NS o Natal male (n = 8): -0.95 (1.38) o Natal female (n = 7): -0.49 (0.84) • Cortical BMD Z-score, mean (SD), *P* = .047 o Natal male (n = 8): -1.80 (1.42) o Natal female (n = 7): -0.42 (0.92) • Selected determinants of bone health

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						○ The only significant determinate of bone health was age at blocker placement. • Age at blocker placement, mean (SD), *P* = .002 ○ Natal female: 11.0 (1.4) ○ Natal male: 12.1 (1.3) • Tanner stage, mean (SD), *P* = NS ○ Natal female: 2.43 (0.50) ○ Natal male: 2.30 (0.47) • PAQ-C, mean (SD), *P* = .04 ○ Natal female: 2.83 (0.57) ○ Natal male: 2.50 (0.69) • Serum 25-hydroxyvitamin, mean (SD), *P* = NS ○ Natal female: 30.8 (7.3) ○ Natal male: 26.9 (11.0) • Daily calcium intake, mean (SD), *P* = NS ○ Natal female: 540 (269) ○ Natal male: 676 (393) • BMI Z-score, mean (SD), *P* = NS ○ Natal female: 0.28 (1.05) ○ Natal male: 0.38 (1.22) • Height Z-score, mean (SD), *P* = NS ○ Natal female: -0.03 (1.17) ○ Natal male: 0.25 (1.05)
			TGNB youth were compared by a list of predictors to predictors that predicted change in BMD scores	TGNB youth were compared by a list of predictors that did not predict change in BMD scores		**Predictor: Natal Female** • TBLH BMD, beta, (95% CI): 0.4 (-0.3, 1.0), *P* = NS • LS BMD, beta, (95% CI): 0.07 (-0.7, 0.9), *P* = NS • TH BMD, beta, (95% CI): 0.9 (0.03, 1.7), *P* = NS • FN BMD, beta, (95% CI): 0.6 (-0.3, 1.5), *P* = NS • TBD BMD, beta, (95% CI): -0.2 (-6.6, 6.1), *P* = NS • CBD BMD, beta, (95% CI): 2.0 (-4.4, 8.3), *P* = NS **Predictor: PAQ-C score** • TBLH BMD, beta, (95% CI): 0.3 (-0.3, 0.9), *P* = NS • LS BMD, beta, (95% CI): 0.002 (-0.7, 0.7), *P* = NS

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• TH BMD, beta, (95% CI): -0.05 (-0.7, 0.6), *P* = NS • FN BMD, beta, (95% CI): 0.2 (-0.5, 0.8), *P* = NS • TBD BMD, beta, (95% CI): 0.1 (-4.1, 4.4), *P* = NS • CBD BMD, beta, (95% CI): 0.2 (-4.1, 4.5), *P* = NS **Predictor: BMI Z-score** • BMI z-score was significantly associated with an increase in TBLH BMD z-scores • TBLH BMD, beta, (95% CI): 0.7 (0.4, 1.1), *P* = < .0001 • LS BMD, beta, (95% CI): 0.3 (-0.05, 0.7), *P* = NS • TH BMD, beta, (95% CI): -0.2 (-0.2, 0.6), *P* = NS • FN BMD, beta, (95% CI): 0.2 (-0.2, 0.6), *P* = NS • TBD BMD, beta, (95% CI): -0.5 (-3.1, 2.1), *P* = NS • CBD BMD, beta, (95% CI): -0.06 (-2.7, 2.6), *P* = NS **Predictor: Tanner stage** • TBLH BMD, beta, (95% CI): -0.2 (-1.0, 0.6), *P* = NS • LS BMD, beta, (95% CI): 0.4 (-0.5, 1.3), *P* = NS • TH BMD, beta, (95% CI): 0.3 (-0.7, 1.2), *P* = NS • FN BMD, beta, (95% CI): 0.3 (-0.7, 1.4), *P* = NS • TBD BMD, beta, (95% CI): 1.2 (-4.0, 6.5), *P* = NS • CBD BMD, beta, (95% CI): 0.8 (-4.5 to 6.0), *P* = NS **Predictor: Age at blocker placement** • Age at blocker placement was significantly associated with a decrease in TH and FN BMD z-scores, but no other scores • TBLH BMD, beta, (95% CI): 0.06 (-0.3 to 0.4), *P* = NS • LS BMD, beta, (95% CI): -0.1 (-0.5, 0.3), *P* = NS • TH BMD, beta, (95% CI): -0.5 (-0.9, 0.002), *P* = .049 • FN BMD, beta, (95% CI): -0.6 (-1.1, -0.1), *P* = .02 • TBD BMD, beta, (95% CI): -0.06 (-1.4, 1.2), *P* = NS • CBD BMD, beta, (95% CI): -0.2 -1.5 to 1.1), *P* = NS **Predictor: Daily calcium Intake** • TBLH BMD, beta, (95% CI): 0.0003 (-0.0008, 0.001), *P* = NS • LS BMD, beta, (95% CI): -0.00003 (-0.001, 0.001), *P* = NS • TH BMD, beta, (95% CI): -0.001 (-0.003, 0.0006), *P* = NS

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• FN BMD, beta, (95% CI): -0.0009 (-0.003, 0.0008), *P* = NS • TBD BMD, beta, (95% CI): -0.001 (-0.005, 0.003), *P* = NS • CBD BMD, beta, (95% CI): -0.0009 (-0.004, 0.003), *P* = NS **Predictor: Serum 25-OH D** • Serum 25-OH D levels were significantly associated with an increase in TH BMD z-scores • TBLH BMD, beta, (95% CI): -0.0007 (-0.04, 0.03), *P* = NS • LS BMD, beta, (95% CI): 0.001 (-0.02, 0.05), *P* = NS • TH BMD, beta, (95% CI): 0.04 (0.0006, 0.08), *P* = .048 • FN BMD, beta, (95% CI): -0.0009 (-0.008, 0.08), *P* = NS • TBD BMD, beta, (95% CI): -0.04 (-0.4, 0.3), *P* = NS • CBD BMD, beta, (95% CI): -0.06 (-0.4, 0.3), *P* = NS
Marwa (2022)[87] a multidisciplinary gender-affirming clinic in [redacted] Texas, between June 2014 and June 2019	N = 119 TGNB adolescents **Eligibility**: Transgender youth ages 9-21 years who had a dual X-ray absorptiometry (DXA) scan of the lumbar spine (LS) before or within 180 days of starting puberty suppression and/or gender-affirming hormone therapy (estrogen or testosterone). DXA scans of the LS are performed at baseline and every 1–2 years as part of standard of care guidelines in all patients being started on puberty suppression and/or gender-affirming hormone therapy **Sampling method**: 314 patient electronic records were retrospectively reviewed, 170 patients had lumbar spine BMD measurements done. Of 170, 51 patients were excluded (40 patients had a BMD measurement after 180 days of starting puberty suppression or cross-sex hormone therapy and 11 patient had BMD measurements but reports did not	• Age: The mean age (± SD) was 14.7 ±2.6 years for AMAB and 15.0 ±2.6 years for AFAB • Medical condition: Vitamin D deficiency was found in 30.4% of AMAB and in 32.4% of AFAB • Tanner stages: Advanced puberty was present in 73.9% of AMAB and in 91.3% in AFAB • BMI z-score: AFABs had a slightly higher mean BMI z-score of 0.576 - 0.976 compared with 0.056 - 1.69 in the AMAB; however, the difference was not statistically significant • Race: White participants were 87.0% of AMAB and 93.2% of AFAB • Ethnicity: Non-Hispanic were 89.1% of AMAB and 86.3% of AFAB	TGNB AMAB adolescents with Puberty suppression and/or gender-affirming hormone therapy (estrogen) (n = 46)	TGNB AFAB adolescents Puberty suppression and/or gender-affirming hormone therapy (testosterone; n = 73)	• LS BMD Z-score **Cohort:** outcomes are measured after the exposure has been measured (retrospective review of electronic medical records)	**LS BMD** • AMAB patients had a statistically significant lower adjusted LS mean BMD Z-score (-0.605 ± 1.42) compared with AFAB patients (0.043 ± 1.09) when using the gender assigned at birth reference database, *P* = .01. • The mean difference between genders was magnified when using the affirmed gender reference database (AMAB -1.753 ± 1.62, AFAB 1.045 ± 1.06, *P* < .001). • The difference between groups was not evident in patients in early puberty (AMAB -0.051 ± 1.32, AFAB 0.038 ± 0.89, *P* = NS) • The difference between groups was evident in patients in advanced puberty (AMAB -0.800 ± 1.42, AFAB 0.001 ± 1.12, *P* = .006). • In multivariate model, AMAB gender was a determinants of lower LS BMD z-score using the gender assigned at birth reference database [R2 = 0.206, regression F(3,109) = 9.4, *P* < .001]

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
	specify the device used for measurements) **Subset definition**: BMD outcome was compared between n = 46 patients (38.7%) AMAB and n = 73 patients (61.3%) AFAB (both univariate analysis and multivariate analysis). Tanner stage (coded as a binary variable with Tanner stages II and III (for breasts or testicular size) being defined as "early puberty" and stages IV or V as "advanced puberty")					
Navabi (2021)[92] Endocrine diversity clinic [redacted] Ontario	Transgender youth with GD (N = 170) **Eligibility:** Patients < 18 yrs of age with a clinic visit between January 2006 to April 2017, and at least 1 DXA measurement **Sampling method:** Reviewed 198 medical records, with 172 meeting eligibility criteria **Subset definition:** Comparisons were made between transgender males (n = 119) and transgender females (n = 51)	• Mean aBMD z-score at lumbar spine (SD), *P* < .001: ○ Transgender males: 0.04 (1.10) ○ Transgender females: −0.9 (−1.8 to 0.00) • Mean BMAD z-score at lumbar spine (SD), *P* < .001 ○ Transgender males: −0.10 (1.00) ○ Transgender females: −0.22 (1.41) • Mean aBMD z-score at left total hip (SD), *P* < .001 ○ Transgender males: 0.10 (1.06) ○ Transgender females: −0.44 (1.39) • Mean BMC z-score (SD) *P* = .001 ○ Transgender males: 0.05 (1.30) ○ Transgender females: −0.66 (1.35)	Transgender males (n = 119)	Transgender females (n = 51)	• Demographic characteristics for baseline bone mineral density **Cross-sectional:** exposures/ outcomes were measured at the same time	• Transgender females had significantly lower z-scores at lumbar spine aBMD and BMAD, and left total hip aBMD, and BMC compared to transgender males
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between patients with a BMI ≤ 85 percentile (n = 71) and those with a BMI > 85 percentile (n = 47)	N/R	Baseline BMI percentile *below* the obesity risk threshold (≤ 85; n = 71)	Baseline BMI percentile *above* the obesity risk threshold (> 85; n = 47)	• GnRH analog-induced bone mineral content changes **Cross-sectional:** exposures/ outcomes were measured at the same time	• Mean change in BMC z-score (SD): ○ BMI ≤ 85 percentile: −0.26 (0.49) ○ BMI > 85 percentile: −0.37 (0.49) • Difference (95% CI): 0.11 (−0.07 to 0.30), *P* = NS

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Schagen (2020)[94] Setting: N/R	Adolescents diagnosed with GD, eligible for hormonal treatment (N = 121) **Eligibility:** Diagnosed with GD (per DSM-IV-TR), eligible for treatment according to guidelines, had DXA scans available at the start of GnRH analog treatment, and were seen from 1998 to 2009 **Sampling method:** N/R **Subset definition:** Comparisons were made between transgender females (n = 51) and transgender males (n = 70)	• Mean age at the start of GnRH analogs (yrs, SD), *P* = NS: ○ Transgender females: 14.1 (1.7) ○ Transgender males: 14.5 (2.0) • Mean age at the start of CSH (yrs, SD), P value = 0.005 ○ Transgender females: 16.2 (1.2) ○ Transgender males: 16.9 (1.1) • Duration of GnRH analogs use before starting CSH (yrs, SD), *P* = NS: ○ Transgender females: 2.0 (0.94) ○ Transgender males: 1.8 (1.11)	Transgender females starting GnRH analogs (n = 51)	Transgender males starting GnRH analogs (n = 70)	• Demographic characteristics **Cross-sectional:** exposures/outcomes were measured at the same time	• Transgender males were significantly older at the start of CSH compared to transgender females
	Population, eligibility, and sampling method is the same as above. **Subset definition:** Comparisons were made between early pubertal transgender females (n = 15) and males (n = 14), and late-pubertal transgender females (n = 36) and males (n = 56)	• Mean BMAD z-score at the lumbar spine in transgender females at the start of GnRH analogs: ○ Early pubertal (n = 15): −0.33 (0.33) ○ Late pubertal (n = 36): −0.65 (0.20) • Mean BMAD z-score at the hip in transgender females at the start of GnRH analogs: ○ Early pubertal (n = 15): −0.94 (0.27) ○ Late pubertal (n = 36): −1.01 (0.17) Mean BMAD z-score at the lumbar • spine in transgender males at the start of GnRH analogs: ○ Early puberty (n = 14): −0.15 (0.29) ○ Late puberty (n = 56): 0.33 (0.14) • Mean BMAD z-score at the hip in transgender males at the start of GnRH analogs: ○ Early puberty (n = 14): −0.23 (0.25) ○ Late puberty (n = 56): 0.04 (0.12)	Early pubertal transgender subjects: • Early pubertal transgender females (n = 15) • Early pubertal transgender males (n = 14)	Late-pubertal transgender subjects: • Late-pubertal transgender females (n = 36) • Late-pubertal transgender males (n = 56)	• BMD z-scores • Serum bone markers (P1NP, P3NP, 1CTP, osteocalcin) **Cohort:** outcomes were measured at baseline, 12 months, 24 months, and 36 months	• Numerically, pubertal and late-pubertal transgender males had higher BMAD z-scores at the lumbar spine and hip than pubertal and late-pubertal transgender females at the start of GnRH analog treatment • At baseline, there were no significant difference between any of the bone markers of early and late transgender females • At baseline, early pubertal transgender males had significantly higher P1NP, P3NP, 1CTP, and osteocalcin than late-pubertal transgender males • Early pubertal transgender females and males were on GnRH analogs for a significantly longer time than late-pubertal transgender and males (*P* < .001) ○ Early pubertal transgender females: 2.5 yrs ○ Early pubertal transgender males: 4.0 yrs ○ Late-pubertal transgender females: 1.5 yrs ○ Late-pubertal transgender males: 1.7 yrs • Before starting CSH, early pubertal transgender females had significantly higher levels of P1NP, P3NP, and 1CTP compared to late-pubertal transgender girls • Early pubertal transgender males had significantly higher levels of P1NP and P3NP prior to starting CSH compared to late-pubertal transgender males

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
Vlot (2017)[99] [redacted] the Netherlands between 2001 and 2011.	Adolescents with diagnosed gender dysphoria (N = 70) **Eligibility**: Adolescents with diagnosed gender dysphoria, a serum BTM measurement of P1NP, osteocalcin or carboxy terminal cross linked telopeptide of type I collagen (ICTP) within 90 days before or after time point D0, C0 and C24, and/or a DXA-scan of the lumbar spine (LS) and/or femoral neck (FN) performed within 90 days before or after time point D0, C0 and C24. **Sampling method**: Adolescents diagnosed with gender dysphoria who were treated with GnRH analogs and CSHT were recruited at their clinic; data and records were retrospectively reviewed. **Subset**: Comparisons were made between trans women (n = 28) and trans men (n = 42). Participants were categorized into young and old pubertal group, based on their bone age at beginning of treatment. Young trans men (n = 7), old trans men (n = 15), young trans women (n = 9) and old trans women (n = 6) were all compared to each other.	All were treated with GnRH analog triptorelin and CSHT (estrogen for trans women and testosterone for trans men) was added in incremental doses from the age of 16 years. • Median ages in years (range) in trans men at start of GnRH analogs, at start of CSHT, and 24 months after initiation of CSHT were 15.1 (11.7-18.6), 16.3 (15.9–19.5) and 18.3 (17.9–21.5), respectively • Median ages in years (range) in trans women, were 13.5 (11.5–18.3), 16.0 (14.0–18.9) and 18.0 (16.0–20.9), respectively. • Median bone ages in years (range) in trans men at start of GnRH analogs, at start of CSHT, and 24 months after initiation of CSHT were 15 (12–17), 16 (12–17) and 17 (14–17), respectively • Median bone ages in years (range) in trans women, were 13.5 (10–17), 14 (13–17) and 16.75 (14.5–17), respectively.	Treated TGNB patient comparisons were made between the following groups: • Trans men ○ Young trans men (n = 7) ○ Old trans men (n = 15) • Trans women ○ Young trans women (n = 9) ○ Old trans women (n = 6)	Treated TGNB patient comparisons were made between the following groups: • Trans men ○ Young trans men (n = 7) ○ Old trans men (n = 15) • Trans women ○ Young trans women (n = 9) ○ Old trans women (n = 6)	• BTMs: The formation markers P1NP and osteocalcin and the resorption marker ICTP were measured in non-fasting state. • BMAD: A DXA-scan was used to measure BMD in g/cm² of the LS and FN of the non-dominant hip. To correct for height and height gain the volumetric bone mineral apparent density (BMAD) in g/cm3 for both LS and FN was calculated. BMAD Z-scores were calculated for sex assigned at birth using an UK reference population. **Cohort Study:** exposures/ outcomes were measured at 3 moments in time: At the start of GnRH analog treatment, at the start of CSHT and 24 months after the start of CSHT	P1NP: median (range), mg/L • At baseline, young trans men showed higher concentrations of P1NP compared to the old trans men (783 (516–1090) vs. 110 (38–471), *P* = .02) • At baseline, young trans women showed higher concentrations of P1NP compared to old trans women (935 (617–1348) vs. 191 (96–792), *P* = .03) • Old trans women showed borderline higher concentrations of P1NP at baseline than old trans men (191 (96–792 vs. 110 (38–471), *P* = 0.05) Osteocalcin median (range), mg/L • At baseline, young trans men showed higher concentrations of osteocalcin compared to the old trans men (5 (2.2–11.7) vs. 2.4 (0.4–4.6), *P* = .02) • At baseline, young trans women showed higher concentrations of osteocalcin compared to old trans women (4.8 (2.6–21.9) vs. 2.29 (0.8–11), *P* = .03) • No difference between trans men and trans women was found. 1CTP: median (range), mg/L • At baseline, young trans men showed higher concentrations of ICTP compared to the old trans men (24 (17–29.9) vs. 7 (5.2–15), *P* = .02). • No significant difference between young trans women and old trans women was found (23 (15–34) vs. 12 (6.9–21), *P* = NS). • Trans men and trans women did not differ regarding ICTP concentrations at baseline. BMAD FN: median (range), g/cm³ • BMAD FN did not differ at baseline between young and old trans men (0.31 (0.26–0.36) vs. 0.33 (0.25–0.39), *P* = NS). • BMAD FN did not differ at baseline between young and old trans women (0.29 (0.20–0.33) vs. 0.30 (0.26–0.36), *P* = NS) was found. • trans men and trans women did not differ regarding their BMAD FN at baseline. BMAD FN Z-scores: median (range)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.5. Clinical studies with between-TGNB-group comparisons examining bone health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention/ risk factor	Comparator	Outcome measures and timing	Results
						• Young trans women group showed a lower BMAD-Z score compared to young trans men at C24 (−1.3 (−3.51–0.92) vs. -0.37 (−2.03–0.85), *P* = .02). BMAD LS, median (range), g/cm^3 • At baseline, the young trans women had a lower BMAD LS than the young trans men (0.21 (0.17–0.25) vs. 0.26 (0.21–0.29), *P* = .003). • At baseline, there was no difference between young and old trans men, young and old trans women, or between old trans men and old trans women. BMAD LS Z-scores: median (range) • At baseline, young trans men showed a lower Z-score compared to old trans men (−0.05 (−0.78–2.94) vs. 0.27 (−1.6–1.8), *P* = .02)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; cm, centimeters; CBD, Cortical BMD; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; DXA, dual-energy radiograph absorptiometry; FN, femoral neck; GAH, gender-affirming hormones; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analog/analog; kg, kilogram; m, meter; LS, lumbar spine; N/R, not reported; N/S, not significant; TGNB, transgender/nonbinary; yr(s), year(s); PAQ-C, Physical Activity Questionnaire for Older-Children; TBD, Trabecular BMD; TBLH, total body less head; TH, total hip

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
Chiniara 2018[76] [redacted] between January 2014 and June 2016	TGNB participants (N = 203) **Eligibility**: Age 12–18 years, presence of gender dysphoria, desire for pubertal suppression or cross-gender hormone administration, ability to read and comprehend English, and deemed appropriate by TYC staff to fill out baseline and follow-up mental health questionnaires (i.e., youth with extreme anxiety or learning disability were excluded). Youth who exhibited discomfort in their assigned gender less than 6 months were also included as they were deemed likely to benefit from puberty suppression. **Sampling method:** Adolescents who did not follow up at the clinic after the first visit were excluded (n = 12). Three adolescents had their initial visit for gender dysphoria at another center and were excluded from this analysis because of missing data. **Subset definition**: Comparisons were made between N = 156 (76.8%) AFAB individuals and N = 47 (23.2%) AMAB individuals During the study period, 115 individuals were treated with GnRH analog therapy.	• Age: Mean age ± standard deviation in the assigned female group was 16.3 ±1.63 and in the assigned male group was 16.1 ±1.70, with between groups P value of 0.606. • Tanner stage: Mean Tanner stage ± standard deviation in the assigned female group was 4.42 ±0.76 and in the assigned male group was 4.03 ±1.1, with between groups P value of 0.040. The majority of assigned females N = 61 (54.5%) were on Tanner stage 5 and the majority of assigned males N = 14 (45.2%) were on Tanner stage 5 as well. • Bone age: Mean bone age ± standard deviation in the assigned female group was 15.9 ±1.3 and in the assigned male group was 15.8 ±2.2, with between groups P value of 0.991. • Height: Mean height ± standard deviation, in cm, in the assigned female group was 162.8 ±7.1 and in the assigned male group was 167.2 ±11.5. Mean height Z score ± standard deviation in the assigned female group was 0.11 ±1.02 and in the assigned male group was –0.50 ±1.06, with between groups P value of 0.002. • Weight: Mean weight ± standard deviation, in kg, in the assigned female group was 64.7 ±15.8 and in the assigned male group was 64.7 ±19.3. Mean weight Z score ± standard deviation in the assigned female group was 0.75 ±1.20 and in the assigned male group was 0.19 ±1.37, with between groups P value of 0.020.	AFAB on testosterone (n = 156)	AMAB on estradiol (n = 47)	**Laboratory data:** The baseline blood tests were performed according to the initial 2009 Endocrine Society guidelines. In a subset of individuals, blood testing was repeated while receiving gender-affirming hormones (after 6–12 months) according to the initial 2009 Endocrine Society guidelines including • Total cholesterol • High-density lipoprotein • Low-density lipoprotein • Triglycerides • Hemoglobin • Red blood cell count **Cohort Study:** outcomes are measured after the exposure has been measured (retrospective chart review)	Hemoglobin levels • Significantly increased in AFAB on testosterone, *P* = 0.002, highest value 166 g/L • Significantly decreased in AMAB on estradiol, *P* = 0.019, lowest value 132 g/L • Statistically significant sex hormone-associated differences, *P* < .05 • Hemoglobin levels stayed within normal limits Red blood cell count • Significantly increased in AFAB, highest value 5.38 × 1012 • Significantly decreased in AMAB, lowest 4.34 × 1012 • Statistically significant sex hormone-associated differences, *P* = 0.001 Lipid levels • No significant change from baseline following therapy in either AFAB nor AMAB, but this could be due to the limited number of repeat lipid profile tests (AFAB, n = 8; AMAB, n = 4).

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		• BMI: Mean BMI ± standard deviation in the assigned female group was 24.2 ±5.4 and in the assigned male group was 23.0 ±5.8. Mean BMI Z score ± standard deviation in the assigned female group was 0.78 ±1.21 and in the assigned male group was 0.49 ±1.40, with between groups P value of 0.238. • Ethnicity: In this cohort, youth of Caucasian descent were overrepresented, whereas visible minorities were under-represented, except for First Nations youth. There was no statistically significant difference in the ethnicity profile between assigned females and assigned males. • Comorbidities: In this cohort, assigned females had more mood disorders than assigned males. There was a statistically significant difference when comparing comorbidities between the assigned female and assigned male group (*P* = 0.008, Pearson's chi-squared)				
Karakilic Ozturan (2023)[112] A tertiary pediatric endocrinology clinic in Turkey.	TGNB adolescents (N = 28) • **Eligibility**: Participants must have been diagnosed with GD based on DSM-5 diagnostic criteria by a mental health professional after at least six months of psychiatric follow-up and must have been referred to the GD outpatient clinic. They could not start hormone treatment without informed consent from both themselves and their legal guardians. They must have stayed below the age	Age, median (IQR), years: • MTF starting GnRH analogs: 16.7 (1.2) • FTM starting GnRH analogs: 16.7 (1.0) • *P* = NS	MTF adolescents that started GnRH analogs (N = 9)	FTM adolescents that started GnRH analogs (N = 13)	• Physical examination done by the same examiner each visit. Blood pressure was taken, height and weight were measured, and BMI calculated. • Standard deviation scores (SDS) were calculated according to age and natal sex • Complete blood count, glucose and lipid profile was performed at the third and sixth month of treatment and every 6 months thereafter.	BMI, median (IQR) • There was no significant difference in the BMI of the MTF cohort of 24.8 (5.8) kg/m² vs. 23.1 (4.5) kg/m²) in the FTM cohort, *P* = NS BMI SDS, median (IQR) • There was no significant difference in the BMI SDS of the MTF cohort of 0.7 (1.5) vs. 0.7 (1.5) in the FTM cohort, *P* = NS Systolic BP, median (IQR) • There was no significant difference in the systolic BP of the MTF cohort of 110 (20) mmHg vs. 107.5 (11) mmHg in the FTM cohort, *P* = NS Diastolic BP, median (IQR)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	of 18 during the follow-up period of the study (3-6 months). • **Sampling Method**: Authors retrospectively examined the medical records of all adolescents diagnosed with GD after at least 6 months of psychiatric follow-up and that were referred to their GD outpatient clinic between 2016 and 2022. • Subset Definition: There were n = 13 MTF participants and n = 15 FTM participants. From this group, comparisons were made between: o MTF starting GnRH analogs (n = 6) vs FTM starting GnRH analogs (n = 13) o MTF who took GnRH analogs and then started CSH (n = 6) vs MTF who took combined androgen receptor blocker and then started CSH (n = 6) o MTF participants who were starting CSH (combined group whose previous treatment was GnRH analogs and combined androgen receptor blocker) (n = 12) vs. FTM starting CSH (n = 9)				**Cross Sectional:** Exposures/ Outcomes were measured at one point in time at the initiation of GnRH analogs	• The MTF cohort had a significantly higher diastolic BP of 80 (10) mmHg vs. 69 (8.8) mmHg in the FTM cohort, *P* = .023 PRL, median (IQR) • There was no significant difference in the PRL levels of the MTF cohort of 8.4 (10.8) ng/mL vs. 15.2 (4.1) ng/mL in the FTM cohort, *P* = NS Glucose, median (IQR) • There was no significant difference in the glucose levels of the MTF cohort of 86.5 (5.1) mg/dL vs. 86 (10.5) mg/dL in the FTM cohort, *P* = NS Insulin, median (IQR) • There was no significant difference in the insulin levels of the MTF cohort of 13.3 (16.6) ug/mL vs. 9.0 (4.4) ug/mL in the FTM cohort, *P* = NS HbA1c, median (IQR) • There was no significant difference in the HbA1c % of the MTF cohort of 5.4 (0.4) % vs. 5.0 (0.2) %in the FTM cohort, *P* = NS Total cholesterol, median (IQR) • There was no significant difference in the total cholesterol levels of the MTF cohort of 183 (54.9) mg/dL vs. 157.7 (47.5) mg/dL in the FTM cohort, *P* = NS Triglycerides, median (IQR) • The MTF cohort had significantly higher triglyceride levels of 115 (26.8) mg/dL vs. 63 (13.9) mg/dL in the FTM cohort, *P* = .005 HDL, median (IQR) • The MTF cohort had significantly lower HDL levels of 40 (1.9) mg/dL vs. 55 (4.7) mg/dL in the FTM cohort, *P* < .001 LDL, median (IQR) • There was no significant difference in the LDL levels of the MTF cohort of 130 (48.5) mg/dL vs. 91.5 (50.3) mg/dL in the FTM cohort, *P* = NS

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1) • MTF with combined androgen receptor blocker treatment: 17.5 (1.3) • *P* = NS	MTF adolescents that used GnRH analogs before starting CSH (N = 6)	MTF adolescents that used combined androgen receptor blockers before starting CSH (N = 6)	• Physical examination done by the same examiner each visit. Blood pressure was taken, height and weight were measured, and BMI calculated. • Standard deviation scores (SDS) were calculated according to age and natal sex • Complete blood count, glucose and lipid profile was performed at the third and sixth month of treatment and every 6 months thereafter. **Cross-sectional:** Outcomes were measured at one point of time before participants started CSH	BMI, median (IQR) • There was no significant difference in the BMI of the GnRH analog group of 20.1 (0.7) kg/m² vs. 19.8 (5.9) kg/m² in the combined androgen receptor blocker group, *P* = NS BMI SDS, median (IQR) • There was no significant difference in the BMI SDS of the GnRH analog group of -1.2 (0.7) vs. -0.9 (2.1) in the combined androgen receptor blocker group, *P* = NS Systolic BP, median (IQR) • There was no significant difference in the systolic BP of the GnRH analog group of 105 (10) mmHg vs. 105 (15) mmHg in the combined androgen receptor blocker group, *P* = NS Diastolic BP, median (IQR) • There was no significant difference in the diastolic BP of the GnRH analog group of 67.5 (6.3) mmHg vs. 62.5 (8.8) mmHg in the combined androgen receptor blocker group, *P* = NS PRL, median (IQR) • There was no significant difference in the PRL levels of the GnRH analog group of 16.1 (3.8) ng/mL vs. 12.3 (4.0) ng/mL in the combined androgen receptor blocker group, *P* = NS Glucose, median (IQR) • There was no significant difference in the glucose levels of the GnRH analog group of 90 (5.0) mg/mL vs. 93.5 (7.8) mg/mL in the combined androgen receptor blocker group, *P* = NS Insulin, median (IQR) • There was no significant difference in the insulin levels of the GnRH analog group of 9.7 (3.2) ug/mL vs. 9.1 (2.3) ug/mL in the combined androgen receptor blocker group, *P* = NS HbA1c, median (IQR) • There was no significant difference in the HbA1c % of the GnRH analog group of 5.6 (0) % vs. 5.1 (0.5) % in the combined androgen receptor blocker group, *P* = NS Total cholesterol, median (IQR)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• There was no significant difference in the total cholesterol levels of the GnRH analog group of 167.8 (45.3) mg/dL vs. 166.3 (14.1) mg/dL in the combined androgen receptor blocker group, *P* = NS Triglycerides, median (IQR) • There was no significant difference in triglyceride levels of the GnRH analog group of 87.5 (59.4) mg/dL vs. 74.6 (31.4) mg/dL in the combined androgen receptor blocker group, *P* = NS HDL, median (IQR) • There was no significant difference in HDL levels of the GnRH analog group of 59.1 (19.3) mg/dL vs. 55.5 (16.1) mg/dL in the combined androgen receptor blocker group, *P* = NS LDL, median (IQR) • There was no significant difference in LDL levels of the GnRH analog group of 95.3 (20.8) mg/dL vs. 90 (17.3) mg/dL in the combined androgen receptor blocker group, *P* = NS
		Age, median (IQR), years: • MTF with GnRH analog treatment: 17.3 (1.1) • MTF with combined androgen receptor blocker treatment 17.5 (1.3) • FTM: 17.8 (0.4) • *P* = NS	MTF adolescents that used either GnRH analogs or combined androgen receptor blockers before starting CSH (N = 12)	FTM adolescents that used GnRH analogs before starting CSH (N = 9)	• Physical examination done by the same examiner each visit. Blood pressure was taken, height and weight were measured, and BMI calculated. • Standard deviation scores (SDS) were calculated according to age and natal sex • Complete blood count, glucose and lipid profile was performed at the third and sixth month of treatment and every 6 months thereafter. Cross-sectional: Outcomes and measures were taken at one point of time at the start of CSH	BMI, median (IQR) • There was a no significant difference in the BMI of the MTF cohort [20.1 (0.7) kg/m² and 19.8 (5.9) kg/m²] compared to the FTM cohort at 24.5 (6.9) kg/m², *P* = NS BMI SDS, Median, IQR • There was a no significant difference in the BMI SDS of the MTF cohort [1.2 (0.7) and -0.9 (2.1)] compared to the FTM cohort at 1.1 (2.9), *P* = NS Systolic BP, median (IQR) • There was no significant difference in the systolic BP of the MTF cohort of 105 (10) mmHg and 105 (15) mmHg vs. 110 (14) in the FTM cohort, *P* = NS Diastolic BP, median (IQR) • There was no significant difference in the diastolic BP of the MTF cohort of 67.5 (6.3) mmHg and 62.5 (8.8) mmHg vs. 70 (7.5) mmHg in the FTM cohort, *P* = NS PRL, median (IQR)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• There was no significant difference in the PRL levels of the MTF cohort of 16.1 (3.8) ng/mL and 12.3 (4.0) ng/mL vs. 12.7 (5.1) ng/mL in the FTM cohort, *P* = NS Glucose, median (IQR) • There was no significant difference in the glucose levels of the MTF cohort of 90 (5.0) mg/mL and 93.5 (7.8) mg/mL vs. 89 (4.0) mg/dL in the FTM cohort, *P* = NS Insulin, median (IQR) • There was no significant difference in the insulin levels of the MTF cohort of 9.7 (3.2) ug/mL and 9.1 (2.3) ug/mL vs. 12.6 (3.2) in the FTM cohort, *P* = NS HbA1c, median (IQR) • There was no significant difference in the HbA1c % of the MTF cohort of 5.6 (0) % and 5.1 (0.5) % vs. 5.2 (0.1) % in the FTM cohort, *P* = NS Total cholesterol, median (IQR) • There was no significant difference in the total cholesterol levels of the MTF cohort of 183 (54.9) mg/dL and 157.7 (47.5) mg/dL vs. 158 (46) mg/dL in the FTM cohort, *P* = NS Triglycerides, median (IQR) • There was no significant difference in the triglyceride levels of the MTF cohort of 87.5 (59.4) mg/dL and 74.6 (31.4) mg/dL vs. 57 (14.1) in the FTM cohort, *P* = NS HDL, median (IQR) • There was no significant difference in the HDL levels of the MTF cohort of 59.1 (19.3) mg/dL and 55.5 (16.1) mg/dL vs. 52.3 (16.1) mg/dL in the FTM cohort, *P* = NS LDL, median (IQR) • There was no significant difference in the LDL levels of the MTF cohort of 95.3 (20.8) mg/dL and 90 (17.3) mg/dL vs. 94.5 (42.5) mg/dL in the FTM cohort, *P* = NS
Martinez-Martin (2023)[86] Outpatient gender identity clinic, [redacted]	TGNB subjects (N = 302) **Eligibility**: Subjects who started CSHT at the clinic since it opened in March 2000 and < 30 years of age,	Mean age (yrs, SD): • Spironolactone: 17.1 (4.1) • LHRH analog: 16.2 (1.1)	Transgender women taking estradiol + spironolactone (n = 54)	Transgender women taking estradiol + an LHRH analog (n = 26)	• 5-yr follow-up of baseline characteristics • Incidence of HTN	Mean weight change at 5-yr follow-up (kg, SD), *P* < .05: • Spironolactone: 5.3 (3.2) • LHRH analog: 8.4 (6.5)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
[redacted] (Spain)	with at least 5 years of follow-up. Patients were excluded if they were only treated with LHRH analogs, discontinued hormonal therapy or switched to androgen blockers due to having pre-existing HTN, or refused to give informed consent **Sampling method**: 811 medical records were reviewed. After excluding 509 patients, 302 were included in the study **Subset definition**: Comparisons were made between transgender women taking estradiol + spironolactone (n = 54) and transgender women taking estradiol + an LHRH analog (n = 26)	Mean weight (kg, SD): • Spironolactone: 68.5 (11.6) • LHRH analog: 65.6 (10.1) Mean glucose (mmol/L, SD): • Spironolactone: 5.2 (0.6) • LHRH analog: 4.9 (0.4) Mean cLDL (mmol/L, SD): • Spironolactone: 2.4 (0.6) • LHRH analog: 2.3 (0.7) Mean triglycerides (mmol/L, SD): • Spironolactone: 1.6 (0.8) • LHRH analog: 1.5 (0.9) Mean SBP (mmHg, SD): • Spironolactone: 121 (12) • LHRH analog: 119 (13)			**Cohort**: outcomes are measured at the 5-yr follow-up	Mean glucose change at 5-yr follow-up (mmol/L, SD), *P* = NS: • Spironolactone: 0.3 (0.3) • LHRH analog: 0.5 (0.4) Mean cLDL change at 5-yr follow-up (mmol/L, SD), *P* = NS: • Spironolactone: 0.4 (0.3) • LHRH analog: 0.5 (0.4) Mean triglyceride change at 5-yr follow-up (mmol/L, SD), *P* = NS: • Spironolactone: 0.4 (0.2) • LHRH analog: 0.6 (0.4) Mean SBP change at 5-yr follow-up (mmHg, SD), *P* < .05: • Spironolactone: 2 (1) • LHRH analog: 6 (2) Those who had HTN at the 5-yr follow-up (n, %), *P* = NS: • Spironolactone: 1 (1.8) • LHRH analog: 2 (7.7%) Yearly incidence of HTN (%, 95% CI), *P* = NS: • Spironolactone: 0.37 (0.00 to 0.74) • LHRH analog: 1.54 (0.45 to 2.63) Spironolactone and LHRH analog use were nonsignificant predictors for the development of HTN Spironolactone was shown to have a marginally protective effect (OR: 0.632, *P* = NS), but LHRH analog use did not (OR: 1.103, *P* = NS)

Maru (2021)[128] [redacted]	Patients with GD, with or without T1DM (N = 1,114)
	Eligibility: Patients with GD presenting to the clinic between January 1, 2007 and December 31, 2018.
	Sampling method: Patients with GD and T1DM were identified by diagnostic ICD-9 or -10 codes
		Mean age at first gender clinic visit (yrs, SD), *P* < .05:
		• TGD: 13 (3.7)
		• TGD + T1DM: 16 (2.7)
		Race, *P* = NS:
		• White:
		  ○ TGD: 806 (72)
		  ○ TGD + T1DM: 8 (72)
			TGD patients with GD who presented to the clinic between January 2007 and December 2018 (N = 1,114)	TGD patients with GD and T1DM who presented to the clinic between January 2007 and December 2018 (n = 11)	Demographic characteristics
					Cross-sectional: exposures/ outcomes were measured at the same time
						There were no significant differences between TGD patients and those with T1DM for race, designated sex, affirmed gender, or proportion receiving hormonal treatment (ie, GnRH analogs or CSHT)
						Patients with T1DM had their first gender clinic visit at a significantly older age than the overall clinic population (*P* = .007)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Subset definition: Comparisons were made between TGD patients (N = 1,114) and TGD patients with T1DM (n = 11)	• Hispanic/Latino: ○ TGD: 61 (5.5) ○ TGD + T1DM: 1 (9) • African American: ○ TGD: 30 (2.7) ○ TGD + T1DM: 2 (18) • American Indian or Alaskan Native: ○ TGD: 6 (0.5) ○ TGD + T1DM: 0 (0) • Asian: ○ TGD: 27 (2.4) ○ TGD + T1DM: 0 (0) • Other/unknown: ○ TGD: 184 (17) ○ TGD + T1DM: 0 (0) Designated sex, *P* = NS: • Male: ○ TGD: 390 (35) ○ TGD + T1DM: 2 (18) • Female: ○ TGD: 724 (65) ○ TGD + T1DM: 9 (82) Affirmed gender, *P* = NS: • Male: ○ TGD: 663 (60) ○ TGD + T1DM: 8 (73) • Female: ○ TGD: 353 (32) ○ TGD + T1DM: 2 (18) • Nonbinary: ○ TGD: 98 (8.8) ○ TGD + T1DM: 1 (0.09)				

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		Received GnRH analogs, *P* = NS: • TGD: 177 (16) • TGD + T1DM: 2 (18) Received CSHT, *P* = NS: • TGD: 482 (43) • TGD + T1DM: 9 (82)				
Millington (2019)[88] [redacted] from 2007 to 2017	N = 85 TGNB participants • Subjects with hyperkalemia: n = 6 • Subjects without hyperkalemia: n = 79 **Eligibility**: Gender-diverse youth of any age seen in the hospital from 2007 to 2017 and subjects who were prescribed spironolactone for the purposes of gender transition were included in the analysis. **Sampling method:** By retrospective chart review, N = 90 gender-diverse adolescents were prescribed spironolactone during the study period. N = 2 patients were prescribed spironolactone for indications other than gender transition and were excluded. N = 3 patients were excluded because there were no potassium measurements recorded after spironolactone was initiated. As a result, N = 85 subjects were included in the analysis.	• Age: Mean (SD) age at spironolactone start, in years, in all subjects was 16.6 (1.7), in subjects without hyperkalemia group was 16.7 (1.7), and in subjects with hyperkalemia group was 16.0 (1.4). • Gender identity: Female gender identity, n (%), in all subjects was 82 (96%), in subjects without hyperkalemia group was 76 (96%), and in subjects with hyperkalemia group was 6 (100%). • Race: For race, n (%), majority in all subjects was white 59 (69%), in subjects without hyperkalemia group was white 54 (68%), and in subjects with hyperkalemia group was white 5 (83%). • GnRH analog: 19 (22%), 18 (23%), and 1 (17%) in all subjects, in subjects without hyperkalemia group, and in subjects with hyperkalemia group, respectively, were using GnRH analog. • Estrogen: 73 (86%), 68 (86%), and 5 (83%) in all subjects, in subjects without hyperkalemia group, and in subjects with hyperkalemia group, respectively, were using estrogen. • Potassium measurements: Median (range) number of potassium measurements per subject in all subjects was 3 (1–10), in subjects	Spironolactone (100-200 mg/d, > 200 mg/d)	Spironolactone (< 100 mg/d)	• **Potassium measurements:** Potassium measurements were available for up to 7 years of spironolactone therapy. Hyperkalemia was defined as a serum potassium concentration > 5.0 mmol/L. **Cohort Study**: outcomes are measured after the exposure has been measured (retrospective chart review	Association between dose of spironolactone and hyperkalemia: • For spironolactone < 100 mg/d, number of potassium measurements > 5.0 mmol/L/total number of potassium measurements (%) was 2/17 (11.8%). • For spironolactone 100-200 mg/d, number of potassium measurements > 5.0 mmol/L/total number of potassium measurements (%) was 2/74 (2.7%). • For spironolactone > 200 mg/d, number of potassium measurements > 5.0 mmol/L/total number of potassium measurements (%) was 3/98 (3.1%). • Compared to spironolactone < 100 mg/d, the relative risk (95% CI) of hyperkalemia for spironolactone 100-200 mg/d was 0.23 (0.03–1.52), *P* = NS. • Compared to spironolactone < 100 mg/d, the relative risk (95% CI) of hyperkalemia for spironolactone > 200 mg/d was 0.26 (0.05–1.44), *P* = NS • There was no increased risk of hyperkalemia with a higher spironolactone dose. Serum Potassium concentrations vs dose/treatment length • Serum potassium concentration is not correlated with spironolactone dose (*P* = NS) • There is a significant trend toward lower serum potassium concentration with longer duration of treatment. • When the potassium measurements > 5.0 mmol/L were excluded, there was no correlation between serum potassium concentration and duration of spironolactone exposure. Incidence of hyperkalemia:

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		without hyperkalemia group was 3 (1–10), and in subjects with hyperkalemia group was 4.5 (1–8). • Baseline potassium measurement: Baseline potassium measurement available, n (%), in all subjects was 70 (82%), in subjects without hyperkalemia group was 65 (82%), and in subjects with hyperkalemia group was 5 (83%). • Serum potassium: Mean (SD) serum potassium, in mmol/L, in all subjects was 4.25 (0.4), in all subjects without hyperkalemia group was 4.20 (0.3), and in subjects with hyperkalemia group was 4.65 (0.5). • Spironolactone dose: Mean (SD) spironolactone dose, in mg/d, in all subjects was 105 (42), in all subjects without hyperkalemia group was 105 (42), and in subjects with hyperkalemia group was 108 (49).				• Eight potassium measurements in six subjects exceeded 5.0 mmol/L. When these measurements were excluded, the rate of hyperkalemia was 2.2%. • There were no cases of hyperkalemia in the baseline measurements. • All cases of hyperkalemia occurred early in the treatment course (< 6 months after starting spironolactone). • There were no potassium measurements > 6.0 mmol/L.
Millington (2021)[89] [redacted] between July 2016 and September 2018	N = 269 TGNB adolescents **Eligibility**: no prior GnRH analog use, starting CSH **Sampling method:** recruited (not more detail provided) **Subset definition:** Comparisons were made between obese and non-obese TGNB adolescents DMAB receiving testosterone (n = 83)	Baseline HDL-C levels (mean, SD, 95%CI), *P* = .01 • Non-obese: 46.1 mg/dL (8.8), 95% CI (43.8 to 48.4) • Obese: 36.0 mg/dL (1.0), 95% CI (35.2 to 36.8)	Obese DMAB	Non-obese DMAB	• Laboratory and anthropometric data were collected as part of clinical care at baseline and at 6 and 12 months after beginning CSH. Obesity was defined as a baseline body mass index more than the 95th percentile for designated sex. **Cohort Study:** Outcomes were measured at baseline and then 6 months after treatment with CSH	HDL-C level, mean (SD) • Participants who were DMAB with obesity had lower HDL-C levels at baseline than participants who were DMAB without obesity, *P* = .01 • Participants who were DMAB with obesity showed no significant change in HDL-C levels after 6 months of estradiol treatment from 36.0 [1.0] mg/dL to 41.3 [4.0] mg/dL; 95% CI, 35.2-36.8 vs 37.6-45.0; *P* = NS, compared to all participants who were DMAB, HDL-C levels increased by 11.2 (8.8) mg/dL (95% CI, 8.6-13.8; *P* < .001) • Obesity attenuated the benefit of estradiol treatment on HDL-C levels after 6 months
	N = 269 TGNB adolescents **Eligibility**: no prior GnRH analog use, starting CSH	Baseline HDL-C levels (mean, SD, 95%CI), *P* = NS • Non-obese: 53.5 mg/dL (12.4), 95% CI (51.3 to 55.0)	Obese DFAB	Non-obese DFAB	• Laboratory and anthropometric data were collected as part of clinical care at baseline and at 6 and 12 months after beginning	HDL-C level, mean (SD) • For participants who were DFAB, baseline HDL-C levels were not significantly different between participants with and without obesity, *P* = NS

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Sampling method: recruited (not more detail provided) **Subset definition**: Comparisons were made between obese and non-obese TGNB adolescents DFAB receiving testosterone (n = 186)	• Obese: 48.9 mg/dL (12.2), 95% CI (44.8 to 53.0)			CSH. Obesity was defined as a baseline body mass index more than the 95th percentile for designated sex. **Cohort Study:** Outcomes were measured at baseline and then 6 months after treatment with CSH	• The fall in HDL-C levels of DFAB participants with testosterone was significantly more pronounced in participants with obesity than without obesity (−12.1 [9.9] mg/dL vs −5.5 [9.7] mg/dL; 95% CI, −16.3 to −7.9 vs −7.7 to −3.4; *P* = .004) • Obesity exacerbated the negative association of testosterone treatment outcomes after 6 months, with the decrease in HDL-C levels being more pronounced.
Millington (2022)[90] Four large hospitals-[redacted], that were taking part in the Trans Youth Care United States Study	N = 286 TGNB patients Eligibility: clinician diagnosed gender therapy with gender affirming therapy deemed appropriate, received care at the clinic, age 8-20 and reads and understands English. Those who previously used CSH were enrolled in the puberty blocker cohort or had severe psychiatric symptoms were excluded Sampling method: patients were selected from clinic if they met inclusion criteria. Subset definition: DMAB (n = 92) and DFAB (n = 194) measured at baseline and 6 mo increments	**DMAB**: • Age: 17.3 years • Gender: ○ 51 identified as trans female ○ 36 as female ○ 1 as gender fluid ○ 4 as non-binary • CSHT: ○ 77 were taking oral estrogen ○ 12 were taking transdermal estrogen ○ 3 were taking IM estrogen. ○ 58 used spironolactone **DFAB**: Age: 16.2 years Gender: 78 identified as male ○ 103 as transgender male ○ 2 as gender fluid ○ 1 as gender queer ○ 10 as non-binary CSHT: ○ 189 were taking testosterone SQ ○ 5 were taking testosterone gel. ○ 1 used spironolactone	DFAB- testosterone- average SQ dose was 40 mg/week, average transdermal dose was 40.5 mg/day after 12 months of treatment	DMAB at baseline	• Serum Creatinine (SCr) levels were compared at one point in time-baseline of the DMAB group and 12 months of treatment for the DFAB group • SCr was then adjusted by age and gender to calculate SCr/Q male and SCr/Q female **Cross sectional:** Exposure and outcome are measured at a single point in time. Baseline (DMAB) and 12 mo. post intervention (DFAB) levels were being compared.	DFAB has similar SCr to DMAB at baseline after 12 months of testosterone treatment (0.82 vs 0.83) (*P* = NS)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Same as above	Same as above	DMAB- estrogen, average oral dose 4 mg/day, average transdermal dose 0,5 mg/day, average IM dose was 15 mg/week after 12 months of treatment	DFAB at baseline	Same outcomes **Cross sectional:** Exposure at outcome are measured at a single point in time. Baseline (DFAB) and 12 mo. post intervention (DMAB) levels were being compared.	12 months of estradiol treatment decreased SCr, but not to the level of DFAB at baseline (0.76 mg/Dl vs 0.68 mg/dL, *P* = .0003)
	Same as above	Same as above	DMAB- taking spironolactone at baseline	DMAB not taking spironolactone at baseline	Same outcomes **Cross sectional:** Exposure at outcome are measured at a single point in time at baseline	No difference in baseline SCr or SCr/Q between groups. • SCr: 0.83 vs 0.79, *P* = NS • SCr/Q: 1.0 vs 1.0, *P* = NS
Mullins (2021)[91] [redacted]	TGNB adolescents (N = 611) Eligibility Inclusion criteria: • initiation of CSHT before March 24, 2019 • age 13 to 24 years at initiation of CSHT. • The exclusion criterion was age- participant had to be 13 years at CSHT start. **Sampling Method**: Charts were reviewed for inclusion criteria. Among 1406 individual patients seen in the CCHMC Transgender Health Clinic, 611 subjects were eligible for inclusion in the study cohort. **Subset**: Comparisons were made between TGF (n = 429) and TGM (n = 182) participants who were taking CSHT	Age at presentation, mean (IQR) • Total cohort: 17 (15-19) years • TGM: 17 [15–19] years • TGW: 18 [15.5–20] years • TGM were slightly younger at first presentation compared with TGM, *P* = .0019). Sex, n (%) • 428 (70%) subjects were assigned female at birth • 183 (30%) were assigned male at birth. Affirmed Gender, n (%) • 176 (28.8%) individuals identified as female • 416 (68.1%) as male • 19 (3.1%) as nonbinary or gender nonconforming. Race, n (%) • White (n = 544; 89%) • African American (n = 50; 8.2%); • Hispanic. (n = 14;2.3%)	TGM on testosterone treatment (n = 429)	TGF on estrogen treatment (estradiol) (n = 182)	• Charts were evaluated for development of thrombosis **Cohort:** Outcomes were measured after a median of 574 days of treatment.	• No individual in either cohort developed a VTE or arterial thrombosis (including stroke) while on CSHT • These data suggest that CSHT in youth, titrated within physiologic range, does not carry a significant risk of thrombosis in the short-term, even with the presence of preexisting thrombosis risk factors.

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
		CSHT treatment • 182(29.8%) TGW initiated estrogen • 429 (70.2%) TGM initiated testosterone Median duration of treatment (IQR) • Total cohort: 574 days (283-962) • TGW: 554 days (283-1037) • TGM: 577 days (283-923) Treatment initiation age, yr, (IQR) • TGM: 17 (15-19) • TGW: 18 (15.5-20) • The TGM cohort was slightly younger at initiation of CSHT compared with the TGW cohort, *P* = .004 Risk factors for thrombosis, n (%) • BMI 25-30 -Overweight: 148 (24.2) • BMI > 30- Obesity: 211 (34.5) • Tobacco use: 94 (15.4) • Migraine with aura (documented): 28 (2.6) • Family history of thrombosis(documented): 49 (8.0) • Family history of risk factors for thrombosis(documented): 5 (0.8) • Inflammatory bowel disease: 3(0.5) • Juvenile rheumatoid arthritis: 1 (0.2) • Previous hormonal use (documented): 328 (53.7) • Thrombosis before CSHT: 3 (0.5) • Treated with anticoagulation: 3 • Referred to hematology for evaluation: 17 (2.8)				

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
Valentine (2022)[98] PEDSNet, a Pediatric Learning Health System Network	Transgender youth (N = 4172) **Eligibility:** TGNB youth subjects had a diagnosis of gender dysphoria or related diagnosis. **Sampling Method**: Clinical data available from electronic health care records from the health system from 2009 onward for patients with in-person encounters with a provider were reviewed for inclusion. The data for all TGNB patients and at least one outpatient visit from 2009-2019 was extracted from the PEDSnet database on Nov 2019. **Subset**: Comparisons were made between TGNB youth taking GAHT vs. TGNB youth not taking GAHT.	Age at first visit, y: median (25th-75th percentile): • 10.0 (4.4-14.6), Age at last visit, y: median (25th-75th percentile): • 16.7 (14.6-18.3)	TGNB youth with diagnosis of GD prescribed GAHT (N = 1412) • N = 267 with a prescription for GnRH analogs alone • N = 832 with a prescription for testosterone without GnRH analogs • N = 349 with a prescription for estrogen without GnRH analogs • N = 106 with a prescription for testosterone with GnRH analogs • N = 125 with a prescription for estrogen with GnRH analogs	TGNB youth with diagnosis of GD not prescribed GAHT (N = 2760)	Cardiometabolic outcomes were obtained from electronic health records including: • Weight (whether overweight or obese) • Dyslipidemia • Liver dysfunction • Hypertension • Dysglycemia • PCOS **Cohort:** Outcomes were measured after exposures	Testosterone (without GnRH analogs) vs. no GAHT • In the adjusted analysis, there was an increased odds of being overweight/ having obesity (1.8; 95% CI, 1.5-2.1; *P* < .0001), in those taking testosterone compared to those not on GAHT. • In the adjusted analysis[a], there was an increased odds of having dyslipidemia (1.7; 95% CI, 1.1-1.9; *P* ≤ .01), in those taking testosterone compared to those not on GAHT • In the adjusted analysis[a], hypertension (1.6; 95% CI, 1.2-2.2; *P* < .01) in those taking testosterone compared to those not on GAHT. • There was no statistically significant increase in the unadjusted analysis in odds for liver dysfunction, PCOS, or dysglycemia for those on testosterone compared to those not on GAHT. Testosterone + GnRH analogs vs. no GAHT • In the adjusted analysis[a], there was an increased odds of having dyslipidemia (3.7; 95% CI, 2.0-6.7; *P* < .0001), in those on testosterone + GnRH analogs compared to those who are not taking GAHT • In the adjusted analysis[a], there was an increased odds of having liver dysfunction (2.5; 95% CI, 1.4-4.3; *P* < .01) in those on testosterone + GnRH analogs compared to those who are not taking GAHT. • There was no statistically significant increase in odds in the unadjusted analysis for overweight/obesity, dysglycemia, hypertension, or PCOS for those on testosterone + GnRH analogs compared to those not on GAHT. GnRH analogs vs. no GAHT • In both the adjusted[a] and the non-adjusted analyses, there was no statistically significant increase in odds for cardiometabolic outcomes (overweight/obesity, liver dysfunction, dyslipidemia, dysglycemia, hypertension, or PCOS) for those on a GnRH analog compared to those not on GAHT. Estradiol + GnRH analogs vs. no GAHT

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• In the adjusted analysis, there was no statistically significant increase in odds for cardiometabolic outcomes (overweight/obesity, liver dysfunction, dyslipidemia, dysglycemia, hypertension, or PCOS) for those on estradiol + GnRH analogs compared to those not on GAHT. • In the unadjusted analysis, there was an increased odds of having liver dysfunction (2.1; 95% CI, 1.3-3.4; *P* < .01), in those prescribed both estradiol and GnRH analogs compared to those not prescribed GAHT. • In the unadjusted analysis, there was an increased odds of having hypertension (2.1; 95% CI, 1.2-3.6; *P* < .01), in those prescribed both estradiol and GnRH analogs compared to those not prescribed GAHT. Estradiol (no GnRH analogs) vs. no GAHT • In the adjusted analyses[a], there was no statistically significant increase in odds for cardiometabolic outcomes (overweight/obesity, liver dysfunction, dyslipidemia, dysglycemia, hypertension, or PCOS) for those on estradiol compared to those not on GAHT. • In the unadjusted analysis[a], compared to those not prescribed GAHT, individuals prescribed estradiol had higher odds of dyslipidemia (1.9; 95% CI, 1.3-2.7; *P* = .001), • In the unadjusted analysis, compared to those not prescribed GAHT, individuals prescribed estradiol had higher odds of liver dysfunction (1.6; 95% CI, 1.2-2.3; *P* < .01) • In the unadjusted analysis, compared to those not prescribed GAHT, individuals prescribed estradiol had higher odds of hypertension (2.3; 95% CI, 1.7-3.2; *P* < .0001).
Vehmas (2022)[125] [redacted] (Finland)	Transgender adolescents desiring gender-affirming hormonal treatment (N = 124) **Eligibility**: Adolescents diagnosed with GD, referred to gender identity services at Helsinki University Hospital before 18 years of age for GD symptoms, and further referred to the adolescent gynecology clinic	Assigned sex at birth: • AMAB: n = 20 • AFAB: n = 104 Median age at the first contact with gender identity services (yr, range; N = 124): • 16.7 (12.1 to 18.0) Median age at GD diagnosis (yr, range; N = 124):	FTM (n = 104)	MTF (n = 20)	• Blood pressure **Cross-sectional:** exposures/ outcomes were measured at the same time	Mean systolic blood pressure (mmHg, SD), *P* = .003 • FTM: 128.7 (10.5) • MTF: 137.9 (12.7) Mean diastolic blood pressure (mmHg, SD), *P* = NS • FTM: 76.8 (8.1) • MTF: 75.8 (8.5)

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

Table I.J.6. Clinical studies with between-TGNB-group comparisons examining cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics n (%, unless otherwise noted), P value, if reported	Exposure/intervention	Comparator	Outcome measures and timing	Results
	for gender-affirming hormonal assessment **Sampling method**: Referred by gender identity services **Subset definition**: Comparisons were made between MTF (n = 20) and FTM (n = 104) transgender adolescents	• 18.1 (14.8 to 20.1) Median age at the time of assessment at the adolescent gynecology clinic (yr, range; N = 124): • 17.7 (14.6 to 19.8)				

[a] *Analysis was adjusted for overweight/obesity, depression, and a prescription for an antipsychotic (Valentine 2022).*

Table abbreviations: CI, confidence interval; cLDL, low-density lipoprotein cholesterol; FTM, female-to-male; GAHT, gender-affirming hormone therapy; GnRHa, gonadotropin-releasing hormone analog/analog; Hg, mercury; HTN, hypertension; ICD, International Classification of Disease; kg, kilogram; L, liter; LHRH, luteinizing hormone-releasing hormone; mm, millimeters; mmol, millimole; MTF, male-to-female; N/S, not significant; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 diabetes mellitus; TGD, transgender/gender diverse; TGF, transgender female; TGNB, transgender, non-binary, gender diverse; TGM, transgender male; yr(s), year(s)

Return to TOC

APPENDIX I.K: DATA EXTRACTED FROM STUDIES COMPARING TGNB PATIENTS TO THEIR CISGENDER PEERS, ORGANIZED BY OUTCOME

Return to TOC

Table I.K.1. Clinical studies comparing TGNB to cisgender peers regarding mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
Durwood (2017)[109] Part of Trans Youth Project - a national, longitudinal study of socially transitioned transgender children (no description about the location)	**Population**: N = 164 • Transgender: n = 63 children • Cisgender: n = 63 age- and gender-matched controls • Siblings: n = 38, aged 9-14 years **Eligibility criteria**: To be included as a transgender participant in the study, children needed to identify as the gender opposite their natal sex in everyday life, to have socially transitioned by using the pronoun associated with their asserted gender in all contexts, and be enrolled in the study from March 2015 to February 2016 (when the present measurements were included). **Sampling method:** • Transgender group: No related description • Cisgender group: The siblings were recruited through the same methods as the transgender group and the matched controls were recruited through a university database of families interested in participating in child development research.	**Transgender group**: Transgender children came from 23 US states and 1 Canadian province. • n = 33 children in this group were assigned boys, n = 30 assigned girls. • Mean age (SD) in years = 10.8 (1.3) • Majority white, non-Hispanic N = 37 **Cisgender group, Control group**: • n = 33 participants in this group were assigned boys, n = 30 assigned girls • mean age (SD) in years = 10.9 (1.4) • Majority white, non-Hispanic n = 41. **Cisgender group, Siblings group**: • n = 21 participants in this group were assigned boys, n = 17 assigned girls • mean age (SD) in years = 10.6 (1.2) • majority white, non-Hispanic n = 25.	Transgender group: n = 62 (One child who had no medical intervention but who was experiencing puberty is excluded from this part) • Cross-sex hormones: N = 5 • Hormone blockers: N = 18 • No medical interventions: N = 39	Cisgender group: • Control group (matched by age) n = 63 • Sibling group n = 38	• **Mental health outcomes:** Children reported on anxiety and depression symptoms using the pediatric short form of the National Institutes of Health's Patient Reported Outcomes Measurement Information System (PROMIS) scale, and parents completed the proxy versions of the anxiety and depression PROMIS scales. Participants' scores across items were summed and then converted to a standardized T score. T scores are normed such that a score of 50 represents the national average for children, with 10 points representing a standard deviation and a score of at least 63 indicating clinically significant anxiety or depression (top 10% of all children). **Cross sectional:** outcomes and measurements were measured at the same time	Depression: Mean (SD) • T score on self-reported depression ○ No statistically significant difference in self-reported depressive symptoms across the 3 groups (F = 1.18, *P* = NS). ○ Transgender adolescents: 48.7 (9.4) ○ Cisgender controls: 46.4 (8.0) ○ Cisgender siblings: 47.9 (7.9) • T score on parent-reported depression ○ No statistically significant difference in parent-reported depressive symptoms across the 3 groups (F = 0.32, *P* = NS). ○ Transgender adolescents: 50.2 (8.8) ○ Cisgender controls: 49.4 (7.8) ○ Cisgender siblings 48.9 (7.1) Anxiety: Mean (SD) • T score on self-reported anxiety ○ No statistically significant difference in self-reported anxiety symptoms across the 3 study groups (F = 2.62, *P* = NS). ○ Transgender adolescents: 52.0 (9.6) ○ Cisgender controls: 49.0 (7.7) ○ Cisgender siblings: 52.8 (10.5) • T score on parent-reported anxiety ○ Statistically significant difference in parent-reported anxiety symptoms across the 3 study groups (F = 6.22, *P* = .002). ○ Transgender adolescents: 54.9 (9.0) ○ Cisgender controls: 49.6 (8.6) ○ Cisgender siblings: 51.0 (8.2)
López de Lara (2020)[62]	**N=53 adolescents** • n=23 TGNB youth	Transgender adolescents: • mean age: 16 years (range 14-18)	**Transgender cohort** At baseline before treatment	**Cisgender cohort**	• Depression: assessed with BDI-II	• **Anxiety**, mean (SD)

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CSH, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s); GAH, gender-affirming hormone; GD, gender dysphoria; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; TGNB, transgender, nonbinary, gender-diverse; YSR, youth self-report

Return to TOC

Table I.K.1. Clinical studies comparing TGNB to cisgender peers regarding mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
[redacted] Spain: Pediatric endocrinology clinic [redacted]	• n=30 matched cisgender controls (matched for age, ethnicity and socioeconomic status.) • **Eligibility**: adolescents aged 14 to 18 yo, absence of psychiatric comorbidity, Tanner state 2 or higher, understanding of risks and benefits of CSH • **Sampling method**: requested volunteers	• assigned sex at birth: ○ 69% female ○ 31% male • 91% Caucasian and Spanish descent • 52% parents with a university education • 30.4% had previously used mental health services • sexual orientation ○ 65% heterosexual, ○ 13% homosexual ○ 21% bisexual Cisgender adolescents: • mean age:16 years (range 14-18) • assigned sex at birth ○ 60% female ○ 40% male • 100% are of Caucasian and Spanish descent • 40% had parents with a university education • 30% had previously used mental health services • sexual orientation, ○ 90% were heterosexual ○ 10% were homosexual • 0% were bisexual			• Anxiety: assessed with STAI-S and STAI-T Outcomes and measurements were measured at the same time before transgender cohort had received hormone treatment	○ At baseline, TGNB youth had significantly higher STAI-S anxiety scores at 33.3 (9.1) compared to cisgender peers at 11.8 (9.1), $P < 0.001$ ○ At baseline, TGNB youth had significantly higher STAI-T anxiety scores at 33 (7.2) compared to cisgender peers at 14.2 (4.8), $P < 0.001$ • **Depression**, mean (SD) ○ At baseline, TGNB youth had significantly higher BDI-II scores at 19.3 (5.5) compared to cisgender peers at 7.2 (3.9), $P < 0.001$
			Transgender cohort After one year of CSHT (oral estradiol or intramuscular testosterone)	**Cisgender cohort**	• Depression: assessed with BDI-II • Anxiety: assessed with STAI-S and STAI-T Outcomes and measurements were measured at the same time after transgender cohort had received hormone treatment for one year	• **Anxiety,** mean (SD) ○ After 12 months of hormone therapy, there was no significant difference in STAI-S anxiety scores between TGNB adolescents at 16.8 (8.1), and cisgender adolescents at 12.3 (3.8), P = NS ○ After 12 months of hormone therapy, there was no significant difference in STAI-T anxiety scores between TGNB adolescents at 18.5 (8.4), and cisgender adolescents at 14.2 (4.8), P = NS • **Depression**, mean (SD) • After 12 months of hormone therapy, while the BDI-II depression scores decreased in TGNB youth and they were much closer to the scores of their cisgender peers, they were still slightly significantly higher at 9.7 (3.9) compared to 7.4 (3.6), $P = 0.034$
van der Miesen (2020)[124] [redacted] the Netherlands, between 2012 and 2015	N = 1101 adolescents **Eligibility criteria**: • Not clearly stated **Sampling method**: • **Transgender cohort:** Adolescents who just started the diagnostic procedure were assessed during their first sessions at the VUmc.	Transgender subjects who did not started any affirmative medical treatment yet: • Mean age (SD) in years = 14.47 (2.18); 116 assigned boys at birth and 156 assigned girls at birth Transgender subjects receiving affirmative care and about to start CSH treatment:	Transgender cohort: on puberty suppression and about to start CSH treatment (not specified) (n = 178)	Cisgender cohort (n = 651)	Psychological functioning outcomes: • The Dutch version of the YSR was used. • Self-harm/suicidality was examined by two YSR items, item 18 and 91. • Effect sizes Cohen's d: .80 or higher is a large effect size, .50-.79 a medium effect size,	Suicidality: • Analyses comparing the transgender group at referral, the transgender group using puberty blockers, and the cisgender sample show that groups differed from each other on suicidality. ($P < .001$) • Post hoc analyses showed no differences found between adolescents using puberty suppression and the comparison group on self-harm/suicidality. • Mean scores (SD) on the Youth Self-Report for suicidality for transgender adolescents receiving affirmative care was 0.17

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CSH, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s); GAH, gender-affirming hormone; GD, gender dysphoria; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; TGNB, transgender, nonbinary, gender-diverse; YSR, youth self-report

Return to TOC

Table I.K.1. Clinical studies comparing TGNB to cisgender peers regarding mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	Adolescents diagnosed with GD were assessed before the start of CSH. During both assessments, parents and children completed several questionnaires. During 2012 to 2015, 504 adolescents were seen in their gender identity service. 53 participants did not complete the assessment process and therefore, did not participate in this study. The reason for dropout was failure to complete the questionnaire or alternation of symptoms of GD. Of the adolescents diagnosed with GD, 179 were about to start CSH treatment. One participant did not complete the questionnaire and was thus excluded. • **Cisgender cohort:** Data from the comparison group of cisgender adolescents from the general population were recruited by means of the help of different secondary schools in different provinces in the Netherlands. After consent of the parents, the adolescents completed a paper-pencil survey during regular class times. **Subsets**: • n = 272 transgender adolescents referred to a specialized gender identity clinic. (Data not extract for this cohort for outcomes since they did not yet receive any affirmative medical treatment.)	• Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth Cisgender adolescents: • Mean age (SD) in years = 15.39 (1.36); 346 assigned boys at birth and 305 assigned girls at birth			.20-.49 small, and effect sizes < .20 are negligible **Cross-sectional:** All measures were taken on the same day.	(0.52) vs. 0.19 (0.60) for cisgender adolescents. Effect sizes Cohen's d of GP vs. T1 was 0.04.

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CSH, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s); GAH, gender-affirming hormone; GD, gender dysphoria; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; TGNB, transgender, nonbinary, gender-diverse; YSR, youth self-report

Return to TOC

Table I.K.1. Clinical studies comparing TGNB to cisgender peers regarding mental health outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	• n = 178 Transgender adolescents receiving affirmative care and about to start CSH treatment • n = 651 cisgender adolescents: Dutch high school adolescents from the general population.					

[a] *The author-reported number of participants on any treatment was 34; however, when adding the number of participants taking a GnRH analog, testosterone, or estrogen, the total number equals 37 (Avila 2019)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; BES, Body Esteem Scale for Adolescents and Adults; BIS, Body Image Scale; CSH, cross-sex hormones; EDE-Q, Eating Disorders Examination Questionnaire; FBeK, "Fragebofen zur Beurteilung des eisenen Körpers" (Body image assessment questionnaire); FTM, female-to-male; GD, gender dysphoria; GMSR-A, Gender Minority Stress and Resilience Measure for Adolescents; GnRHa, gonadotropin-releasing hormone analog; mBMI, median body mass index; MRI, magnetic resonance imaging; N/A, not applicable; N/R, not reported; SD, standard deviation; TCS, Transgender Congruence Scale; TGNB, transgender/nonbinary; UGDS, Utrecht Gender Dysphoria Scale; yr(s), year(s); GAH, gender-affirming hormone; GD, gender dysphoria; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; TGNB, transgender, nonbinary, gender-diverse; YSR, youth self-report

Return to TOC

Table I.K.2. Clinical studies comparing TGNB to cisgender peers regarding psychosocial outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
Costa (2015)[77] [redacted]	**Population**: N = 201 GD adolescents seeking treatment (including immediately eligible and delayed eligible) • Of 101 immediately eligible group, n = 35 at 18 months • n = 169 Children/adolescents without observed psychological/psychiatric symptoms **Eligibility criteria**: referred to the GIDS, completed the diagnostic procedure, invited for follow-up **Sampling method:** consecutive enrollment between 2010 to 2014; 100% agreed to participate (page 2)	Full cohort: • mean (SD) baseline age was 15.52 years (1.41), • mean (SD) age at the start of GnRH analog was 16.48 years (1.26)	TGNB adolescents • n = 201 at baseline seeking treatment • n = 101 immediately eligible GD-who had 18 months of psychological support and 12 months of puberty suppression treatment	Children/adolescents without observed psychological/ psychiatric symptoms not taking puberty suppression treatment.	CGAS was used to assess participants psychosocial functioning. **Cohort**: Measurements were taken at several points in time and compared.	CGAS, mean (SD) • Baseline ○ GD adolescents scores of 57.7 (2.3) at baseline were significantly lower than scores found in children/adolescents without observed psychological/psychiatric symptoms, 67.1 (12), t = 7.4, *P* < .001 • After 18 months of psychological support/12 months of puberty suppression ○ GD adolescents had a mean score of 67.40 (13.93), which was not significantly different from the score of 67.1 (12) in children/adolescents without observed psychological/psychiatric symptoms, t = 0.01, *P* = NS
Durwood (2017)[109] Part of Trans Youth Project - a national, longitudinal study of socially transitioned transgender children (no description about the location)	**Population**: N = 310 • Transgender: n = 116 children • Cisgender: n = 122 age- and gender-matched controls • Siblings: n = 72, aged 6-14 years **Eligibility criteria**: To be included as a transgender participant in the study, children needed to identify as the gender opposite their natal sex in everyday life, to have socially transitioned by using the pronoun associated with their asserted gender in all contexts, and be enrolled in the study from March 2015 to February 2016 (when the present measurements were included). **Sampling method**: • Transgender group: No related description • Cisgender group: The siblings were recruited through the same methods as the	Transgender group: • Transgender children came from 23 US states and 1 Canadian province. • n = 48 children in this group were assigned boys, n = 68 assigned girls. • Mean age (SD) in years = 9.3 (2.0) • Majority white, non-Hispanic N = 75 Cisgender group, Control group: • N = 49 participants in this group were assigned boys, N = 73 assigned girls • mean age (SD) in years = 9.2 (2.0) • Majority white, non-Hispanic N = 79. Cisgender group, Siblings group: • N = 40 participants in this group were assigned boys, N = 32 assigned girls • mean age (SD) in years = 9.1 (1.8) • majority white, non-Hispanic N = 45. • No significant difference in gender, race or age between groups (*P* = NS)	Transgender group: Of 63 TG youth age 9-14 that also completed depression and anxiety screening, treatment data was collected: • Cross-sex hormones: n = 5 • Hormone blockers: n = 18	Cisgender group: • Control group (matched by age) n = 122 • Sibling group n = 72	• Self-worth scores were reported using the Global Self-Worth Subscale from the Harter Self-Perception Profile for Children **Cross-sectional**: Exposures/Outcomes measured at the same time	**Self-worth:** Transgender children did not differ from age-and gender-matched controls or siblings in self-worth. No statistically significant effect of condition (F = 1.96, *P* = .142), a marginal effect of age group (F = 2.66, *P* = .072), and no significant interaction (F = 0.18, *P* = .949) was found. **Children in all groups** reported self-worth that was higher than the midpoint (2.5) of the scale, indicating high self-worth overall • transgender, *P* < .001 • controls, *P* < .001 • siblings, *P* < .001 **6-8 years age group:** mean (SD). One-sample t test for these three values indicates high self-esteem (*P* < .001). • transgender: 3.50 (0.54) • controls: 3.62 (0.39) • siblings: 3.62 (0.40) **9-11 years age group:** mean (SD). One-sample t test for these three values indicates high self-esteem (*P* < .001). • transgender: 3.47 (0.55) • controls: 3.68 (0.35) • siblings: 3.64 (0.47)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: CGAS, children's global assessment scale; fMRI, functional magnetic resonance imaging; FTM, female to male; GD, gender dysphoria; MTF, male to female; SD, standard deviation; TG, transgender; TGNB: transgender, non-binary, gender diverse; TOL, Tower of London task; YSR, youth self-report

Return to TOC

Table I.K.2. Clinical studies comparing TGNB to cisgender peers regarding psychosocial outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	transgender group and the matched controls were recruited through a university database of families interested in participating in child development research.					**12-14 years age group:** mean (SD). One-sample t test for transgender youth and cisgender controls indicates high self-esteem ($P < .001$) and for cisgender siblings, high self-esteem ($P = 0.023$). • transgender: 3.30 (0.51) • controls: 3.37 (0.64), • siblings: 3.43 (0.59)
López de Lara (2020)[62] [redacted] Spain: Pediatric endocrinology clinic[redacted]	**N=53 adolescents** • n=23 TGNB youth • n=30 matched cisgender controls (matched for age, ethnicity and socioeconomic status.) • **Eligibility**: adolescents aged 14 to 18 yo, absence of psychiatric comorbidity, Tanner state 2 or higher, understanding of risks and benefits of CSH • **Sampling method**: requested volunteers	Transgender adolescents: • mean age: 16 years (range 14-18) • assigned sex at birth: o 69% female o 31% male • 91% Caucasian and Spanish descent • 52% parents with a university education • 30.4% had previously used mental health services • sexual orientation o 65% heterosexual, o 13% homosexual o 21% bisexual Cisgender adolescents: • mean age:16 years (range 14-18) • assigned sex at birth o 60% female o 40% male • 100% are of Caucasian and Spanish descent • 40% had parents with a university education • 30% had previously used mental health services • sexual orientation, o 90% were heterosexual o 10% were homosexual • 0% were bisexual	**Transgender group** At baseline before treatment	**Cisgender group**	• Behavior problems: assessed with SDQ • Outcomes and measurements were measured at the same time before transgender cohort had received hormone treatment	• **Behavioral problems**, mean (SD) o Strength and Difficulties Questionnaire: At baseline, TGNB youth had significantly more emotional symptoms, peer problems and total difficulties compared to cisgender peers**.** o Total difficulties, mean (SD), $P < 0.001$ Transgender: 14.7 (3.3) Cisgender: 11.3 (2.3) ▪ Prosocial, mean (SD), P= NS Transgender: 8 (1.6) Cisgender: 7.7 (1.2) ▪ Emotional symptoms, mean (SD), $P < 0.001$ Transgender: 5.2 (1.6) Cisgender: 3.7 (1) ▪ Conduct problems, mean (SD), P= NS Transgender: 2.7 (0.8) Cisgender: 2.3 (1.2) ▪ Hyperactivity, mean (SD), P= NS Transgender: 4 (1.9) Cisgender: 3.8 (0.9) Peer problems, mean (SD), $P < 0.001$ Transgender: 2.6 (1.3) Cisgender: 1.3 (0.4)
			Transgender cohort After one year of CSHT (oral estradiol or intramuscular testosterone)	**Cisgender cohort**	• Behavior problems: assessed with SDQ • Outcomes and measurements were measured at the same time after transgender cohort had received hormone treatment for one year	• **Behavioral problems**, mean (SD) o Strength and Difficulties Questionnaire: After 12 months of hormone therapy, TGNB youth still had significantly more peer problems compared to cisgender peers, but otherwise had comparable strengths and difficulties. o Total difficulties, mean (SD), P= NS Transgender: 10.3 (2.9) Cisgender: 11.3 (2.3)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: CGAS, children's global assessment scale; fMRI, functional magnetic resonance imaging; FTM, female to male; GD, gender dysphoria; MTF, male to female; SD, standard deviation; TG, transgender; TGNB: transgender, non-binary, gender diverse; TOL, Tower of London task; YSR, youth self-report

Return to TOC

Table I.K.2. Clinical studies comparing TGNB to cisgender peers regarding psychosocial outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						▪ Prosocial, mean (SD), *P* < 0.001 Transgender: 9 (1.2) Cisgender: 7.5 (1.2) ▪ Emotional symptoms, mean (SD), *P*= NS Transgender: 3.4 (1.2) Cisgender: 3.7 (1) ▪ Conduct problems, mean (SD), *P*= NS Transgender: 1.8 (1) Cisgender: 2.6 (1.6) ▪ Hyperactivity, mean (SD), *P* = 0.002 Transgender: 2.6 (1.8) Cisgender: 3.9 (0.8) Peer problems, mean (SD), *P* < 0.001 Transgender: 2.3 (0.8) Cisgender: 1 (0.2)
Staphorsius (2015)[119] [redacted] the Netherlands)	Population: N = 65 adolescents **Subset groups:** • n = 8 treated MTF • n = 12 treated FTM • n = 21 control M • n = 24 control F **Eligibility**: • **Treated group:** Diagnosed with GD (per DSM-IV-TR), and adolescent age. To receive a GnRH analog, patients must be at least 12 years of age, and have breast development of Tanner stage B2 (natal girls) or genital development of Tanner stage G2 to G3 (natal boys). • **Control group:** No inclusion criteria noted, except being an adolescent. Group exclusion criteria still applied and could also not be receiving any puberty delaying medication or any form of hormones besides oral contraceptives.	• Mean age (yr, SD): ○ Treated MTF: 15.4 (0.7) ○ Treated FTM: 16.1 (1.7) ○ Control M: 14.9 (1.5) ○ Control F: 14.4 (1.8) • Mean IQ (SD): ○ Treated MTF: 94.0 (10.3) ○ Treated FTM: 95.8 (15.6) ○ Control M : 110.7 (15.)1 ○ Control F: 103.0 (17.3) • Mean Tanner stage (SD): ○ Treated MTF: 4.1 (1.0) ○ Treated FTM: 4.1 (1.1) ○ Control M: 4.2 (1.2) ○ Control F: 4.3 (0.9) • Mean duration of triptorelin (Decapeptyl-CR) use (yr, SD): ○ Treated MTF: 1.8 (0.8) ○ Treated FTM: 1.4 (1.1)	Puberty suppression using a GnRH analog (SubQ or IV triptorelin 3.75 mg every 4 weeks) • MTF: n = 8 • FTM: n = 12	Control group of adolescent peers	• TOL performance, an executive functioning task, and brain activation using fMRI **Cross-sectional**: exposures/ outcomes were measured at the same time	**TOL performance:** Mean percentage of correct trials (accuracy) (SD): Post hoc analysis showed that treated MTF had a significantly lower accuracy score than the control groups (*P* = 0.02) compared to control boys and (*P* = .04) compared to control girls. No other accuracy significant differences was found between groups. • Treated MTF: 73.9 (9.1) • Treated FTM:85.7 (10.5) • Control M:88.5 (6.8) • Control F: 87.2 (11.9) **Mean reaction time** in seconds (SD): No significant differences existed between groups. • Treated MTF: 10.9 (4.1) • Treated FTM: 9.9 (3.1) • Control M: 9.6 (2.5) • Control F: 9.0 (1.8) **Brain activation:** • Treated MTF showed greater activation compared to their experienced gender (F) in bilateral DLPFC, left RLPFC, left precuneus and right precuneus (trend) • Treated MTFs also showed greater left RLPFC activation relative to their natal sex (M)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: CGAS, children's global assessment scale; fMRI, functional magnetic resonance imaging; FTM, female to male; GD, gender dysphoria; MTF, male to female; SD, standard deviation; TG, transgender; TGNB: transgender, non-binary, gender diverse; TOL, Tower of London task; YSR, youth self-report

Return to TOC

Table I.K.2. Clinical studies comparing TGNB to cisgender peers regarding psychosocial outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	• **Exclusion criteria**: included uncontrolled endocrine disorders, neurological or psychiatric conditions that could alter study results, contraindication for MRI scan, psychotropic medication use, lack sufficient communication of Dutch language • **Sampling method**: Participants were recruited from the VU University Medical Center in Amsterdam. Relatives and friends of the participants were asked to participate to serve as age-matched controls. 3 siblings participated, but the majority were friends.					• Treated FTMs differed from their experienced gender (M) by showing less bilateral precuneus activation, corresponding with the activation differences between the control groups. • Treated FTMs also showed lower activation of the right precuneus activation than girls (F)
van der Miesen (2020)[124] [redacted] the Netherlands, between 2012 and 2015	**Population**: N = 1101 adolescents **Subset**: • n = 272 transgender adolescents referred to a specialized gender identity clinic. (data not extract for this cohort for outcomes since they did not yet receive any affirmative medical treatment) • n = 178 transgender adolescents receiving affirmative care and about to start CSH treatment • n = 651 cisgender adolescents: Dutch high school adolescents from the general population. **Eligibility criteria**: Not clearly stated **Sampling method**: • **Transgender cohort:** Adolescents who just started the diagnostic procedure were assessed during their first sessions at the VUmc. Adolescents diagnosed with GD	Transgender subjects who did not started any affirmative medical treatment yet: • Mean age (SD) in years = 14.47 (2.18); 116 assigned boys at birth and 156 assigned girls at birth Transgender subjects receiving affirmative care and about to start CSH treatment: • Mean age (SD) in years = 16.75 (1.24); 68 assigned boys at birth and 110 assigned girls at birth Cisgender adolescents: • Mean age (SD) in years = 15.39 (1.36); 346 assigned boys at birth and 305 assigned girls at birth	Transgender cohort: on puberty suppression and about to start CSH treatment (not specify in the article)	Cisgender cohort: no related description	Psychological functioning outcomes: • The Dutch version of the YSR was used to assess internalizing and externalizing problem behavior, self-harm/suicidality, and poor peer relations. • Peer Relations scale was created from three YSR items: "I don't get along with other kids" (Item 25), "I get teased a lot" (Item 38), and "I am not liked by other kids" (Item 48). • Effect sizes Cohen's d: .80 or higher is a large effect size, .50-.79 a medium effect size, .20-.49 small, and effect sizes < .20 are negligible **Cross-sectional:** Exposures/ outcome measures were taken on the same day.	Psychological functioning: • Analyses comparing the transgender group at referral, the transgender group using puberty blockers, and the cisgender sample show that groups differed from each other on internalizing, and poor peer relations ($P < .001$) but not on externalizing (P = NS). • Post hoc analyses show that the transgender adolescents using puberty suppression scored significantly lower on internalizing problems but higher on peer relations compared with the comparison group. Internalizing: • Mean scores (SD) on the Youth Self-Report for internalizing for transgender adolescents receiving affirmative care was 7.76 (6.68) vs. 9.71 (7.73) for cisgender adolescents. Effect sizes Cohen's d of GP vs. T1 was 0.30. Externalizing: • Mean scores (SD) on the Youth Self-Report for externalizing for transgender adolescents receiving affirmative care was 9.82 (5.79) vs. 10.25 (6.10) for cisgender adolescents. Effect sizes Cohen's d of GP vs. T1 was 0.07. Peer relations:

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: CGAS, children's global assessment scale; fMRI, functional magnetic resonance imaging; FTM, female to male; GD, gender dysphoria; MTF, male to female; SD, standard deviation; TG, transgender; TGNB: transgender, non-binary, gender diverse; TOL, Tower of London task; YSR, youth self-report

Return to TOC

Table I.K.2. Clinical studies comparing TGNB to cisgender peers regarding psychosocial outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	were assessed before the start of CSH. During both assessments, parents and children completed several questionnaires. During 2012 to 2015, 504 adolescents were seen in their gender identity service. 53 participants did not complete the assessment process and therefore, did not participate in this study. The reason for dropout was failure to complete the questionnaire or alternation of symptoms of GD. Of the adolescents diagnosed with GD, 179 were about to start CSH treatment. One participant did not complete the questionnaire and was thus excluded. • **Cisgender cohort**: Data from the comparison group of cisgender adolescents from the general population were recruited by means of the help of different secondary schools in different provinces in the Netherlands. After consent of the parents, the adolescents completed a paper-pencil survey during regular class times.					• Mean scores (SD) on the Youth Self-Report for peer relations for transgender adolescents receiving affirmative care was 0.70 (1.06) vs. 0.41 (0.81) for cisgender adolescents. Effect sizes Cohen's d of GP vs. T1 was -0.31.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: CGAS, children's global assessment scale; fMRI, functional magnetic resonance imaging; FTM, female to male; GD, gender dysphoria; MTF, male to female; SD, standard deviation; TG, transgender; TGNB: transgender, non-binary, gender diverse; TOL, Tower of London task; YSR, youth self-report

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
Alvares (2022)[132] A gender specialty endocrine clinic [redacted] Brazil	N = 42 • Transgender women: n = 15 patients • Cisgender women: n = 13 healthy and asymptomatic subjects • Cisgender men: n = 14 healthy and asymptomatic subjects **Eligibility criteria:** • Transgender women: DSM diagnosis for GD, started androgen blockade after age 12, regular estrogen use in the last year, age 25-45, BMI 18-34.9, no current or prior illness that could affect strength/aerobic tests, chronic disease or chronic medication use • Cisgender peers: Age 25-45 years, BMI 18-34.9, no history of sexual differentiation disorder or hormonal disorders, no current or prior illness that could affect strength/aerobic tests, no chronic disease or chronic medication use **Sampling method:** No information was given about how transgender or cisgender subjects were selected/recruited. Cisgender peers were matched to transgender women on age and physical activity level (per the IPAQ [ie, International Physical Activity Questionnaire])	Transgender women: • Age at start of study: mean 34.2 (SD 5.2) years • Age at start of hormone therapy: median 17 years Cisgender women: • Age at start of study: mean 35.6 (SD 4.1) years Cisgender men: • Age at start of study: mean 36.7 (SD 3.8) years	Transgender women on estrogen treatment: n = 15 (100%) • Estradiol valerate: ○ n = 1 patient at 1 mg/day ○ n = 4 patients at 2 mg/day • Conjugated estrogens: ○ n = 4 patients at 0.625 mg/day ○ n = 3 patients at 1.25 mg/day • 17-beta estradiol gel: ○ n = 1 patient at 0.5 mg/day ○ n = 1 patient at 1 mg/day ○ n = 1 patient at 1.5 mg/day • Antiandrogen treatment: n = 11 (73.3%) Cyproterone acetate: n = 11 patients at 50 mg/day • Prior gonadectomy: n = 4 patients • Average duration of CSHT: 14.4 (SD3.5) years	Cisgender women on estrogen treatment: n = 3 • Ethinyl estradiol: ○ n = 1 patient at 0.030 mg/day ○ n = 2 patients at 0.035 mg/day • Antiandrogen treatment: n = 2 • Cyproterone acetate: n = 2 patients at 2 mg/day • Progestin treatment: n = 1 • Drospirenone: n = 1 patient at 3 mg/day Cisgender men: None	• Laboratory blood tests: Total testosterone (electrochemiluminometric) was analyzed in blood samples after same-day collection, immediately before bioimpedance, ergospirometry and strength tests. • Anthropometric measures: evaluated by using the following parameters: height, body weight and body mass index (BMI, weight/(height)2; (kg/m²)." • Body composition outcomes: ○ Assessed by an InBody 720 device (Biospace, Korea) with an 8-point reading through a tactile electrode. The parameters evaluated were weight, BMI, total body fat mass (FM), percentage of body fat mass (%FM), skeletal muscle mass (SMM) and fat-free mass (FFM). ○ The Baumgartner Index (appendicular skeletal muscle mass (ASM) adjusted by height squared), fat mass/height2 (FM/Hgt2) and fat-free mass/height2 (FFM/Hgt2) were calculated to eliminate height as a determinant factor in fat body mass and muscle mass." **Cross-sectional**: Exposures/Outcomes measured at same time.	**Mean BMI:** No significant difference in BMI found between transgender women vs cisgender women or men • 25.5 (SD 2.8) for transgender women vs 23.1 (range 19.4-34.9) for cisgender women (*P* = NS)) • 25.5 (SD 2.8) for transgender women vs 26.3 (SD 3.2) for cisgender men (*P* = NS) **Mean total testosterone:** Transgender women had significantly lower testosterone levels than cisgender men, but no significant difference from cisgender women • 18.0 ng/dL (range 12.0-637.0) in transgender women vs 19.0 (range 12.0-40.1) in cisgender women (*P* = NS)) • 18.0 ng/dL (range 12.0-637.0) in transgender women vs 524.3 (SD 169.0) in cisgender men (*P* < .0001) **Mean skeletal muscle mass:** Transgender women had a significantly higher skeletal muscle mass than cisgender women, but a significantly lower mass vs cisgender men • 30.7 kg (SD 3.3) for transgender women vs 21.9 kg (SD 2.4) for cisgender women (*P* < .0001) • 30.7 kg (SD 3.3) for transgender women vs 36.0 kg (SD 3.2) for cisgender men (*P* < .0001) **Baumgartner index:** Transgender women had a significantly higher index than cisgender women, but a significantly lower index than cisgender men. • 12.6 kg/m² (SD 0.9) for transgender women vs 10.8 kg/m² (SD 1.7) for cisgender women (*P* < .01) • 12.6 kg/m² (SD 0.9) for transgender women vs 14.6 kg/m² (SD 0.8) for cisgender men (*P* < .01) **FFM/height²:** Transgender women had a significantly lower ratio than cisgender men, but no significant difference from cisgender women • 18.3 kg/m² (range 15.9-23.4) for transgender women vs 15.8 kg/m² (range 12.9-22.4) for cisgender women (*P* = NS) • 18.3 kg/m² (range 15.9-23.4) for transgender women vs 20.5 kg/m² (SD 1.2) for cisgender men (*P* < .05) **% FM:** Transgender women had a significantly higher % FM than cisgender men, but no significant difference from cisgender women

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• 29.5% (SD 5.7) for transgender women vs 32.9 (SD 5.7) for cisgender women (*P* = NS) • 29.5% (SD 5.7) for transgender women vs 20.2 (SD 5.7) for cisgender men (*P* < .01)
Beking (2020)[129] [redacted]	**Population**: N = 62 • transgender boys, N = 21 • cisgender boys: N = 20 • cisgender girls N = 21 **Eligibility criteria:** received puberty suppression and testosterone, no continuous psychotropic medication use, no psychiatric or neurologic disorder **Sampling method**: Trans boys were recruited from the center of Expertise on Gender Dysphoria and age-matched cisgender boys and girls were recruited via secondary schools and by inviting friends of the trans boys.	Mean age: • Transgender boys: 16.1 years, SD = 0.7 • Cisgender boys: 15.9, SD = 0.6 • Cisgender girls: 16.4, SD = 1.0 Handedness. Handedness per group (mean, SD, range): • Cisgender boys (8.59, 2.07, 4 to 10) • Cisgender girls (8.56, 2.40, 3 to 10) • Transgender boys (5.67, 5.90, -9 to 10) • Distribution of handedness did not differ between the groups (all Kolmogorov-Smirnoff Z < 0.93, P value > .358)	Transgender boys • Session 1 (baseline): had received 3.75 mg Triptorelin (Decapeptyl-CR®) subcutaneously or intramuscularly every 4 weeks (mean duration = 1.6 years, SD = 1.0) • Session 2 (follow-up): had been receiving testosterone treatment since session 1 (mean duration = 9.8 months, SD = 2.9, range 5.6–14.8 months)	Cisgender male adolescents Cisgender female adolescents	• fMRI data was collected as participants engaged in a face-matching task that has been shown to engage the amygdala. **Cohort**: Measurements were taken at 2 points in time, one at baseline, and one after intervention.	**Functional Amygdala Lateralization** • Session 1: ○ LI did not differ significantly between any of the groups, *P* = NS. ○ Transgender boys tended to be less lateralized in amygdala activation than cis boys: t (57) = 1.82, *P* = NS; and cis girls: t(57) = 1.92, *P* = NS • Session 2: ○ LI did not differ significantly between any of the groups (F (2,54) = 0.19, *P* = NS). • Δ between Session 1 and Session 2: ○ LI differences between session 1 and 2 did not differ significantly between any of the groups, *P* = NS. ○ Transgender boys tended to have larger LI difference scores than cis boys: t(52) = 1.84, *P* = NS; and cis girls: (t(52) = 1.96, *P* = NS **Brain Regions Showing a Significant Main Effect of the Emotional Face Matching Tasks (Between Groups) (through fMRI) (*P* < .05)** • Session 1: ○ Location, T-Values (Note: some are point values, some are ranges because there are multiple location coordinates) ○ Inferior occipital gyrus (both hemispheres), 15.86-16.54 ○ Cerebellum (hemispheric lobule VI, left hemisphere), 14.86 ○ Inferior frontal gyrus (triangular part, both hemispheres), 9.05-11.59 ○ Middle frontal gyrus (right hemisphere), 7.73 ○ Amygdala (left hemisphere), 10.82 ○ Hippocampus (left hemisphere), 7.95 ○ Temporal pole (superior temporal gyrus, left hemisphere), 6.59 ○ Middle temporal gyrus (right hemisphere), 7.33-8.07

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						○ Supplementary motor area (right hemisphere), 7.09 ○ Middle temporal gyrus (left hemisphere), 6.63 • Session 2: ○ Location, T-Values (Note: some are point values, some are ranges because there are multiple location coordinates) ○ Middle occipital gyrus (right hemisphere), 19.02-19.73 ○ Inferior occipital gyrus (right hemisphere), 18.73 ○ Inferior frontal gyrus (triangular part, both hemispheres), 9.69-11.58 ○ Middle frontal gyrus (right hemisphere), 8.66 ○ Inferior frontal gyrus (orbital part, left hemisphere), 6.52 ○ Superior temporal gyrus (right hemisphere), 8.02 ○ Middle temporal gyrus (right hemisphere), 6.05-7.29 ○ Supplementary motor area (right hemisphere), 7.93 ○ Precuneus, 8.66
Burke (2015)[133] [redacted] the Netherlands	**Population**: N = 79 • AFAB TGNB adolescents with GD: N = 21 • AMAB TGNB adolescents with GD: N = 17 • control girls: N = 21 • control boys: N = 20 **Eligibility**: All subjects were adolescents. All subjects in group with GD adolescent group had been treated with GnRH analogs. No other eligibility requirements or details were given. **Sampling Method**: All subjects with GD were recruited via the Venter of Expertise on Gender Dysphoria at the Medical Center. The control participants were recruited via several primary and secondary schools in The Netherlands and by inviting friends and relatives of the participants with GD. All subjects	The mean (± SD) ages were: • 21 girls with GD (16.1 ± 0.8) • 17 boys with GD (15.3 ± 1.2) • 21 control girls (16.3 ± 0.9) • 20 control boys (15.0 ± 0.6)	TGNB Adolescent girls and boys with GD treated with .75 mg of Triptorelin (Decapeptyl-CR®, Ferring, Hoofddorp, The Netherlands), a GnRH analog, by injection for on average 24 months (range 2–48 months), resulting in complete suppression of gonadal hormone production.	Control group of adolescent boys and girls. Female adolescent controls were tested randomly according to their menstrual cycle, and 11 of 21 control girls reported using hormonal contraception.	• Hypothalamic activation when smelling androstadienone was ascertained by fMRI using the following methods: • Normal olfactory function for subjects was ascertained. For the olfactory stimulation in the MRI, androstadienone was diluted and delivered to the subjects' nostrils by means of an air-dilution olfactometer. With a total air flow of about 1 L per minute during the "ON" periods the odor was delivered every 2s for 1s, whereas during the "OFF" periods, subjects received odorless air. The MRI scans were performed on a 3.0 T GE Signa HDxt scanner. A scanning session consisted of six alternating ON-OFF lasting 3.6 min. For co-registration with the functional images, a T1-	**Hypothalamic activation when smelling androstadienone** • AFAB: ○ Compared to adolescent girls (AFAB) with GD, control girls showed a significantly stronger hypothalamic response to androstadienone over time. Thus the comparison of adolescent control girls to girls diagnosed with GD revealed a significant effect of gender (control girls > girls with GD), which was mainly explained by the effect of the TM regressor (t = 4.3; *P* = .002). ○ The activation in adolescent girls (AFAB) with GD was very similar to that in adolescent control boys, remaining stable over the course of stimulation. • AMAB: ○ When adolescent boys (AMAB) with GD were compared to adolescent control boys, a significant effect of condition (ON > OFF) was observed. (*P* < .05) ○ Adolescent boys (AMAB) with GD showed a significantly stronger, thus sex-atypical response, to androstadienone compared to control boys, irrespective of the factor time. (*P* < .05) ○ Adolescent boys (AMAB) with GD showed female-typical hypothalamic responses upon smelling androstadienone without any effects due to sensitization.

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	and their legal guardians gave their informed consent.				weighted scan was obtained. Individual image data were analyzed using boxcar regressors convolved with a synthetic hemodynamic response function and a first-order time modulation (TM) regressor to test for possible effects of adaptatioNSensitization to androstadienone. **Cross-sectional**: Exposures/outcomes measured at the same time	
Burke (2016)[130] [redacted]	**Population**: N = 62 • Transgender boys: ○ Session 1: N = 21 ○ Session 2: N = 21 • Control girls: ○ Session 1: N = 21 ○ Session 2: N = 20 (1 dropped out) • Control boys ○ Session 1: N = 20 ○ Session 2: N = 16 (4 dropped out) **Eligibility**: Transgender boys were recruited if they had been GD since childhood and were taking GnRH analogs and would be taking testosterone. No other inclusion criteria given. Exclusion criteria for participation in the study were any form of neurologic or psychiatric disorder and continuous psychotropic medication use. **Sampling Method**: Adolescent girls with GD who had been gender dysphoric since childhood were recruited via the Center of Expertise	Mean (SD) age • Trans boys: ○ Session 1: 16.1 ± 0.8 ○ Session 2: 17.1 ± 0.7 • Control girls: ○ Session 1: 16.3 ± 1.0 ○ Session 2 17.6 ± 0.8 • Control boys: ○ Session 1: 15.9 ± 0.6 ○ Session 2: 17.2 ± 0.7 • No significant difference between groups Session 1, *P* = 0.34, or session 2, *P* = 0.16 IQ • Trans boys: 100.5 ± 12.7 • Control girls: 110.3 ± 14.7 • Control boys: 113.4 ±14.5 • There was a significant difference between groups (*P* = 0.009), so a one-way ANOVA corrected from group differences in IQ Sexual orientation • Trans boys: 100% gynephilic	Transgender boys (natal girls with GD) who had puberty suppressed, and then started CSH. • **Session 1 (baseline):** Transgender boys had been treated monthly with 3.75 mg of triptorelin (Decapeptyl- CR, Ferring) by injection for on average 24 (range 2–48) months, resulting in complete suppression of gonadal hormone production. • **Session 2:** Transgender boys had been receiving testosterone treatment for on average 10 (range 6–15) months. All natal girls with GD either received a testosterone ester mixture every 2 weeks or testosterone undecanoate every 12 weeks.	Control girls and boys: matched by age.	Subjects underwent fMRI while performing a mental rotation task (MRT). • MRT: Participants were presented with 3D drawing from the mental rotation stimulus library and could rotate the shape. Between 2 presented shapes, participants had to indicate whether the 2 shapes were identical or mirror images. Outcome parameters were the percentage of trials correctly identified and mean reaction time per trial (RT/trial). • fMRI data was used to identify brain activation differences between groups. **Cohort**: Measurements were taken at 2 points in time, after intervention	**% correct** (mean ± SD) • Session 1 ○ F = 0.5 ○ No significant difference between groups (*P* = NS) ○ Transgender boys: 66.7 ± 15.9 ○ Control girls: 67.0 ± 11.6 ○ Control boys: 70.2 ± 10.7 • Session 2 ○ F = 0.5 ○ No significant difference between groups (*P* = NS) ○ Transgender boys: 74.2 ± 9.0 ○ Control girls: 71.7 ± 8.2 ○ Control boys: 71.6 ± 10.3 **RT/trial (seconds)** (mean ± SD) • Session 1: ○ F = 0.04 ○ No significant difference between groups (*P* = NS) ○ Transgender boys: 8.0 ± 2.2 ○ Control girls: 8.2 ± 1.5 ○ Control boys: 8.1 ± 1.6 • Session 2: • F = 1.0

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	on Gender Dysphoria. Age-matched controls were recruited via several secondary schools in the Netherlands and by inviting friends of the participants with GD. All participants and their legal guardians gave their informed consent.	• Control girls: 100% androphilic • Control boys: 100% gynephilic Pubertal stage: There were no significant differences in puberty stages between the groups-all were in pubertal stage 4 or higher.				• No significant difference between groups (*P* = NS) ○ Transgender boys: 6.7 ± 2.1 ○ Control girls: 6.8 ± 1.7 ○ Control boys: 7.5 ± 2.0 0.35 **Differences in brain activation during mental rotation** • Session 1 (baseline) ○ Control girls had higher brain activation than transgender boys in the Frontal R Precentral/inferior frontal operculum activation region of the brain (*P* = 0.034) similar to the sex difference observed between the male and female control groups. ○ No other between-group differences were found • Session 2: ○ Transgender boys had higher brain activation than control girls in the following areas: ○ Parietal R Superior parietal/inferior parietal region of the brain (*P* = 0.06, authors noted as significant) ○ Parietal L Cuneus/superior occipital region of the brain (*P* = .002) ○ No other significant interaction effects were found between transgender boys and the control groups
Nokoff (2020)[131] [redacted] Colorado	Population: N = 143 • Transgender men: n = 21 patients ○ TG men (n = 19) matched with 19 cisgender men (n = 19) ○ TG men (n = 19) matched with cisgender women (n = 42) ○ 17 TG men in both comparisons • Transgender women: n = 14 patients ○ TG women (n = 11) matched with Cisgender women (n = 23)	Mean age (SD) years • Transgender women (n = 14): 16 (1.4) • Matched cis females (n = 23): 15.9 (1.4) • Matched cis males (n = 24): 15.7 (1.4) • Transgender men (n = 21): 17 (1.4) • Matched cis females (n = 42): 15.2 • Matched cis males (n = 19): 15.3 (1.6)	**TM vs CF** TGNB male cohort (TM) with testosterone therapy for at least 3 months. The average dose of testosterone was 217 (88) mcg/month for the average duration of 11.2 (5.9) months. 12 were taking IM injections, 9 were using SQ. 1 participant had recently discontinued taking GnRH analogs and 3 had used them in the past	Matched cisgender female cohort (CF) matched by puberty stage (Tanner stage 5) and BMI ± 6%	Body composition measurements were collected: • BMI-calculated from weight and height measured twice to calculate BMI. • fat mass and percentage • lean mass and percentage • leptin • hormone levels were calculated from fasting blood samples • total estradiol • total testosterone • SHBG • free androgen index	**TM vs CF** **Body Composition** measurements (estimated from graph): • Lean mass (%): TM had a significantly higher lean mass (*P* = .039) and percent lean tissue than CF (68% vs 64%, *P* = .002) • Body fat (%): TM had significantly lower fat mass (*P* = 0.029) and % body fat compared to CF (28.75% vs 32.81%, *P* = .002) **Leptin** (ng/mL): TM had significantly lower leptin levels than CF: (13.75 vs 18.5 *P* = .0018) **Hormone Levels:** • Total estradiol (pg/mL) mean (SD): There was no significant difference in levels between TM and CF: 43 (23) vs 63 (40), *P* = NS • Total testosterone (ng/dL) mean (SD): The TM cohort had significantly higher levels than the CF cohort: 363 (220) vs 39 (13) *P* < .001

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	○ TG women (n = 13) matched with cisgender men (n = 24) ○ 10 TG women are in both comparisons **Eligibility criteria:** • Transgender patients: had been taking testosterone or estradiol for the last 3 months. Patients were excluded if they had significant medical or psychiatric comorbidities • Cisgender peers: Controls taken from the RESISTANT and HIP study. The RESISTANT study selected individuals between 12 and 19 that were > 1 Tanner stage, sedentary and were excluded if they had hypertension, hemoglobin < 9 mg/dL, serum creatinine > 1.5 mg/dL, had medication dependent asthma or another condition that would cause insulin resistance. The HIP study selected adolescents in early puberty that were Tanner Stage 2-3 who were normal weight or obese through pediatric practices during 2009 to 2015. Diabetes, prediabetes or another condition that affected glucose metabolism was reason for exclusion. **Sampling method:** • Transgender patient were recruited from the TRUE Center for Gender Diversity at Children's Hospital Colorado • Cisgender patients' data were used from previous studies- the HIP and RESISTANT study. CM				**Cross sectional**: transgender patients had their measurements taken on the same day while cisgender patients were taken from previous research	• SHBG (nmol/L) mean (SD): The TM cohort had significantly lower levels than the CF cohort: 24 (11) vs 47 (25) *P* < .001 • Free androgen index mean (SD): The TM cohort had significantly higher levels than the CF cohort: 65 (47) vs 4 (2) *P* < .001
			TM vs CM			**TM vs CM**
			TGNB male cohort (TM) with testosterone therapy for at least 3 months. The average dose of testosterone was 217 (88) mcg/month for the average duration of 11.2 (5.9) months. 12 were taking IM injections, 9 were using SQ. 1 participant had recently discontinued taking GnRH analogs and 3 had used them in the past	Matched cisgender male cohort (CM) matched by puberty stage (Tanner stage 5) and BMI ± 6%		**Body Composition measurements** (estimated from graph): • Lean mass (%): TM had a lower and lean mass (*P* < .001) and lean mass % compared to CM: (69% vs 73%, *P* = .029) • Body fat (%): TM had a higher % body fat compared to CM: (27.8% vs 24.4%, *P* = .047) **Leptin** (ng/mL): The TM cohort had non-significantly higher leptin levels than the CM cohort: 12.5 vs 8.25, *P* = NS **Hormone Levels** • Total estradiol (pg/mL) mean (SD): The TM cohort had significantly higher levels than the CM cohort: 46 (22) vs 24 (11), *P* = .004 • Total testosterone (ng/dL) mean (SD): There was no significant difference in levels between the TM and CM cohort: 378 (219) vs 445 (152), *P* = NS • SHBG (nmol/L) mean (SD): There was no significant difference in levels between the TM and CM cohort: 26 (11) vs 36 (13), *P* = NS • Free androgen index mean (SD): There was no significant difference in the index between the TM and CM cohort: 64 (47) vs 48 (16), *P* = NS
			TF vs CF			**TF vs CF**
			TGNB female cohort (TF) with estrogen therapy for at least 3 months Taking an average dose of estradiol of 1.5 (1) mg/day with an average treatment duration of 12.3 (9.9) months. Four trans females were on a GnRH analog and 6 had been on them in the past. 7 TF were on spironolactone and 1 was	Matched cisgender female cohort (CF) matched by age (within a year) and BMI percentile ± 12.5%		**Body Composition** measurements (estimated from graph): • Lean mass (%): TF had a significantly higher lean mass (*P* = .004) and percent lean tissue than CF (66% vs 62%, *P* = .032). • Body fat (%): TF had significantly lower % body fat compared to CF (31% vs 35%, *P* = .033) **Leptin** (ng/mL): TM had non-significantly lower leptin than CF (17.75 vs 19, *P* = NS) **Hormone Levels**

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	and CF matched with TM were matched based on pubertal stage and BMI. CM and CF matched to TF were matched based on age and BMI.		on IM medroxyprogesterone acetate			• Total estradiol (pg/mL) mean (SD): There was no significant difference in levels between TF and CF: 98 (135) vs 96 (127), *P* = NS • Total testosterone (ng/dL) mean (SD): The TF cohort had significantly higher levels than the CF cohort: 224 (182) vs 43 (10) *P* = .012 • SHBG (nmol/L) mean (SD): There was no significant difference in levels between the TM cohort and the CF cohort: 49 (36) vs 50 (30), *P* = NS • Free androgen index, mean (SD): The TF cohort had a significantly higher index than the CF cohort: 33 (36) vs 5 (3) *P* < .01
			TF vs CM			**TF vs CM**
			TGNB female cohort (TF) with estrogen therapy for at least 3 months Taking an average dose of estradiol of 1.5 (1) mg/day with an average treatment duration of 12.3 (9.9) months. Four trans females were on a GnRH analog and 6 had been on them in the past. 7 TF were on spironolactone and 1 was on IM medroxyprogesterone acetate	Matched cisgender male cohort (CM) matched by age (within a year) and BMI percentile ± 12.5%		**Body Composition measurements** (estimated from graph): • Lean mass (%): TF had lower percent lean tissue than CF (69% vs 77%, *P* = 0.001) • Body fat (%): TF had a higher fat mass (*P* = 0.004) and % body fat compared to CM: (28% vs 20%, *P* = .001) **Leptin** (ng/mL): TF had significantly higher leptin levels compared to CM: (13.75 vs 6.25, *P* < .001) **Hormone Levels** • Total estradiol (pg/mL) mean (SD): The TF cohort had significantly higher levels than the CM cohort: 124 (162) vs 23 (9) *P* = .005 • Total testosterone (ng/dL) mean (SD): The TF cohort had significantly lower levels than the CM cohort: 252 (214) vs 412 (168) *P* = .012 • SHBG (nmol/L) mean (SD): There is no significant difference in levels between TF and CM: 50 (48) vs 40 (16), *P* = NS • Free androgen index mean (SD): There is no significant difference in the index between TF and CM: 36 (34) vs 37 (16), *P* = NS
Nokoff (2021)[131] [redacted] Colorado[redacted]	**Population**: N = 48 • Transgender males: n = 9 patients who had been on a GnRH analog for ≥ 3 months (before initiation of testosterone or estradiol)	**Transgender males:** • mean age (SD) in years = 13.8 (1.7) • mean age (SD) at initiation of GnRH analogs in years = 12.1 (1.9)	Transgender males and females had been on a GnRH analogs for at least 3 months	Cisgender males and females: Matched on sex assigned at birth, age, and BMI	**Body composition**: fat-free mass and fat mass was measured by dual-energy X-ray absorptiometry **Hormone level.** Serum/plasma fasted blood samples were assayed for:	**Body composition:** (mean ± SD) • Transgender males had a higher percent body fat (36 ± 7 vs. 32 ± 5%, *P* = .042) and lower total lean mass (32.3 ± 5.2 vs. 36.4 ± 7.8 kg, *P* = .009), but not percent lean mass than cisgender females.

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
between 2016 and 2019	• Transgender females: n = 8 patients who had been on a GnRH analog for ≥ 3 months (before initiation of testosterone or estradiol) • Cisgender males: n = 17 • Cisgender females: n = 14 **Eligibility criteria:** • Transgender cohort: Transgender youth who had been on a GnRH analog for ≥ 3 months were recruited between 2016 and 2019 from the hospital; youth were excluded if they had significant medical or psychiatric comorbidities (including diabetes or antipsychotic treatment), or were using hormones not prescribed by a physician • Cisgender cohort: Healthy cisgender controls were obtained from two studies performed at our institution: the RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study and the Health Influences in Puberty (HIP) study **Sampling method:** • Transgender cohort: All transgender females and five transgender males were recruited from the same cross-sectional study. An additional four transgender males were recruited from a separate longitudinal study, and data from their baseline visit are included here, when they were on a GnRH analog alone. None of the participants were	• mean GnRH analog duration (SD) in months = 20.9 (19.8) • majority white n = 6 (67%) with Hispanic/Latino n = 4 (44%) • depression at baseline n = 2 (22%) • anxiety at baseline n = 1 (11%) • most N = 3 (33%) were at pubic hair Tanner stage 4, most n = 3 (33%) were at breast/testicular Tanner stage 3. • n = 5 (63%) had hypertension • n = 5 (63%) hypercholesterolemia • n = 4 (50%) had type 2 diabetes. **Transgender females:** • Mean age (SD) in years = 13.7 (1.2) • mean age (SD) at initiation of GnRH analogs in years = 12.8 (1.3) • mean GnRH analog duration (SD) in months = 11.3 (7) • majority white n = 7 (88%) with half of Hispanic/Latino n = 4 (50%) and half of not Hispanic/Latino n = 4 (50%) • depression at baseline, n = 3 (38%) • anxiety at baseline, n = 1 (12%) • most n = 3 (38%) were at pubic hair Tanner stage 2, most n = 5 (63%) were at breast/testicular Tanner stage 2. • n = 5 (63%) had hypertension • n = 3 (38%) hypercholesterolemia • n = 1 (13%) had type 2 diabetes. **Cisgender males:** • mean age (SD) in years = 13.9 (0.9) • majority white n = 13 (76%) with not Hispanic/Latino n = 13 (76%),			• Estradiol • Testosterone • SHBL Cross-sectional study: Outcomes and measures taken at the same time.	• Transgender females had higher percent body fat (31 ± 9 vs. 24 ± 10%, *P* = .002) and lower percent lean mass (66 ± 8 vs. 74 ± 10%, *P* < .001) than cisgender males. **Hormone levels:** (mean ± SD) • Total Estradiol (pg/mL): o Transgender males had significantly lower estradiol (15 ± 5) than cisgender females (58 ± 45), *P* < .05 o Transgender female levels (12 ± 3) were not significantly different from the levels of cisgender males (14 ± 5), *P* = NS • Total Testosterone (ng/dL) o Transgender male levels (29 ± 12) showed no significant difference from cisgender female levels (38 ± 12), *P* = NS o Transgender females had significantly lower testosterone (50 ± 52) than cisgender males (231 ± 153), *P* ≤ .001 • SHBL (nmol/L) o Transgender male levels (53 ± 34) were not significantly different from cisgender females (47 ± 19), *P* = NS o Transgender female levels (50 ± 24) were not significantly different from cisgender males (54 ± 26), *P* = NS

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	receiving testosterone or estradiol treatment at the time of this study. • Cisgender cohort: Transgender males (assigned female sex at birth, male gender identity) were matched to cisgender females and transgender females (assigned male sex at birth, female gender identity) were matched to cisgender males.	• most n = 5 (29%) were at pubic hair Tanner stage 2, most n = 7 (41%) were at breast/testicular Tanner stage 2. • n = 9 (75%) had hypertension • n = 8 (67%) hypercholesterolemia • n = 4 (33%) had type 2 diabetes. **Cisgender females:** • mean age (SD) in years = 13.9 (1.7) • majority white n = 10 (71%) with not Hispanic/Latino n = 9 (64%) • most n = 4 (29%) were at pubic hair Tanner stage 4, most n = 9 (64%) were at breast/testicular Tanner stage 5. • n = 6 (75%) had hypertension • n = 7 (88%) hypercholesterolemia • n = 7 (64%) had type 2 diabetes.				
Schulmeister (2022)[95] Four academic medical centers with multidisciplinary clinics [redacted] between July 2016 and September 2018	N = 281 youth • TGNB cohort: n = 55 subjects • BMDCS cohort [cisgender]: n = 226 subjects **Eligibility criteria**: TGD youth initiating GnRH analog treatment for puberty suppression were recruited between July 2016 and September 2018. Participants were included in the analysis if they had been treated with a GnRH analogs for at least 10 months and no more than 14 months. Individuals taking stimulant medication for treatment of ADHD were included in the analysis. Participants were excluded from the study if they had previously undergone GnRH analog treatment, had a diagnosis of precocious puberty, had serious psychiatric symptoms, or could not	Transgender cohort: • 26 (47%) were DMAB and 29 (53%) were DFAB. • Mean age (range) in years at GnRH analog initiation = 11.5 (9.0 to 14.5). • Most individuals in the cohort started GnRH analogs in early puberty (Tanner stage II or III). • Of those participants DMAB, most were Tanner stage II at the initiation of GnRH analogs (21 individuals, 81%), 3 (12%) were Tanner III, and 2 (8%) were Tanner IV. • Of those participants DFAB, 13 (45%) were Tanner II at initiation of GnRH analogs, 13 (45%) were Tanner III, and 3 (10%) were Tanner IV. Cisgender cohort:	Transgender cohort: GnRH analog treatment	BMDCS cohort: no hormonal intervention	**Anthropometric data:** • Collected in the course of clinical care were abstracted from the medical record and recorded prior to the participant beginning GnRH analogs (baseline) and at 6- and 12-month follow-up visits. • Annualized HV was calculated as the difference between the baseline and the 12-month visit heights (expressed in centimeters), divided by the time between the two visits (expressed as a fraction of one year). **Tanner stages data:** Tanner stages were assigned by the participant's clinician in the course of clinical care using the	**Height velocity:** • The median (IQR) HV for transgender cohort after starting GnRH analogs was 5.1 (3.7–5.6) cm/year. Compared to prepubertal, presumed cisgender youth in the BMDCS, transgender youth treated with GnRH analogs had similar HV when controlled for mid-age (*P* = NS). • When stratified by Tanner stage and controlled for mid-age, TGNB youth who started on a GnRH analogs at Tanner stage II or stage III had HV comparable to prepubertal youth in BMDCS (5.3 (4.1–5.6) cm/year vs. 6.1 (4.3–6.5) cm/year, *P* = NS and 4.4 (3.3–6.0) cm/year vs. 6.1 (4.3–6.5) cm/year, *P* = NS). • Individuals starting on GnRH analogs at Tanner stage IV had significantly lower HV compared to pre-pubertal youth in the BMDCS (1.6 (1.5–2.9) cm/year vs. 6.1 (4.3–6.5) cm/year, *P* = .006).

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.3. Clinical studies comparing TGNB to cisgender peers regarding body change outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	read or understand English. Participants were excluded from analysis if they initiated treatment with cross-sex hormones (CSH; estradiol or testosterone) prior to their 12-month follow-up visit. **Sampling method:** Participants were recruited prior to GnRH analog initiation from four gender specialty clinics in the United States. A comparison group of prepubertal, presumed cisgender youth not receiving hormonal intervention was drawn from BMDCS.	• 118 (52%) were DMAB and 108 (48%) were DFAB. • The BMDCS cohort was younger than the TGD cohort (11.0 ± 2.8 years vs. 11.9 ± 1.2 years, *P* = 0.01). • All participants in BMDCS were prepubertal (Tanner I) at baseline.			standards of Marshall and Tanner. **Cohort**: Outcomes were measured after the exposures had been measured (clinical records review).	

Table abbreviations: AMAB, assigned male at birth; AFAB, assigned female at birth; BMDCS, Bone Mineral Density in Childhood Study; BMI, body mass index; DFAB, defined female at birth; DHEAS, dehydroepiandrosterone sulfate; DMAB, defined male at birth; FFM, fat free mass; FM, fat mass; fMRI, functional magnetic resonance imaging; GAHT, gender affirming hormone therapy; GnRHa, gonadotropin releasing hormone analog; HV, height velocity; IQR, interquartile range; LI, lateralization index; MRT, mental rotation task; RT, reaction time; SD, standard deviation; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass; TGD, transgender; TGNB, Transgender, non-binary; TM, time modulation

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
Millington (2022)[90] Four large hospitals-[redacted] that were taking part in the Trans Youth Care United States Study	**N= 286 TGNB patients** N=1188 NHANES study Participants **Eligibility**: • TGNB cohort: clinician diagnosed gender therapy with CSHT deemed appropriate, received care at the clinic, age 8-20 and reads and understands English. Those that previously used CSH, were enrolled in the puberty blocker cohort or had severe psychiatric symptoms were excluded. • Cisgender cohort came from the NHANES study participants and were matched by age and sex. NHANES study participants were nonpregnant, age 12-22. **Sampling method**: patients were selected from clinic if they met inclusion criteria. No information on NHANES participants. **Subset definition:** • TGNB cohort (N=286): DMAB (n=92) and DFAB (n=194) measured at baseline and 6 mo increments • NHANES cohort (N=1188): female (n=584) and male (n=604)	**DMAB**: • Age: 17.3 years • Gender: ○ 51 identified as trans female ○ 36 as female ○ 1 as gender fluid ○ 4 as non-binary • CSHT: ○ 77 were taking oral estrogen ○ 12 were taking transdermal estrogen ○ 3 were taking IM estrogen. ○ 58 used spironolactone **DFAB**: • Age: 16.2 years • Gender ○ 78 identified as male ○ 103 as transgender male ○ 2 as gender fluid ○ 1 as gender queer ○ 10 as non-binary • CSHT ○ 189 were taking testosterone SQ ○ 5 were taking testosterone gel. ○ 1 used spironolactone **NHANES participants** • Age: 12-22	DFAB: testosterone, average SQ dose was 40 mg/week, average transdermal dose was 40.5 mg/day	Comparison group was taken from participants of the NHANES study, matched by age and sex	• Serum Creatinine (SCr) measured in Z-score adjusted for age and gender **Cohort:** Outcome was measured after exposure, measurements taken at baseline and 12 months.	SCr Z-score, mean ± SD • At baseline, DFAB participants had a higher baseline SCr than female NHANES participants (+0.3 ± 1.0, *P* = .002). • At 12 months this difference was more pronounced (+1.4 ± 1.0, *P* < .0001 compared to baseline). • At 12 months, the DFAB participants' Z score was more similar to that of male NHANES participants (-0.3 ± 0.8) than that of female NHANES participants
			DMAB: estrogen, average oral dose 4 mg/day, average transdermal dose 0,5 mg/day, average IM dose was 15 mg/week	Comparison group was taken from participants of the NHANES study, matched by age and sex		SCr Z-score, mean ± SD • At baseline, DMAB SCr did not differ from reference group of male NHANES participants (-0.2 ± 0.9, *P* = NS). • After 12 months of treatment with estrogen, the difference between the reference group were more pronounced (-1.1 ± 0.9, *P* < .0001 compared to baseline). • After 12 months, their values were closer to female NHANES participants (-0.6 ± 1.0) than male NHANES participants.
Nokoff (2020)[131] [redacted]	**Population**: N = 143 • Transgender women: N = 14 patients	Mean age (SD) • Transgender women (n = 14): 16 (1.4) years.	**TM vs CF**		Cardiometabolic markers collected:	**TM vs CF**
			TGNB male cohort with testosterone therapy for at least 3 months	Matched cisgender female cohort matched by puberty		There were significant differences in HDL levels between the trans male and cis female cohorts. All other differences were non-significant.

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
[redacted] Colorado	○ TG women (n = 11) matched with Cisgender women (n = 23) ○ TG women (n = 13) matched with cisgender men (n = 24) ○ 10 TG women are in both comparisons • Transgender men: N = 21 patients ○ TG men (n = 19) matched with 19 cisgender men (n = 19) ○ TG men (n = 19) matched with cisgender women (n = 42) ○ 17 TG men in both comparisons **Eligibility criteria:** • Transgender patients: had been taking testosterone or estradiol for the last 3 months. Patients were excluded if they had significant medical or psychiatric comorbidities • Cisgender peers: Controls taken from the RESISTANT and HIP study. The RESISTANT study selected individuals between 12 and 19 that were > 1 Tanner stage, sedentary and were excluded if they had hypertension, hemoglobin < 9 mg/dL, serum creatinine > 1.5 mg/dL, had medication dependent asthma or another condition that would cause	• Matched cis females (n = 23): 15.9 (1.4) years • Matched cis males (n = 24): 15.7 (1.4) years • Transgender men (n = 21): 17 (1.4) years. • Matched cis females (n = 42): 15.2 (1.9) • Matched cis males (n = 19): 15.3 (1.6) years	Average dose of testosterone was 217 (88) mcg/month for the average duration of 11.2 (5.9) months. 12 were taking IM injections, 9 were using SQ. 1 participant had recently discontinued taking GnRH analogs and 3 had used them in the past	stage (tanner stage 5) and BMI ± 6%	• BMI-calculated from weight and height measured twice to calculate BMI. • Diastolic and systolic blood pressure-measured with appropriate cuff after sitting for 5 min. Fasting blood samples were used to collect: • Inverse of fasting insulin-used to measure insulin sensitivity. • HOMA-IR-calculated as (glucose x insulin)/405 • Fasting glucose • Hemoglobin A1c • AST • ALT • Total cholesterol • TG • HDL • LDL-calculated using the Friedewald formula **Cross sectional**: transgender patients had their measurements taken on the same day while cisgender patients were taken from previous research	• BMI (%) mean (SD): There was no significant difference between trans male and the cis female cohort: 71 (22) vs. 71 (21), *P* = NS • Diastolic BP (mm HG) mean (SD): There was no significant difference between trans male and the cis female cohort: 70 (7) vs. 66 (6), *P* = NS • Systolic BP (mm HG) mean (SD): There was no significant difference between the trans male and the cis female cohort: 108 (9) vs. 111 (8), *P* = NS • Inverse of fasting insulin (mL/mU) mean (SD): There was no significant difference between the trans male and the cis female cohort: 0.08 (0.028) vs 0.097 (0.052), *P* = NS • HOMA-IR mean (SD): There was no significant difference between the trans male and the cis female cohort: 3.3 (2) vs 3.2 (1.5), *P* = NS • Fasting glucose (mg/dL) mean (SD): There was no significant difference between the trans male and the cis female cohort: 89 (5) vs 85 (6), *P* = NS • Hemoglobin A1c (%) mean (SD): There was no significant difference between the trans male and the cis female cohort: 5.3 (0.2) vs 5.2 (0.2), *P* = NS • AST (U/L) mean (SD): ○ trans male cohort had significantly higher AST levels than the cis female cohort: 39 (5) vs 29 (8) *P* = .001 ○ trans female and the cis male cohort: 37 (4) vs 34 (18), *P* = NS • ALT (U/L) mean (SD): There was no significant difference between the trans male and the cis female cohort: 26 (5) vs 26 (7), *P* = NS • Total Cholesterol (mg/dL) mean (SD): There was no significant difference between the trans male and the cis female cohort: 147 (16) vs 153 (29), *P* = NS • TG (mg/dL) mean (SD): There was no significant difference between the trans male and the cis female cohort: 75 (21) vs 100 (45), *P* = NS

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	insulin resistance. The HIP study selected adolescents in early puberty that were Tanner Stage 2-3 who were normal weight or obese through pediatric practices during 2009 to 2015. Diabetes, prediabetes or another condition that affected glucose metabolism was reason for exclusion. **Sampling method:** • Transgender patients were recruited from the TRUE Center for Gender Diversity at Children's Hospital Colorado • Cisgender patients' data were used from previous studies- the HIP and RESISTANT study. CM and CF matched with TM were matched based on pubertal stage and BMI. CM and CF matched to TF were matched based on age and BMI.					• HDL (mg/dL) mean (SD): The trans male cohort had significantly lower HDL than the cis female cohort: 40 (5) vs 46 (7), *P* = .043 • LDL (mg/dL) mean (SD): There was no significant difference between the trans male and the cis female cohort: 92 (16) vs 87 (22), *P* = NS
			TM vs CM			**TM vs CM**
			TGNB male cohort with testosterone therapy for at least 3 months. Average dose of testosterone was 217 (88) mcg/month for the average duration of 11.2 (5.9) months. 12 were taking IM injections, 9 were using SQ. 1 participant had recently discontinued taking GnRH analogs and 3 had used them in the past	Matched cisgender male cohort matched by puberty stage (tanner stage 5) and BMI ± 6%		There were significant differences in systolic BP and ALT levels between the trans male and cis male cohort. All others comparisons were non-significant. • BMI (%) mean (SD): There was no significant difference between trans male and the cis male cohort: 63 (28) vs. 64 (28), *P* = NS • Diastolic BP (mm HG) mean (SD): There was no significant difference between the trans male and the cis male cohort: 69 (8) vs. 67 (10), *P* = NS • Systolic BP (mm HG) mean (SD): The trans male cohort had a significantly lower mean systolic BP than the cis male cohort: 108 (9) vs. 115 (13), *P* = .005 • Inverse of fasting insulin (mL/mU) mean (SD): There was no significant difference between the trans male and the cis male cohort: 0.088 (0.023) vs 0.145 (0.1.09), *P* = NS • HOMA-IR mean (SD): There was no significant difference between the trans male and the cis male cohort: 2.7 (0.8) vs 2.2 (1.4), *P* = NS • Fasting glucose (mg/dL) mean (SD): There was no significant difference between the trans male and the cis male cohort: 88 (5) vs 86 (10), *P* = NS • Hemoglobin A1c (%) mean (SD): There was no significant difference between the trans male and the cis male cohort: 5.3 (0.3) vs 5.3 (0.3), *P* = NS • AST (U/L) mean (SD): There was no significant difference between the trans male and the cis male cohort: 39 (4) vs 36 (16), *P* = NS

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• ALT (U/L) mean (SD): The trans male cohort had significantly lower levels of ALT than the cis female cohort: 25 (6) vs 34 (17), *P* < .001 • Total Cholesterol (mg/dL) mean (SD): There was no significant difference between the trans male and the cis male cohort: 143 (19) vs 146 (22), *P* = NS • TG (mg/dL) mean (SD): There was no significant difference between the trans male and the cis male cohort: 76 (23) vs 91 (30), *P* = NS • HDL (mg/dL) mean (SD): There was no significant difference between the trans male and the cis male cohort: 41 (5) vs 46 (9), *P* = NS • LDL (mg/dL) mean (SD): There was no significant difference between the trans male and the cis male cohort: 87 (19) vs 82 (19), *P* = NS
			TF vs CF			**TF vs CF**
			TGNB female cohort with estrogen therapy for at least 3 months Average dose of estradiol of 1.5 (1) mg/day with an average treatment duration of 12.3 (9.9) months. Four trans females were on a GnRH analog and 6 had been on them in the past. 7 TF were on spironolactone and 1 was on IM medroxyprogesterone acetate	Matched cisgender female cohort matched by age (within a year) and BMI percentile ± 12.5%		There was a significant difference in AST levels between the trans female and cis female cohort. All other comparisons were non-significant. • BMI (%) mean (SD): There was no significant difference between trans female and the cis female cohort: 55 (34) vs. 58 (30), *P* = NS • Diastolic BP (mm HG) mean (SD): There was no significant difference between trans female and the cis female cohort: 70(7) vs 66 (7) *P* = NS • Systolic BP (mm HG) mean (SD): There was no significant difference between the trans female and the cis female cohort: 107 (12) vs 113 (7), *P* = NS • Inverse of fasting insulin (mL/mU) mean (SD): There was no significant difference between trans female and the cis female cohort: - 0.066 (0.02) vs 0.098 (0.045), *P* = NS • HOMA-IR mean (SD): There was no significant difference between trans female and the cis female cohort: 3.8 (2.1) vs 2.8 (1.4), *P* = NS

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• Fasting glucose (mg/dL) mean (SD): There was no significant difference between trans female and the cis female cohort: 89 (5) vs 82 (12), *P* = NS • Hemoglobin A1c (%) mean (SD): There was no significant difference between trans female and the cis female cohort: 5.2 (0.4) vs 5.0 (0.2), *P* = NS • AST (U/L) mean (SD): The trans female cohort had significantly higher AST levels than the cis female cohort: 37 (4) vs 23 (6), *P* < .001 • ALT (U/L) mean (SD): There was no significant difference between trans female and the cis female cohort: 25.5 (5) vs 26.6 (6), *P* = NS • Total Cholesterol (mg/dL) mean (SD): There was no significant difference between trans female and the cis female cohort: 148 (23) vs 145 (20), *P* = NS • TG (mg/dL) mean (SD): There was no significant difference between trans female and the cis female cohort: 77 (34) vs 74 (21), *P* = NS • HDL (mg/dL) mean (SD): There was no significant difference between trans female and the cis female cohort: 49 (10) vs 46 (10), *P* = NS • LDL (mg/dL) mean (SD): There was no significant difference between trans female and the cis female cohort: 83 (20) vs 84 (20), *P* = NS
			TF vs CM			**TF vs CM**
			TGNB female cohort with estrogen therapy for at least 3 months Average dose of estradiol of 1.5 (1) mg/day with an average treatment duration of 12.3 (9.9) months. Four trans females were on a GnRH analog and 6 had been on them in the past. 7 TF were on spironolactone and 1 was on	Matched cisgender male cohort matched by age (within a year) and BMI percentile ± 12.5%		There were significant differences in systolic BP, inverse of fasting glucose, HOMA-IR and HDL measurements between the trans female and cis male cohort. All other comparisons were non- significant. • BMI (%) mean (SD): There was no significant difference between trans female and the cis male cohort: 46 (37) vs 45 (36), *P* = NS • Diastolic BP (mm HG) mean (SD): There was no significant difference between trans female and the cis female cohort: 70 (6) vs 67 (5), *P* = NS

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
			IM medroxyprogesterone acetate			• Systolic BP (mm HG) mean (SD): The trans female cohort had a significantly lower mean systolic BP than the cis male cohort: 106 (11) vs 116 (8) *P* = .007 • Inverse of fasting insulin (mL/mU) mean (SD): The trans female cohort had significantly lower inverse fasting of insulin compared to cis males: 0.078 (0.025) vs 0.142 (0.064) *P* = .011 • HOMA-IR mean (SD): The trans female cohort had a significantly higher HOMA-IR compared to the cis male cohort: 3.4 (2.2) vs 2.1 (1.2), *P* = .012 • Fasting glucose (mg/dL) mean (SD): There was no significant difference between trans female and the cis male cohort: 90 (4) vs 86 (6), *P* = NS • Hemoglobin A1c (%) mean (SD): There was no significant difference between trans female and the cis male cohort: 5.2 (0.4) vs 5.1 (0.3), *P* = NS • AST (U/L) mean (SD): There was no significant difference between trans female and the cis male cohort: 37 (4) vs 34 (18), *P* = NS • ALT (U/L) mean (SD): There was no significant difference between trans female and the cis male cohort: 24 (5) vs 32 (18), *P* = NS • Total Cholesterol (mg/dL) mean (SD): There was no significant difference between trans female and the cis male cohort: 152 (22) vs 136 (25), *P* = NS • TG (mg/dL) mean (SD): There was no significant difference between trans female and the cis male cohort: 81 (34) vs 97 (30), *P* = NS • HDL (mg/dL) mean (SD): The trans female cohort had significantly higher HDL levels than the cis male cohort: 50 (10) vs 43 (6), *P* = .023 • LDL (mg/dL) mean (SD): There was no significant difference between trans female and the cis male cohort: 85 (20) vs 74 (22), *P* = NS
Nokoff (2021)[134]	Population: N = 48	**AFAB**			Cardiovascular outcomes:	**AFAB**

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
[redacted] Colorado[redacted] between 2016 and 2019	• Transgender males: n = 9 patients who had been on a GnRH analog for ≥ 3 months (before initiation of testosterone or estradiol) • Transgender females: N = 8 patients who had been on a GnRH analog for ≥ 3 months (before initiation of testosterone or estradiol) • Cisgender males: N = 17 • Cisgender females: N = 14 Eligibility criteria: • Transgender cohort: Transgender youth who had been on a GnRH analog for ≥ 3 months were recruited between 2016 and 2019 from the hospital; youth were excluded if they had significant medical or psychiatric comorbidities (including diabetes or antipsychotic treatment), or were using hormones not prescribed by a physician • Cisgender cohort: Healthy cisgender controls were obtained from two studies performed at our institution: the RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study and the Health Influences in Puberty (HIP) study Sampling method:	Transgender males: • mean age (SD) in years = 13.8 (1.7) • mean age (SD) at initiation of GnRH analogs in years = 12.1 (1.9) • mean GnRH analog duration (SD) in months = 20.9 (19.8) • majority white n = 6 (67%) with Hispanic/Latino n = 4 (44%) • depression at baseline n = 2 (22%) • anxiety at baseline n = 1 (11%) • most n = 3 (33%) were at pubic hair Tanner stage 4 • most n = 3 (33%) were at breast/testicular Tanner stage 3. • n = 5 (63%) had hypertension • n = 5 (63%) hypercholesterolemia • n = 4 (50%) had type 2 diabetes Cisgender females: • mean age (SD) in years = 13.9 (1.7) • majority white n = 10 (71%) with not Hispanic/Latino n = 9 (64%) • most n = 4 (29%) were at pubic hair Tanner stage 4 • most n = 9 (64%) were at breast/testicular Tanner stage 5. • n = 6 (75%) had hypertension • n = 7 (88%) hypercholesterolemia • n = 7 (64%) had type 2 diabetes.	Transgender males: had been on a GnRH analog for at least 3 months	Cisgender females: Matched on sex assigned at birth, age, and BMI	• Weight- measured twice and averaged. The 2000 Centers for Disease Control and Prevention Growth Charts were used to calculate BMI percentiles using sex assigned at birth • Blood pressure was measured after ~5 min of seated rest, with an age- and size-appropriate manual cuff. Measured twice and averaged. Fasting blood samples were used to collect: • HbA1c • Inverse of the fasting insulin concentration (1/[fasting insulin])-used to calculate insulin sensitivity • HOMA-IR. • Total cholesterol • Triglycerides • HDL cholesterol d • LDL cholesterol was calculated using the Friedewald formula (for units in mg/dL). Body composition: fat-free mass and fat mass) was measured by dual-energy X-ray absorptiometry Hormone levels. Serum/plasma fasted blood samples were assayed for:	BMI (percentile): • the comparison is not statistically significant (*P* = NS). • transgender males had mean ± SD BMI in percentile of 62 ± 32 • cisgender females had mean ± SD BMI in percentile of 67 ± 29 Blood pressure: no significant differences between cohorts • SBP: ○ transgender males had mean ± SD SBP in mmHg of 104 ± 13 ○ cisgender females had mean ± SD SBP in mmHg of 114 ± 11 ○ comparison not statistically significant (*P* = NS) ○ transgender males had mean ± SD SBP in percentile of 41 ± 32 ○ cisgender females had mean ± SD SBP in percentile of 68 ± 24 ○ comparison not statistically significant (*P* = NS). • DBP ○ transgender males had mean ± SD DBP in mmHg of 67 ± 5 ○ cisgender females had mean ± SD SBP in mmHg of 65 ± 9 ○ comparison not statistically significant (*P* = NS) ○ transgender males had mean ± SD SBP in percentile of 59 ± 20 ○ cisgender females had mean ± SD DBP in percentile of 55 ± 25 ○ comparison not statistically significant (*P* = NS) Fasting glucose: • transgender males had a significantly higher fasting glucose than cisgender females. (*P* < .05). • transgender males had mean ±SD fasting glucose in mg/dL of 89 ± 4

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	• Transgender cohort: All transgender females and five transgender males were recruited from the same cross-sectional study. An additional four transgender males were recruited from a separate longitudinal study, and data from their baseline visit are included here, when they were on a GnRH analog alone. None of the participants were receiving testosterone or estradiol treatment at the time of this study. • Cisgender cohort: Transgender males (assigned female sex at birth, male gender identity) were matched to cisgender females and transgender females (assigned male sex at birth, female gender identity) were matched to cisgender males.				• AST • ALT **Cross-sectional study**: Exposures/outcomes measured at the same time	• cisgender females had mean ±SD fasting glucose in mg/dL of 79 ±13 Insulin sensitivity: • transgender males had a significantly lower insulin sensitivity compared to cisgender females ($P < .05$). • transgender males had mean ± SD inverse of fasting insulin in mL/lU of 0.067 ± 0.020 • cisgender females had mean ± SD inverse of fasting insulin in mL/lU of 0.103 ± 0.049 HOMA-IR: • transgender males had significantly higher HOMA-IR when compared to cisgender females ($P \leq .01$). • transgender males had mean ± SD HOMA-IR of 3.7 ± 1.7 • cisgender females had mean ± SD HOMA-IR of 2.3 ± 1.1 Hemoglobin A1C: • transgender males had a significantly higher HbA1c % then cisgender females ($P \leq .05$). • transgender males had mean ± SD Hemoglobin A1C of 5.4% ± 0.2 • cisgender females had mean ± SD Hemoglobin A1C of 5.2% ± 0.2 Total cholesterol: • the comparison is not statistically significant (P = NS). • transgender males had mean ± SD total cholesterol in mg/dL of 158 ± 21 • cisgender females had mean ± SD total cholesterol in mg/dL of 152 ± 27 Triglycerides: • the comparison is not statistically significant (P = NS). • transgender males had mean ± SD triglycerides in mg/dL of 87 ± 43 • cisgender females had mean ± SD triglycerides in mg/dL of 89 ± 24

[a] odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)

[b] odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						HDL: • the comparison is not statistically significant (*P* = NS). • transgender males had mean ± SD HDL in mg/dL of 53 ± 16 • cisgender females had mean ± SD HDL in mg/dL of 48 ± 13 LDL: • the comparison is not statistically significant (*P* = NS). • transgender males had mean ± SD LDL in mg/dL of 88 ± 14 • cisgender females had mean ± SD LDL in mg/dL of 86 ± 23 Liver Enzymes: • AST ○ transgender males had a significantly higher AST level compared to cisgender females (*P* < 0.05) ○ transgender males had mean ± SD in U/L of 42 ± 11 ○ cisgender females had mean ± SD in U/L of 31 ± 10 • ALT ○ the comparison is not statistically significant (*P* = NS) ○ transgender males had mean ± SD in U/L of 28 ± 13 ○ cisgender females had mean ± SD in U/L of 24 ± 9
		AMAB				**AMAB**
		Transgender females: • mean age (SD) in years = 13.7 (1.2) • mean age (SD) at initiation of GnRH analogs in years = 12.8 (1.3) • mean GnRH analog duration (SD) in months = 11.3 (7) • majority white n = 7 (88%) with half of Hispanic/Latino n = 4 (50%) and half of not Hispanic/Latino n = 4 (50%) • depression at baseline, n = 3 (38%) • anxiety at baseline, n = 1 (12%)	Transgender female: had been on a GnRH analog for at least 3 months	Cisgender male: Matched on sex assigned at birth, age, and BMI		BMI (percentile): • the comparison is not statistically significant (*P* = NS). • transgender females had mean ± SD BMI in percentile of 44 ± 39 • cisgender males had mean ± SD BMI in percentile of 45 ± 38 Blood pressure: • SBP: ○ transgender females had mean ± SD SBP in mmHg of 97 ± 6 ○ cisgender males had mean ± SD SBP in mmHg of 108 ± 7 ○ transgender females had significantly lower SBP than cisgender males (*P* ≤ .01)

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
		• most n = 3 (38%) were at pubic hair Tanner stage 2, • most n = 5 (63%) were at breast/testicular Tanner stage 2. • n = 5 (63%) had hypertension • n = 3 (38%) hypercholesterolemia • n = 1 (13%) had type 2 diabetes. Cisgender males: • mean age (SD) in years = 13.9 (0.9) • majority white n = 13 (76%) with not Hispanic/Latino n = 13 (76%), • most n = 5 (29%) were at pubic hair Tanner stage 2, most n = 7 (41%) were at breast/testicular Tanner stage 2. • n = 9 (75%) had hypertension • n = 8 (67%) hypercholesterolemia • n = 4 (33%) had type 2 diabetes.				○ transgender females had mean ± SD SBP in percentile of 15 ± 12 ○ cisgender males had mean ± SD SBP in percentile of 52 ± 21 ○ transgender females had significantly lower SBP percentiles than cisgender males ($P \leq .001$). • DBP ○ transgender females had mean ± SD DBP in mmHg of 65 ± 11 ○ cisgender males had mean ± SD DBP in mmHg of 65 ± 3 ○ comparison not statistically significant (P = NS) ○ transgender females had mean ± SD DBP in percentile of 55 ± 28 ○ cisgender males had mean ± SD DBP in percentile of 57 ± 9 ○ comparison not statistically significant (P = NS). Fasting glucose: • the comparison is not statistically significant (P = NS). • transgender females had mean ± SD fasting glucose in mg/dL of 88 ± 7 and • cisgender males had mean ± SD fasting glucose in mg/dL of 84 ± 5, Insulin sensitivity: • transgender females had a significantly lower insulin sensitivity compared to cisgender males ($P < .05$). • transgender females had mean ± SD inverse of fasting insulin in mL/lU of 0.076 ± 0.029 • cisgender males had mean ± SD inverse of fasting insulin in mL/lU of 0.135 ± 0.049 HOMA-IR: • transgender females had significantly higher HOMA-IR when compared to cisgender males ($P < 005$). • transgender females had mean ± SD HOMA-IR of 3.5 ± 1.4 • cisgender males had mean ± SD HOMA-IR of 2.2 ± 1.3

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						Hemoglobin A1C: • transgender females had a significantly higher HbA1c % then cisgender males (*P* ≤ .01). • transgender females had mean ± SD Hemoglobin A1C of 5.4% ± 0.1 • cisgender males had mean ± SD Hemoglobin A1C of 5.1% ± 0.2 Total cholesterol: • the comparison is not statistically significant (*P* = NS). • transgender females had mean ± SD total cholesterol in mg/dL of 143 ± 16 • cisgender males had mean ± SD total cholesterol in mg/dL of 151 ± 35 Triglycerides: • the comparison is not statistically significant (*P* = NS). • transgender females had mean ± SD triglycerides in mg/dL of 78 ± 28 • cisgender males had mean ± SD triglycerides in mg/dL of 117 ± 115 HDL: • the comparison is not statistically significant (*P* = NS). • transgender females had mean ± SD HDL in mg/dL of 51 ± 6 • cisgender males had mean ± SD HDL in mg/dL of 54 ± 13, LDL: • the comparison is not statistically significant (*P* = NS) • transgender females had mean ± SD LDL in mg/dL of 76 ± 14 • cisgender males had mean ± SD LDL in mg/dL of 74 ± 17 Liver Enzymes: • AST ○ transgender females had a significantly higher AST level compared to cisgender males (*P* ≤ .01) ○ transgender females had mean ± SD in U/L of 43 ± 9

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						○ cisgender males had mean ± SD in U/L of 31 ± 5 • ALT ○ the comparison is not statistically significant (*P* = NS) ○ transgender females had mean ± SD in U/L of 34 ± 17 ○ cisgender males had mean ± SD in U/L of 24 ± 6
Valentine (2021)[97] At a large Midwestern pediatric academic center with a multidisciplinary program serving transgender and gender-diverse youth	**Population**: N = 124 • Transgender males: N = 42 patients receiving testosterone therapy • Cisgender females: N = 82 BMI-matched cisgender female adolescents **Eligibility criteria:** • Transgender cohort: 14-21 years old and taking testosterone from 2014–2018 were eligible • Cisgender cohort: seen in their 13 primary care centers, without any chronic conditions such as attention deficit hyperactivity disorder, asthma, or conditions managed by our subspecialty clinics **Sampling method:** • Transgender cohort: Transgender males (14–21 years) taking testosterone from 2014–2018 were identified (no other description about the sampling method). • Cisgender cohort: Initial BMIs of cisgender females were matched to the pre-testosterone BMIs of the transgender male cohort, and a random number generator used	• Transgender males: ○ mean age (range) in years = 16.6 years (14–19 years) ○ majority white, with bi-/multiracial subjects being the second most common race represented ○ total cholesterol, LDL, HDL, and triglycerides, in mg/dL, at baseline were 156 ± 30, 87 ± 29, 45 (39, 59) and 90 (69, 111), respectively. ○ time (range) between visits was an average of 4.9 months (0.5–17.7). ○ average total follow-up time (range) was 10.8 months (2.6–25.7). • Cisgender females: ○ mean age (range) in years = 15.5 years (14–21 years) ○ majority black/African American, with white subjects as the second most common racial group ○ total cholesterol, LDL, HDL, and triglycerides, in mg/dL, at baseline were 166 ± 30, 97 ± 26, 44 (38, 54) and 92 (63, 170), respectively. ○ time (range) between visits was an average of 5.0 months (0.8–21.0). ○ average total follow-up time (range) was 12.7 months (1.0–27.1)	Transgender male cohort: Testosterone cypionate dosing started at 50mg intramuscularly (IM) monthly and subsequently increased to 50–150 mg IM every other week.	Cisgender cohort: not on testosterone treatment, matched to the pre-testosterone BMI's of transgender male cohort	• **BMI** was calculated using age, sex assigned at birth, height and weight at time of visit, and is presented as a percentile. The 2000 CDC Growth Charts were used to calculate percentiles. Mean values with standard deviations were calculated to evaluate change in BMI of transgender male adolescents while on testosterone, as well as change in BMI for a similar time interval of the cisgender females. • Both short- and long-term follow-ups were evaluated, with short-term follow-up assessing changes in BMI between each clinic visit, and long-term follow-up assessing changes in BMI between first and final follow-up clinic visits. **Cohort study**: Outcomes are measured after the exposure has been measured (retrospective review).	There was a significant increase in BMI percentiles and z-scores in the transgender males after starting testosterone as compared with BMI-matched cis-gender females for both the short- and long-term follow-up periods. BMI (percentile): • The transgender group had a significant increase in BMI of + 1.28 percentiles from visit to visit, and of + 3.29 percentiles from baseline through final follow-up. • The cisgender group showed an opposite trend of a significant decrease in BMI of -0.70 percentiles from visit to visit and of -1.77 percentiles from baseline through final follow-up. BMI (z-score): • In the transgender group, there was a significant increase in BMI z-score of + 0.08 from visit to visit, and of + 0.20 through the entire follow-up period. • In the cisgender group, there was a BMI z-score decrease of -0.01 from visit to visit, and of -0.05 through the entire follow-up period. Follow-up: • In transgender group: short-term follow-up, *P* = 0.004 and long-term follow-up, *P* = .002 • In cisgender group, short term follow up, *P* = 0.004 and long term follow up, *P* = .001.

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	these matched patients to create a 2:1 match of cisgender females to the transgender males.	• There was no significant difference in lipids between the cohorts • There was a significant difference in age (*P* = .003) between the cohorts • There was a significant difference in ethnicity (*P* = .0001) between the cohorts • There was no significant difference in the BMI percentiles and z-scores at baseline between the cohorts (*P* = NS)				
Valentine (2022)[98] PEDSNet, a Pediatric Learning Health System Network, USA	**Population**: N = 20,625 • TGNB youth: n = 4172 • TGNB female: n = 2766 (66.3%) • TGNB male: n = 1407 (33.7%) • Control youth: n = 16,453 • Control female: n = 11,130 (66.9%) • Control male: n = 5518 (33.1%) **Eligibility**: • TGNB youth subjects had a diagnosis of gender dysphoria or related diagnosis. • Control youth patients were seen within the same time frame. No specific eligibility criteria listed. **Sampling Method**: Clinical data available from electronic health care records from the health system from 2009 onward for patients with in-person encounters with a provider were reviewed for inclusion. The data for all TGNB patients and at least one outpatient visit from 2009-2019 was extracted from the PEDSnet database on Nov	Age at first visit, y: median (25th-75th percentile) • TGNB: 10.0 (4.4-14.6), • Control group: 9.8 (4.1-14.3) Age at last visit, y: median (25th-75th percentile) • TGNB group: 16.7 (14.6-18.3) • Control group: 16.6 (14.3-18.4) Groups were matched and were mostly white (72.5%,) and non-Hispanic (84.8%)	TGNB youth with diagnosis of GD • n = 1412 with a CSHT prescription • n = 267 with a prescription for GnRH analogs alone • n = 832 with a prescription for testosterone without GnRH analogs • n = 349 with a prescription for estrogen without GnRH analogs • n = 106 with a prescription for testosterone with GnRH analogs • n = 125 with a prescription for estrogen with GnRH analogs	Matched control group of peers: • Cases and controls were matched on the predicted probability of having the diagnosis of GD. • A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site.	Electronic health records were reviewed using SNOMED concept codes and were defined as having either a diagnosis or 2 abnormal measurements to capture data for the following metrics: • Overweight/obese • Dyslipidemia • Liver dysfunction • Dysglycemia • Hypertension • PCOS EHRs were reviewed for the following lab and anthropometric data: • BP • BMI • Liver enzymes • Lipids • TG • HbA1C **Cross-sectional study**: Exposures/outcomes measured at the same time	Overweight/obese: # (%) • TGNB youth had higher unadjusted odds than controls of having the diagnosis of overweight/obesity (odds ratio[a] 1.5; 95% CI, 1.4-1.7; *P* < .0001) • In the adjusted model[b], TGNB youth still had higher odds than controls of having the diagnosis of overweight/obesity (odds ratio[a] 1.1; 95% CI, 1.1-1.2; *P* < .0001) • TGNB with female EHR sex had higher odds of overweight/ obesity than female controls (odds ratio 1.8; 95% CI, 1.7-2.0; *P* < .0001) • TGNB youth: 1764 (42.3) • Control youth: 5263 (32.0) Dyslipidemia: # (%) • TGNB youth had higher unadjusted odds than controls of having the diagnosis of dyslipidemia (odds ratio[a] 1.8; 95% CI, 1.5-2.1; *P* < .0001) • In the adjusted model[b], there was no difference in odds between TGNB and control youth subjects (odds ratio[a] 1.2; 95% CI 1.0-1.4, *P* = NS) • TGNB youth: 351 (8.4) • Control youth: 806 (4.9) Liver dysfunction: # (%) • TGNB youth had higher unadjusted odds than controls of having the diagnosis of liver dysfunction (odds ratio[a] 1.4; 95% CI, 1.2-1.5; *P* < .0001)

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
	2019. A random sample of 197,039 patients with at least one out-patient visit during the same time period who did not have a diagnosis of GD were used as a pool of controls. Controls were evaluated for the prevalence of well-characterized pediatric diagnoses and the prevalence in the control pool was similar to PEDSnet as a whole. Propensity scores were used to match control to cases (approximately 4:1.) A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm.					• In the adjusted model[b], TGNB youth had lower odds than controls of having the diagnosis of liver dysfunction (odds ratio[a] 0.8; 95% CI, 0.7-0.9; *P* = .003) • TGNB youth: 460 (11.0) • Control youth: 1360 (8.3) Dysglycemia: # (%) • There was no difference in odds between TGNB and control youth subjects (odds ratio[a] 0.9; 95% CI, 0.8-1.2, *P* = NS) • In the adjusted model[b,] TGNB youth had lower odds than controls of having the diagnosis of dysglycemia (odds ratio[a] 0.6; 95% CI, 0.5-0.8; *P* < .001) • TGNB with a male EHR sex had lower odds of dysglycemia than male controls (odds ratio 0.6, 95% CI, 0.4-0.9, *P* = .01) • TGNB youth: 90 (2.2) • Control youth: 375 (2.3) Hypertension: # (%) • TGNB youth had higher unadjusted odds than controls of having the diagnosis of hypertension (odds ratio[a] 1.2; 95% CI, 1.1-1.4; *P* < .0001) • In the adjusted model[b], there was no difference in odds between TGNB and control youth subjects (odds ratio[a] 0.9; 95% CI 0.8-1.1, *P* = NS) • TGNB youth: 373 (8.9) • Control youth: 1214 (7.4) PCOS: # (%) • Among those with female EHR sex, TGNB youth had higher unadjusted odds of having a PCOS diagnosis compared to controls (odds ratio[a] 1.7; 95% CI, 1.2-2.6; *P* < .01) • In the adjusted model[b], there was no difference in odds between TGNB and control youth female EHR subjects (odds ratio[a] 0.9; 95% CI 0.8-1.5, *P* = NS) • TGNB youth: 42 (1.5) • Control youth: 96 (0.9) Lab and anthropometric data median (25th-75th percentile)

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						• Systolic BP, mm Hg: ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 1701): 116 (108-124) ○ Control youth (n = 6026): 114 (106-121) • Diastolic BP, mm Hg ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 1701): 67 (62-73) ○ Control youth (n = 6026): 66 (60-72) • BMI ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 3829): 23 (20-28) ○ Control youth (n = 14,633): 22 (19-26) • BMI, % ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 3829): 77 (41-95) ○ Control youth (n = 14,633): 69 (39-90) • ALT, IU/L ○ No significant difference between groups (*P* = NS) ○ TGNB youth (n = 1627): 24 (17-31) ○ Control youth (n = 3940): 24 (16-32) • AST, IU/L ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 1449): 25 (20-32) ○ Control youth (n = 3798): 27 (21-36) • Total cholesterol, mg/dL ○ No significant difference between groups (*P* = NS) ○ TGNB youth (n = 1633): 156 (138-178)

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

Table I.K.4. Clinical studies comparing TGNB to cisgender peers regarding cardiovascular outcomes

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Comparator	Outcome measures and timing	Results
						○ Control youth (n = 1907): 156 (137-180) • HDL, mg/dL ○ No significant difference between groups (*P* = NS) ○ TGNB youth (n = 1618): 46 (39-55) ○ Control youth (n = 1837): 47 (39-56) • LDL, mg/dL ○ No significant difference between groups (*P* = NS) ○ TGNB youth (n = 1142): 87 (70-106) ○ Control youth (n = 1266): 86 (70-104) • Triglycerides, mg/dL ○ No significant difference between groups (*P* = NS) ○ TGNB youth (n = 1633): 93 (67-135) ○ Control youth (n = 2021): 91 (66-132) • HbA1c, % ○ Statistically but not a clinically significant difference between groups (*P* < .0001) ○ TGNB youth (n = 532): 5.3 (5.1, 5.5) ○ Control youth (n = 959): 5.4 (5.2-6.7)

[a] *odds were extracted from figure 1 in study. Unadjusted and adjusted ORs were calculated in propensity matched cohorts. A priori covariates used for matching include: year of birth, age at last visit, sex listed in chart, race, ethnicity, insurance status, duration in database and site. Cases and controls were matched on the predicted probability of having the diagnosis of GD using a greedy match algorithm. (Valentine, 2022)*

[b] *odds were further adjusted for overweight/obesity, depression, and antipsychotic prescription (Valentine, 2022)*

Abbreviations: AFAB, assigned female at birth; ALT, alanine aminotransferase; AMAB, assigned male at birth; AST, aspartate aminotransferase ; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EHR, electronic health record; HbA1c, Hemoglobin A1C; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; N/S, not significant; PCOS, Polycystic ovary syndrome; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TGNB, transgender, non-binary or gender-diverse

Return to TOC

APPENDIX I.L: DATA EXTRACTED FROM STUDIES COMPARING TGNB PATIENTS BEFORE AND AFTER (PRE-POST) INTERVENTION, ORGANIZED BY OUTCOME

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Achille (2021)[55] A US [redacted] NY) pediatric endocrine gender dysphoria clinic	**TGNB Adolescents (N = 50)** • **Eligibility**: Participants were recruited at the clinic, and a vast majority consented/assented. This study was limited to the subset of all patients who completed 3 rounds of questionnaires at 6-month intervals. Patients were excluded if they had sex chromosome abnormalities or disorders of sexual differentiation. • **Sampling method**: Patients must have completed 3 waves of questionnaires at 6-month intervals, for a total of approximately 12 months of observation. A "vast majority" of 116 patients gave consent/assent. • **Subset definition**: N = 50 TGNB adolescents, including MTF (N = 17) and FTM (N = 33) adolescents.	• **Full cohort**: Mean (SD) age was 16.2 (2.2); 64% were depressed in the prior year; 10% reported suicidality; 90% were seeing a therapist; 34% were on psychiatric medications • **MTF:** Mean (SD) age was 15.5 (1.6); 70.6% were depressed in the prior year; 11.8% reported suicidality; 94.1% were seeing a therapist; 29.4% were on psychiatric medications • **FTM**: Mean (SD) age was 16.6 (2.5); 60.6% were depressed in the prior year; 9.1% reported suicidality; 87.9% were seeing a therapist; 36.4% were on psychiatric medications	Up to 12-months of endocrine treatment including: • puberty blockers (N = 23, 46%), CSHT (N = 35, 70%), • both (N = 11, 22%), or • neither (N = 3, 6%)	• Outcomes were measured upon referral to the pediatric endocrine department for GD and after approximately 12 months of treatment. • Depression and suicide ideation measured using: ○ CESD-R ○ PHQ-9	**Depression**: • CESD-R: Mean baseline CESD-R score was 21.4 at baseline and decreased to 13.9 at 12 months ($P < 0.001$). Mean score at 12 months indicates an absence of clinical depression (ie, < 16) in the average patient. • PHQ-9: Mean depression scores by the PHQ-9 decreased over time as well ($P < 0.001$) [Extracted scores were 8.86 at baseline and 5.29 at follow-up] **Suicide ideation**: (from PHQ-9 questionnaire) • Overall: Suicide ideation was 10% (N = 5) at baseline versus 6% (N = 3) at 12 months (P = NS) • FTM: Suicide ideation was 9.1% (N = 3) at baseline, versus 6.1% (N = 2) at 12 months (P = NS) • MTF: Suicide ideation was 11.8% (N = 2) at baseline, versus 5.9% (N = 1) at 12 months (P = NS)
Allen (2019)[56] [redacted]	**N = 47 TGNB adolescents** • **Eligibility:** Adolescents and young adults (age range 13–20 years) who received services for GD at the clinic. Participants were included if they had pretest and final assessment data points and were treated with CSH for at least 3 months • **Sampling method:** A total of 47 eligible participants had pretest and final assessment data. The pretest for 23 participants occurred at their first contact	• The age of the participants ranged from 13.73 to 19.04 years (mean = 16.59, SD = 1.19). • The range of treatment length was 113-1016 days (mean = 349, SD = 193). • For most of the sample (90%), the duration of treatment was at, or under, 600 days. • Assigned female at birth was n = 33 (70.2%) and assigned male at birth was n = 14 (29.8). • The majority of participants were white n = 39 (83%).	**CSH** treatment	• Suicidality was measured using the ASQ	**Suicidality:** • Participants showed a decrease in the estimated adjusted mean (standard error) of ASQ scores from 1.11 (.22) at T0 to .27 (.12) at T1. • The main effect was significant, meaning suicidality scores were significantly lower at T1 after CSH, $F(1, 44) = 15.09$, $P < .001$, partial $\eta 2 = .26$, demonstrating a large effect size. • The duration of treatment was not significantly related to participants' ASQ scores, $F(1, 44) = .09$, $P = .77$, partial $\eta 2 = .002$.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	with the clinic (the other participants' pretest assessment was completed at a subsequent visits to clinic but prior to starting CSH). Thirteen of the participants first presented to our clinic in 2015; 19 in 2016; 14 in 2017; and one in 2018. Patients are administered questionnaires and screeners at the beginning of their clinic visit, either at the time of the diagnostic evaluation or during a follow-up appointment with the multidisciplinary team. Responses are reviewed by the mental health professional prior to meeting with the patient.	• Of the 47 participants, n = 8 were administered GnRH analogs prior to beginning CSH (GnRH analogs + CSH subgroup) and n = 39 were not received GnRH analogs prior to being administered CSH (CSH-only subgroup).			
Cantu (2020)[74] An academic medical center in the Northwestern United States between September 2017 and June 2019	**N = 80 TGNB adolescents** • **Eligibility**: Youth were included in the current study if they (1) were between the ages of 11 and 18 years, (2) had attended both an initial visit and one follow-up appointment, and (3) completed measures assessing acute distress (PHQ-9 and GAD-7) at both visits • **Sampling method**: All youth ages 11 and older complete anxiety and depression screeners at every visit regardless of mental health diagnoses or symptom severity. Second visit is recommended 3–4 months after the initial visit. • **Subset definition**: All adolescents (N = 80) completed PHQ-9 screeners at both time points and n = 78 youth	• **Full cohort:** Mean (SD) age was 15.1 (1.8); affirmed male gender, n (%), was 58 (72.5); distance in miles, mean (SD), range was 36.2 (39.9); follow-up time in weeks, mean (SD) was 20.4 (10.2) • Only N = 1 (1.3%) individual initiated HT before the initial visit, and 28 youth initiated HT between initial visit and first follow-up. • Of those 28 youth, 6 were started on feminizing hormones and 22 were started on masculinizing. • A total of 17 youth initiated hormone blockers between their initial visit and first follow-up, 4 of which also initiated HT. • N = 77 (96.2%) received neither HT nor hormone blockers at initial visit • N = 38 (47.5%) received neither HT nor hormone blockers at follow up appointment.	At the initial visit or first follow-up appointment, participants were receiving: • hormone blocker only • HT only • both, or • neither	• Participants were evaluated at their initial visit and then at their first follow-up appointment (recommended 3-4 months after initial visit) • Depression measured using PQH-9 and GAD-7	• **PHQ-9** (n = 80) mean (SD) ○ There was a nonsignificant decrease from a score of 10.5 (6.5) at the initial visit to 10 (6.4) at follow-up, *P* = NS • **GAD-7** (n = 78 mean (SD) ○ There was a non-significant decrease from a score of 9.1 (6.1) at the initial visit to 8.8 (5.7) at follow-up, *P* = NS

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	completed GAD-7 screeners at both time points)				
Carmichael (2021)[73] UK [redacted]	N = 44 TGNB adolescents • **Eligibility Criteria**: ○ Patients recruited from those referred to GIDS who were between 12-15 years and had commenced GnRH analog treatment. ○ Had been seen for at least 6 months and attended at least 4 interviews. ○ Psychological stability to withstand the stresses of medical treatment and ○ Displayed severe and persistent GD and actively requesting pubertal suppression ○ Able to give informed consent ○ Met physical/medical criteria of being in established puberty and having normal endocrine function and karyotype consistent with birth registered sex. • **Exclusions:** Inability to fully participate, BMI < 2nd percentile, serious psychiatric conditions, Inability to give consent, low spine or hip BMD • **Sampling Method:** Patients attending GIDS were provided with information and those wishing to find out more discussed with their clinician. Those likely deemed eligible	• Total sample median age at baseline was 13.6 (12.8,14.6), 89% white, all beyond stage 3 pubertal status. • Median age at end of study was 16.1 (16.0,16.4). • Birth registered males started at a median age of 13.4 (12.7,14.1) and birth registered females at 13.9 (13.5, 14.7) all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal function. • No participants had evidence of disorders of sexual differentiation.	Suppression of puberty using GnRH analog triptorelin together with psychosocial support and therapy, from study entry until the end of the GnRH analog monotherapy pathway at age 16 or older. 3.75 mg by IM injection given every 28 days during treatment period. 2 participants given 11.25 mg every 10 weeks.	• Patients were measured at study entry, and then re-evaluated yearly at 12,24 and 36 month until they turned 16. • Measures of Psychological functioning were measured using the CBCL (parent report) and YSR (self-report.) • Reference data from both Australia and the Netherlands were used to calculate z-scores. • Self-harm index: assessed through two questions in each of the CBCL and YSR: Item 18	**Self-harm Index Mean (95% CI)** • There was no significant change in CBCL or YSR self-harm index scores from baseline to any data collection point • Parent report CBCL ○ 12 month ▪ There was no significant change from the baseline score of those that followed up: 0(0,1) to the score at 12 months: 0(0, 1), *P* = NS ○ 24 month ▪ There was no significant change from the baseline score of those that followed up: 0(0,1) to the score at 24 months: 0(0, 1), *P* = NS ○ 36 month ▪ There was no significant change from the baseline score of those that followed up: 0(0,1) to the score at 36 months: 0(0, 1), *P* = NS • **Self-report YSR Mean (95% CI)** ○ 12 months ▪ There was no significant change from the baseline score of those that followed up: 0(0,1) to the score at 12 months: 0(0, 2), *P* = NS ○ 24 months ▪ There was no significant change from the baseline score of those that followed up: 0(0,0) to the score at 24 months: 0(0, 0), *P* = NS

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	were given detailed information and invited to a medical clinic for discussion. Young people needed to commit to regular medical and psychosocial follow up. Informed consent was obtained. 48 young people attended the clinics and 44 wished to participate. 8 young people were not yet eligible, but were able to enter the study when sufficiently advanced in puberty. • **Subset Definition:** N = 44 TGNB adolescents age 12-15, including birth registered male (N = 25) and birth registered female (N = 19) adolescents.				
Chen (2023)[75] USA- Gender clinics [redacted] from July 2016 through June 2019	**N = 315** • **Eligibility**: Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating CSH as part of their clinical care. For minors, parental consent was required to initiate treatment. • **Sampling Method:** Youth were recruited from 4 different sites at the start of CSH therapy. They were enrolled if they met inclusion criteria. • **Subset definition**: N = 315 TGNB adolescents, including: o FTM (n = 190,) MTF (n = 106) and NB (n = 19,) adolescents o Analytical sample n = 291 due to missing key variables at follow-up	Participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) Higher percentage of those designated female at birth (64.8%) then male. Mostly non-Latinx or non-Latin white (58.1%)	CSH therapy	• Outcomes were measured at initiation of therapy, and then at 6,12,18 and 24 months. • **Depression symptoms** were assessed using the 21-item BDI-II. • **Anxiety symptoms** were assessed by the RCMAS2	• **Depression:** Slope mean (95% CI) o There was a significant decline in depression scores showing an annual change on a 63-point scale of −1.27 points (−1.98 to −0.57) (unconditional model); -0.92 points (-3.82 to -0.06) (conditional model) after a period of 2 years of CSH treatment from baseline. o Depression scores range from 0 to 63 (ranges of severity, minimal, 0 to 13; mild, 14 to 19; moderate, 20 to 28; and severe, 29 to 63). The model had an intercept (baseline mean) of 15.46 and estimated slope (change per year) of −1.27. Thus, on average, depression started in the mild range and decreased to the subclinical level by 24 months. o Of 27 participants with depression scores in the severe range at baseline, 18 (67%) reported a depression score in the minimal or moderate ranges at 24 months. (chi-square statistic with 9 degrees of freedom, 49.85; *P* < .001) o Of 33 with depression scores in the moderate range at baseline, 21 (64%) reported a depression score in the minimal or moderate ranges at 24 months (chi-square statistic with 9 degrees of freedom, 49.85; *P* < .001) • **Anxiety:** Slope mean (95% CI) o There was a significant decrease in T scores for anxiety showing an annual change on a 100-point scale of −1.46 points (−2.13 to −0.79) (unconditional

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	○ Designated female at birth (n = 204,) and designated male at birth (n = 111) ○ Had early gender-affirming care-previously using GnRH analog (n = 24) ▪ youth designated female at birth with early gender-affirming care (n = 4) ▪ youth designated male at birth with early gender-affirming care (n = 20) ○ analytic sample (n = 291)				model); -1.95 (-3.81 to -0.09) (conditional model) after a period of 2 years of CSH treatment from baseline. ○ Of 122 participants with baseline scores in the clinical range (T scores, > 60) 47 participants (38.5%) decreased to the non- clinical range at 24 months (chi-square statistic with 1 degree of freedom, 22.05; *P* < .001)
de Vries (2011)[57] [redacted]	**N = 70 TGNB youth** • **Eligibility**: adolescents with gender dysphoria eligible for medical intervention • **Sampling method**: first 70 patients consecutively enrolled from 2000 to 2008 • **Subset:** N = 70 TGNB youth, including N-37 natal females and N = 33 natal males	• **Full cohort:** mean (SD) age at baseline was 13.65 years (1.85); mean (SD) age at the start of GnRH analogs was 14.75 years (1.92); mean (SD) age at the start of CSH was 16.64 years (1.90); mean (SD) time between the start of GnRH analogs and CSH was 1.88 years (1.05); mean (SD) parental full-scale IQ was 98.2 (15.0); for parental marital status, 62.9% had both parents, 37.1% was other; for parents' education status, 10.6% had high, 66.7% had medium, 22.7% had low; for sexual attraction, 88.6% were attracted to their own natal sex, 8.6% were attracted to both sexes; 2.8% were attracted to other • **Natal male** (47%): mean (SD) age at baseline was 13.14 years (1.55); mean (SD) age at the start of GnRH analogs was 14.25 years (1.79); mean (SD) age at the start of CSH was 16.24 years (1.21); mean (SD) time between the start of GnRH analogs and CSH was 1.99 years (0.94); mean (SD) parental full-scale IQ was 97.1 (13.3); for parental marital status, 69.7% had both parents, 30.3% had other; for parents' education status, 3.3% had high, 76.7% had	GnRH analogs (full cohort), N = 29 also started CSH	Participant data was collected before and after starting GnRH analogs • BDI used to assess depressive symptoms • TPI administered to assess the tendency to respond with anger to a threatening or annoying situation. (Scale ranges from 1-4) • STAI administered to assess the tendency to respond with anxiety to a threatening or annoying situation. (Scale ranges from 1-4)	**BDI (n = 41), mean (SD)** • There was a significant decrease in depressive symptoms in full cohort from 8.31 (7.12), at baseline to 4.95 (6.72) at follow-up, *P* = .004 ○ Full cohort: T0- 8.31 (7.12), T1- 4.95 (6.72) ○ Female at birth: T0- 10.34 (8.24), T1- 6.09 (7.93) ○ Male at birth: T0- 5.71 (4.31), T1- 3.50 (4.58) **TPI (n = 41), mean (SD)** • There was a nonsignificant decrease in anger from 18.29 (5.54), at baseline to 17.88 (5.24) at follow-up, *P* = NS ○ Full cohort: T0- 18.29 (5.54), T1- 17.88 (5.24) ○ Female at birth: T0- 6.43 (2.78), T1- 6.39 (2.59) ○ Male at birth: T0- 5.22 (2.76), T1- 5.00 (3.07) **STAI (n = 41), mean (SD)** • There was a nonsignificant decrease in anxiety from 39.43 (10.07), at baseline to 37.95 (9.38) at follow-up, *P* = NS ○ Full cohort: T0- 39.43 (10.07), T1- 37.95 (9.38) ○ Female at birth: T0- 7.00 (2.36), T1- 6.17 (2.62) ○ Male at birth: T0- 4.33 (2.68), T1- 4.39 (2.64)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
		medium, 20.0% had low; for sexual attraction, 87.9% were attracted to their own natal sex, 6.1% were attracted to both sexes; 6.0% were attracted to other • **Natal female** (53%): mean (SD) age at baseline was 14.10 years (1.99); mean (SD) age at the start of GnRH analogs was 15.21 years (1.95); mean (SD) age at the start of CSH was 16.99 years (1.07); mean (SD) time between the start of GnRH analogs and CSH was 1.78 years (1.16); mean (SD) parental full-scale IQ was 99.2 (15.2); for parental marital status, 56.8% had both parents, 43.2% had other; for parents' education status, 16.7% had high, 58.3% had medium, 25.0% had low; for sexual attraction, 89.2% were attracted to their own natal sex, 10.8% were attracted to both sexes; 0% were attracted to other			
de Vries (2014)[79] [redacted]	**N = 55 TGNB youth** • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011 • **Subset:** N = 55 TGNB adolescents, with n = 22 MTF and n = 33 FTM)	Full cohort: the mean age (SD) at assessment pretreatment was 13.6 (1.9) (range: 11.1–17.0), the mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5), the mean age (SD) at the start of CSH was 16.7 (1.1) (range: 13.9–19.0), the mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3), the mean age (SD) at assessment post treatment was 20.7 (1.0) (range: 19.5–22.8); the mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)	CSH and GRS	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS) • BDI used to assess depressive symptoms • TPI administered to assess the tendency to respond with anger to a threatening or annoying situation. (Scale ranges from 1-4) • STAI administered to assess the tendency to respond with anxiety to a threatening or annoying situation. (Scale ranges from 1-4) General linear models examined the repeated measures with an analysis of variance-based model.	• **BDI (depression) (n = 32), mean (SD)** ○ Scores showed a nonsignificant decrease from 7.89 (7.52) at intake to 5.44 (8.40) at post treatment, *P* = NS ○ T0- 7.89 (7.52), T1- 4.10 (6.17), T2- 5.44 (8.40) ○ Linear effect (time) *P* = .23, Significant quadratic effect (time) *P* = .04 • **TPI (Anger) (n = 32), mean (SD)** ○ Scores showed a nonsignificant decrease from 17.55 (5.72) at intake to 16.01 (5.28) at post treatment, *P* = .20 ○ T0- 17.55 (5.72), T1- 17.22 (5.61), T2- 16.01 (5.28) ○ linear effect (time) *P* = NS, quadratic effect (time) *P* = NS • **STAI (Anxiety) (n = 32), mean (SD)** ○ Scores showed a nonsignificant decrease from 39.57 (10.53) at intake to 37.61 (10.39) at post treatment, *P* = NS ○ T0- 39.57 (10.53), T1- 37.52 (9.87), T2- 37.61 (10.39) ○ linear effect (time) *P* = NS, quadratic effect (time) *P* = NS ▪ effect (time) *P* = NS • **Externalizing T-Score**, mean (SD)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				A linear effect signifies an overall change across T0 to T2. Quadratic effect signifies change was not continuous.	○ Scores showed a significant decrease from 57.85 (13.73) at intake to 47.85 (8.59) at post treatment, *P* < .001 ○ T0- 57.85 (13.73), T1- 53.85 (12.77), T2- 47.85 (8.59) ○ Significant linear effect (time) *P* < .001, quadratic effect (time) *P* = NS
	N = 22 MTF TGNB youth • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	**MTF**: for ages, the mean age (SD) at assessment pretreatment was 13.6 (1.8), the mean age (SD) at the start of GnRH analogs was 14.8 (2.0), the mean age (SD) at the start of CSH was 16.5 (1.3), the mean age (SD) at the start of GRS was 19.6 (0.9), the mean age (SD) at assessment post treatment was 21.0 (1.1); the mean full scale intelligence (SD) was 97.8 (14.2)	CSH and GRS		• **BDI (depression) MTF (n = 12), mean (SD)** ○ Scores showed a nonsignificant decrease from 4.73 (4.20) at intake to 3.38 (4.40) at post treatment, *P* = NS. ○ T0- 4.73 (4.20), T1- 2.25 (3.54), T2-3.38 (4.40) • **TPI (Anger) MTF (n = 12), mean (SD)** ○ Scores showed a nonsignificant decrease from 14.17 (3.01) at intake to 5.58 (3.92) at post treatment, *P* = NS ○ T0- 14.17 (3.01), T1- 14.00 (3.36), T2- 5.58 (3.92) • **STAI (Anxiety) MTF (n = 12), mean (SD)** ○ Scores showed a nonsignificant decrease from 31.87 (7.42), at intake to 35.83 (10.22) at post treatment, *P* = NS ○ T0- 31.87 (7.42), T1- 31.71 (8.36), T2- 35.83 (10.22) • **Externalizing T-Score,** mean (SD) ○ Scores showed a nonsignificant decrease from 46.00 (11.58), at intake to 50.24 (11.18)]at post treatment, *P* = NS ○ T0- 46.00 (11.58), T1- 44.71 (9.53), T2- 50.24 (11.18)
	N = 33 FTM TGNB youth • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	**FTM**: for ages, the mean age (SD) at assessment pretreatment was 13.7 (2.0), the mean age (SD) at the start of GnRH analogs was 14.9 (1.9), the mean age (SD) at the start of CSH was 16.8 (1.0), the mean age (SD) at the start of GRS was 19.0 (0.8), the mean age (SD) at assessment post treatment was 20.5 (0.8); the mean full scale intelligence (SD) was 100.4 (14.3)	CSH and GRS		• **BDI (depression) FTM (n = 17), mean (SD)** ○ Scores showed a nonsignificant decrease from 10.09 (8.34), at intake to 36.95 (9.83) at post treatment, *P* = NS ○ T0- 10.09 (8.34), T1- 5.05 (7.08), T2- 6.95 (9.83) • **TPI (Anger) FTM (n = 17), mean (SD)** ○ Scores showed a significant decrease from 19.55 (5.96), at intake to 16.56 (6.06) at post treatment with a P value of 0.05 ○ T0-19.55 (5.96), T1- 19.25 (5.69), T2- 16.56 (6.06) • **STAI (Anxiety) FTM (n = 17), mean (SD)** ○ Scores showed a nonsignificant decrease from 44.41 (9.06), at intake to 39.20 (10.53) at post treatment, *P* = NS ○ T0- 44.41 (9.06), T1- 41.59 (9.03), T2- 39.20 (10.53)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Kaltiala (2020)[138] Finland [redacted]	**N = 52** • **Eligibility** Criteria: The study comprises a retrospective chart review of adolescents referred to one of the two gender identity service facilities between 2011-2017, before age 18, who had been diagnosed with transsexualism and proceeded to cross-sex hormonal treatments and who had completed a follow-up of approximately a year after starting on cross-sex hormones (real-life phase). • **Sampling Method:** Between 2011 and 2017, 57 adolescents at the gender identity facility had been diagnosed with F64.0, transsexualism, and had been offered an opportunity to start hormonal sex reassignment. One of them did not want any treatment, two withdrew and two had started hormonal treatments but had not yet completed the real-life phase at the end of 2017. Thus, 52 patients were included in the study. • **Subset definition**: N = 52 patients in study. N = 11 birth assigned males. N = 41 birth assigned females	Mean age of 18.1 (1.1) years at diagnosis, range 15.2-19.9 years	CSH	• Participants were assessed at an initial gender identity assessment appointment before starting hormone therapy, and then about a year after treatment (called the "real-life phase") • Need for psychiatric treatment data for adolescent development were collected retrospectivity from charts with specific criteria	**Need for Psychiatric Treatment** • There was a nonsignificant decline in the proportion of participants needing overall psychiatric treatment from initial assessment to 12 month follow up from 50% (26/52) to 46% (24/51), *P* = NS ○ Of those not needing psychiatric treatment before or during the assessment (26/52), 73% (19/26) did not need any during the real-life phase but in 27% (7/26), a need had emerged. Of those who had needed (25/51) psychiatric treatment during or before the assessment, 68% (17/25) still needed it during the follow-up but 32% (8/25) did not. (*P* = .004 using cross tabulations with chi square statistics) • There was a significant decline in the proportion of participants needing treatment due to depression from the initial assessment to the 12 month follow up from 54% (28/52) to 15% (8/52), *P* < .001 • There was a significant decline in the proportion of participants needing treatment due to anxiety from the initial assessment to the 12 month follow up from 48% (25/52) to 15% (8/52), *P* < .001 • There was a significant decline in the proportion of participants needing treatment due to suicidality/self-harm from the initial assessment to the 12 month follow up from 35% (18/52) to 4% (2/52), *P* = .001 • There was a nonsignificant decline in the proportion of participants needing treatment due to conduct problems/antisocial behavior from the initial assessment to the 12 month follow up from 14% (7/52) to 6% (3/52), *P* = NS • There was a nonsignificant increase in the proportion of participants needing treatment due to psychotic symptoms/psychosis from the initial assessment to the 12 month follow up from 2% (1/52) to 4% (2/52), *P* = NS • There was a nonsignificant decrease in the proportion of participants needing treatment due to substance abuse from the initial assessment to the 12 month follow up from 4% (2/52) to 2% (1/52), *P* = NS • There was a nonsignificant decrease in the proportion of participants needing treatment due to autism from the initial assessment to the 12 month follow up from 12% (6/52) to 6% (3/52), *P* = NS • There was a nonsignificant decrease in the proportion of participants needing treatment due to ADHD from the initial assessment to the 12 month follow up from 10% (5/52) to 2% (1/52), *P* = NS • There was no significant change in the proportion of participants needing treatment due to eating disorders from the initial assessment to the 12 month follow up staying at 2% (1/52), *P* = NS

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Kuper (2020)[141] At a multidisciplinary program in [redacted] Texas, US initial assessments occurred between August 2014 and March 2018	**N = 148 TGNB adolescents** • **Eligibility**: Youth who received gender-affirming hormone therapy at the clinic • **Sampling method**: Before initiating care, participants and their families participated in an initial assessment with the program's psychologist, psychiatrist, and/or clinical therapist after parents completed a phone intake survey and provided a referral letter from a licensed therapist or counselor documenting the presence of gender dysphoria. Approximately 1 year after this initial assessment, all patients were asked to participate in a yearly reassessment visit. Participants were readministered self-report measures and clinicians again completed a report of depressive symptoms and documented information about suicidal ideation, suicide attempts, NSSI, and mental health treatment. • **Subset definition**: Assigned male at birth n = 55 (37%) and Assigned female at birth n = 94 (63%)	**Full cohort** (N = 148): Most participants are white N = 137 (95%); at the initial assessment, patients ranged in age from 9 to 18 years (mean 15.4; SD 2.0); Participants who started puberty suppression only did so at a mean age of 13.7 years (range 9.8–14.9; SD 1.5), and participants started feminizing or masculinizing hormone therapy at a mean age of 16.2 years (range 13.2–18.6; SD 1.2)	Patients were receiving: • puberty suppression only (n = 25, 17%), • masculinizing or femininizing therapy only (n = 93, 63%), or • both (n = 30, 20%)	Participants were assessed at initial visit and at a yearly assessment visit (range 11-18 months) The mean length of time receiving treatment before follow-up was 10.9 months (range 11–18; SD 3.3) mean (SD) number of months between initial assessment and reassessments was 14.9 (2.1) • Anxiety and depressive symptoms assessed using SCARED and QIDS • Suicidal ideation, suicide attempts, and NSSI assessed by clinicians using QIDS • Body dissatisfaction was measured using the BIS	**SCARED: Mean (SD)** • From baseline to the follow-up period, there were significant in generalized [9.7(5.2) to 8.7 (5.1)], separation [4.0(3.4) to 3.3 (2.7)], and school-related [2.6(2.2) to 2.0(2.1)] anxiety symptoms, $P < .05$. Cohen's d effect sizes were small for change in SCARED total scores (0.27). **QIDS: Mean (SD)** • Within the full sample, a significant decrease in total anxiety symptoms was observed from 32.4 (16.3) at baseline to 28.6 (16.1) at follow-up with a change of 3.8(CI 1.05 to 6.70), and a $P < .001$ • Within the full sample, a significant decrease in self-reported depressive symptoms was observed from 9.4 (5.3) at baseline to 7.3 (4.6) at follow-up with a change of 2.1(CI 1.24 to 2.97), $P < .001$ ○ A significant change was found in self-reported depressive symptom categories ($P < .001$) but not in clinician-reported categories. Cohen's d effect sizes were small to moderate for change in QIDS self-report scores (0.44). **Suicidal ideation, suicide attempts, and NSSI n (%)** • 105 (81) participants had a lifetime history of suicide ideation. 1 month before assessment, 33 (25) experienced this and in the follow-up period, 51 (38) experienced it. ○ Of those who experienced suicidal ideation during the follow-up period, 94% had a lifetime history. • 20 (15) participants had a lifetime history of a suicide attempt. Within 3 months of initial assessment, there were 3(2) suicide attempts, and there were 6(5) attempts during the follow-up period. ○ Of those who had a suicide attempt during the follow-up period, 67% had a lifetime history • 68 (52) participants had a lifetime history of NSSI. Within 3 months of initial assessment, 13 (10) participants had a NSSI and 23 (17) participants had a NSSI during the follow-up period. ○ Of those who had a NSSI during the follow-up period, 87% had a lifetime history.
Lavender (2023)[142] [redacted] UK between 2014 and 2018	**N = 38 TGNB adolescents** • **Eligibility**: younger than 15 years and at Tanner stage 2+, referred by the GIDS for GnRH analog treatment and CSH	• **Full cohort (N = 38):** Most of participants are white (N = 29); mean (SD) age at first endocrine clinic was 13.47 (0.94); mean (SD) age at starting GnRH analogs was 14.01 (0.81); mean (SD) age at starting CSH	GnRH analogs and CSH	• Baseline was assessed at point of referral to endocrinology. Assessed after approximately 1 year on GnRH analogs, and	• **Self-harm and suicidality:** ○ Of the young people and their caregivers who completed the statements regarding self-harm behaviors and suicidality on the YSR or CBCL at baseline, 1 year after GnRH analogs, and 1 year after CSH (n = 11), improvements were

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	treatment at 16 years (and with a minimum of around 1 year on GnRH analogs) • **Sampling method**: Young people referred to endocrinology were sent questionnaires at baseline, after 1 year on GnRH analogs, and after 1 year on CSH treatment. Before August 2020, questionnaires were sent by post to the young people and their caregivers, including a cover letter detailing the purpose of questionnaires and the right to opt out. From August 2020, questionnaire administration moved to an online platform with email links sent to young people and caregivers (Qualtrics, Provo, UT). • **Subset definition**: Assigned female at birth n = 28 and Assigned male at birth n = 10	was 16.10 (0.29); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD) time between start GnRH analogs and CSH was 2.09 (0.85) • **Assigned female young people group (n = 28):** Most are white (N = 22); mean (SD) age at first endocrine clinic was 13.74 (0.68); mean (SD) age at starting GnRH analogs was 14.19 (0.66); mean (SD) age at starting CSH was 16.06 (0.22); mean (SD) time between first endocrine clinic and GnRH analogs was 0.55 (0.36); mean (SD) time between start GnRH analogs and CSH was 2.03 (0.79) • **Assigned male young people group** (n = 10): Most are white (N = 7); mean (SD) age at first endocrine clinic was 12.74 (1.20); mean (SD) age at starting GnRH analogs was 13.51 (0.99); mean (SD) age at starting CSH was 16.25 (0.42); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD) time between start GnRH analogs and CSH was 2.10 (0.86)		then after approximately 1 year on CSH • General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous with time as within-subject factor. • Self-harm and suicidality were assessed using questions on the YSR: "I think about killing myself" and "I deliberately try to hurt or kill myself." • Autistic traits and social motivation were measured using the SRS2	noted in self-harm and suicidality statements from baseline to GnRH analogs, and further improvements with CSH. ○ There was a reduction in percentage of patients answering "very true" to suicidality and self-harm questions from YSR: 9% at baseline to 0% at 1 year after GnRH analogs and 0% 1 year after CSH and from CBCL: 9% at baseline to 0% at 1 year after GnRH analogs and 0% 1 year after CSH ○ There was a reduction in percentage of patients answering "somewhat or sometimes true" to suicidality and self-harm questions from YSR: 55% at baseline to 27% at 1 year after GnRH analogs and 9% 1 year after CSH and from CBCL: 36% at baseline to 18% at 1 year after GnRH analogs and 0% 1 year after CSH. ○ There was an increase in percentage of patients answering "not true" to suicidality and self-harm questions from YSR:36% at baseline to 73% at 1 year after GnRH analogs and 91% 1 year after CSH and from CBCL: 55% at baseline to 82% at 1 year after GnRH analogs and 100% 1 year after CSH. • **SRS-2: Mean (95%CI)** ○ SRS-2 T-scores all lay within the "normal range" and showed non-significant changes from baseline to 1 year on CSH. ○ A significant increase in social motivation T-scores was noted from 9.39 (6.02-12.75) baseline to 12.56 (8.95-16.18) at 1 year on CSH, *P* = .04.
López de Lara (2020)[62] [redacted] Spain: Pediatric endocrinology clinic[redacted]	**N=23 TGNB youth** • **Eligibility**: adolescents aged 14 to 18 yo, absence of psychiatric comorbidity, Tanner state 2 or higher, understanding of risks and benefits of CSH • **Sampling method**: requested volunteers	Transgender adolescents: • mean age: 16 years (range 14-18) • assigned sex at birth: ○ 69% female ○ 31% male • 91% Caucasian and Spanish descent • 52% parents with a university education • 30.4% had previously used mental health services • sexual orientation ○ 65% heterosexual, ○ 13% homosexual ○ 21% bisexual	CSH (oral estradiol, intramuscular testosterone)	Participants were assessed at baseline and 1 year after CSHT • Anxiety: assessed using STAI-S and STAI-T • Depression: assessed using BDI-II	• **Anxiety**, mean (SD) ○ STAI-S: There was a significant decrease in state anxiety scores from 33.3 (9.1) at baseline to 16.8 (8.1) at one year, P < 0.001 ○ STAI-T: There was a significant decrease in trait anxiety scores from 33 (7.2) at baseline to 18.5 (8.4) at one year., *P* < 0.001 • **Depression**, mean (SD) ○ BDI-II: There was a significant decrease in depression scores from 19.3 (5.5) at baseline to 9.7 (3.9) at one year, *P* < 0.001 • There was an increase of normal BDI-II scores (0-9) from 0% at baseline to 69.5% at one year, a decrease of milk scores (10-18) from 60.8% to 26.0%, decrease on moderate scores (19-29) from 34.7% to 4.3% and a decrease in sever scores (>30) from 4.3% to 0%.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.1. Longitudinal pre-post studies evaluating mental health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Tordoff (2022)[96] [redacted] Urban multidisciplinary gender clinic from August 2017 to June 2018	**N = 104 TGNB subjects** • **Eligibility**: TGNB adolescents and young adults seeking gender-affirming care • **Sampling method**: After a referral is placed or a patient self-refers, new patients, their caregivers, or patients with their caregivers are scheduled for a 1-hour phone intake with a care navigator who is a licensed clinical social worker. Patients are then scheduled for an appointment at the clinic with a medical provider. All patients who completed the phone intake and in-person appointment between August 2017 and June 2018 were recruited for this study. Participants completed baseline surveys within 24 hours of their first appointment and were invited to complete follow-up surveys at 3, 6, and 12 months.	The final sample included 104 youths ages 13 to 20 years (mean [SD] age, 15.8 [1.6] years). N = 84 (80.8%), 84 (80.8%), and 65 (62.5%) completed surveys at 3, 6, and 12 months, respectively. 63 transmasculine youths (60.6%), 27 transfeminine youths (26.0%), 10 nonbinary or gender fluid youths (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question on all completed questionnaires (3.8%).	PB, CSH, or both	Participants were assessed at baseline, 3 6 and 12 months • Depression: assessed using PHQ-9; dichotomized PHQ-9 scores into measures of moderate or severe depression (ie, scores ≥ 10) • Generalized anxiety: assessed using GAD-7; dichotomized GAD-7 scores into measures of moderate or severe anxiety (ie, scores ≥ 10) • Suicidality: assessed using PHQ-9 question 9	• **Depression**: ○ There were no statistically significant temporal trends in the bivariate model or model 1. However, among all participants, odds of moderate to severe depression increased at 3 months of follow-up relative to baseline (aOR, 2.12; 95%CI, 0.98-4.60), which was not a significant increase (*P* = NS), and returned to baseline levels at months 6 and 12 prior to adjusting for receipt of PBs or CSHs. • **Generalized anxiety:** ○ There were no statistically significant temporal trends in the bivariate model or model 1. Among all participants, the odds of moderate to severe anxiety increased at 3 months of follow-up relative to baseline (aOR, 1.50; 95%CI, 0.71-3.15), which was not a significant increase (*P* = NS), and decreased at months 6 and 12. • **Suicidality:** ○ There were no statistically significant temporal trends in the bivariate model or model 1. The odds of having any self-harm or suicidal thoughts increased at 6 months of follow-up relative to baseline (aOR, 1.22; 95%CI, 0.63-2.36), which was not a significant increase (*P* = NS), and decreased at months 12.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: ASQ, Ask Suicide-Screening Questions; BDI-II, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Scale; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAD-7, General Anxiety Disorder-7th edition; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; NSSI, non-suicidal self-injury; PB, puberty blockers; PHQ-9, Patient Health Questionnaire Modified for Teens; QID, quick inventory of depressive symptoms; RCMAS2, Revised Children's Manifest Anxiety Scale, Second Edition; SCARED, Screen for Child Anxiety Related Emotional Disorder; SD, standard deviation; SRS-2, Social Responsiveness Scale-2nd edition; STAI, Spielberger's Trait Anxiety Scale; TPI, Spielberger's Trait Anger Scale; TGNB, transgender, non-binary, or gender-diverse

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Achille (2021)[55] A US [redacted] NY) pediatric endocrine gender dysphoria clinic	**TGNB Adolescents (N = 50)** • **Eligibility**: Participants were recruited at the clinic, and a vast majority consented/assented. This study was limited to the subset of all patients who completed 3 rounds of questionnaires at 6-month intervals. Patients were excluded if they had sex chromosome abnormalities or disorders of sexual differentiation. • **Sampling method**: Patients must have completed 3 waves of questionnaires at 6-month intervals, for a total of approximately 12 months of observation. A "vast majority" of 116 patients gave consent/assent. • **Subset definition**: N = 50 TGNB adolescents, including MTF (N = 17) and FTM (N = 33) adolescents.	• **Full cohort**: Mean (SD) age was 16.2 (2.2); 64% were depressed in the prior year; 10% reported suicidality; 90% were seeing a therapist; 34% were on psychiatric medications • **MTF:** Mean (SD) age was 15.5 (1.6); 70.6% were depressed in the prior year; 11.8% reported suicidality; 94.1% were seeing a therapist; 29.4% were on psychiatric medications • **FTM**: Mean (SD) age was 16.6 (2.5); 60.6% were depressed in the prior year; 9.1% reported suicidality; 87.9% were seeing a therapist; 36.4% were on psychiatric medications	Up to 12-months of endocrine treatment including: • puberty blockers (N = 23, 46%), CSHT (N = 35, 70%), • both (N = 11, 22%), or • neither (N = 3, 6%)	• Outcomes were measured upon referral to the pediatric endocrine department for GD and after approximately 12 months of treatment. • Quality of life measured using: ○ QLES-Q-SF	**Quality of Life:** • QLES-Q-SF: Scores improved but did not reach statistical significance (*P* = NS) [Extracted scores were 61.3% at baseline and 72.0% at 12 months]
Allen (2019)[56] [redacted]	**N = 47 TGNB adolescents** • **Eligibility:** Adolescents and young adults (age range 13–20 years) who received services for GD at the clinic. Participants were included if they had pretest and final assessment data points and were treated with CSH for at least 3 months • **Sampling method:** A total of 47 eligible participants had pretest and final assessment data. The pretest for 23 participants occurred at their first contact	• The age of the participants ranged from 13.73 to 19.04 years (mean = 16.59, SD = 1.19). • The range of treatment length was 113-1016 days (mean = 349, SD = 193). • For most of the sample (90%), the duration of treatment was at, or under, 600 days. • Assigned female at birth was n = 33 (70.2%) and assigned male at birth was n = 14 (29.8). • The majority of participants were white n = 39 (83%).	**CSH** treatment	• Psychological well-being was measured using the GWBS of the Pediatric Quality of Life Inventory	**Psychological well-being:** Participants showed an increase in estimated adjusted mean (standard error) of GWBS scores from 61.7 (2.43) at T0 to 70.23 (2.15) at T1. • The main effect was significant, meaning GWBS were significantly higher at T1 after CSH, F(1, 44) = 11.39, *P* < .002, partial η2 = .21, demonstrating a large effect size. • Duration of treatment was not significantly related to participants' general well-being scores, F(1, 44) = .37, *P* = .54, partial η2 = .01, showing a small effect size.

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	with the clinic (the other participants' pretest assessment was completed at a subsequent visits to clinic but prior to starting CSH). Thirteen of the participants first presented to our clinic in 2015; 19 in 2016; 14 in 2017; and one in 2018. Patients are administered questionnaires and screeners at the beginning of their clinic visit, either at the time of the diagnostic evaluation or during a follow-up appointment with the multidisciplinary team. Responses are reviewed by the mental health professional prior to meeting with the patient.	• Of the 47 participants, n = 8 were administered GnRH analogs prior to beginning CSH (GnRH analogs + CSH subgroup) and n = 39 were not received GnRH analogs prior to being administered CSH (CSH-only subgroup).			
Arnoldussen (2022)[135] [redacted] Netherlands	**Population:** N = 70 adolescents • **Eligibility:** Adolescents who were referred between 2000 and 2013, who met the criteria for a "Gender Identity Disorder" diagnosis according to the DSM-IV-TR27 (because that was the DSM used during these years), who received puberty suppression and subsequent gender-affirming hormone treatment, and were at least 6 months post gender- affirming surgery could be included in the larger evaluation study. There were no exclusion criteria. Adolescents were included in the current study if their pretreatment data on self-perception were available. • **Sampling Method:** Between 2000 and 2013, 513 adolescents	• Gender, N (%) ○ Trans men: 49 (70.0%) ○ Trans women: 21 (30.0%) • Age at assessment in years, M (SD) ○ Pre-irreversible gender-affirming treatment (pretreatment assessment): 14.65 (2.08), range 11.23–19.74 ○ Post-irreversible gender-affirming treatment (post treatment assessment): 20.70 (1.49), range 18.97–26.28 • Age at gender-affirming surgery in years: 19.23 (1.27), range 17.98–24.75 • Post-surgical years at post treatment assessment: 1.47 (0.67), range 0.69–4.79 • Living situation of the adolescent at the pretreatment assessment, N(%) ○ Living with both biological parents: 43 (61.4%) ○ Other: 27 (38.6%)	PS, CSH and gender-affirming surgery	• The SPPA was used to examines self-perception on seven different domains: Scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, close friendship, and global self-worth at pre-treatment assessment, before any CSHT, and at least 6 months after gender-affirming surgeries.	• Multilevel modeling (adjusted for gender, age at pretreatment and post treatment assessment, use of puberty suppression at pretreatment assessment, full-scale IQ and living situation) revealed that the domains of physical appearance ($P < .001$) and global self-worth ($P < 0.001$) improved significantly over time. For the domains of scholastic competence, social acceptance, athletic competence, and close friendship, no significant change over time was found (no significant increase nor decrease, all $P > .05$). Only for the domain of behavioral conduct, an interaction effect for gender was found; a significant improvement was only observed for trans men ($P = .003$). • **Self-Perception Descriptive Scores for total sample**, mean (95% CI) ○ Scholastic competence (N = 70), ▪ Pre-irreversible gender-affirming treatment: 14.26 (13.54–14.98) ▪ Post- irreversible gender-affirming treatment: 14.96 (14.22–15.69) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.56 (0.64), $P < .05$; Adjusted 7.14 (5.26), P = NS ▪ Time: Unadjusted 0.70 (0.38), P = NS; Adjusted 0.71 (0.39), P = NS ○ Social acceptance (N = 70), P = NS ▪ Pre-irreversible gender-affirming treatment: 14.81 (14.05–15.58)

[a] P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	were referred consecutively to the CEGD. Of these 513 adolescents, a total of 179 were eligible for the larger evaluation study, among whom 107 participated. Of the 107 people who participated in the larger evaluation study, pretreatment data on self-perception were available for 70 of them and they were therefore included in the current study. As 70 individuals of the 179 eligible were eventually included in this study, the participation rate was 39.1%. • **Subset definition:** n = 49 trans men and n = 21 trans women	• Full-scale IQ, M (SD): 99.63 (14.23), range 72–135			▪ Post- irreversible gender-affirming treatment: 15.23 (14.48–15.98) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 14.40 (0.76), *P* < .05; Adjusted 22.34 (5.10), *P* < .05 ▪ Time: Unadjusted 0.41 (0.46), *P* = NS; Adjusted 0.43 (0.48), *P* = NS ○ Athletic competence (N = 69), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 12.86 (11.87–13.84) ▪ Post- irreversible gender-affirming treatment: 12.54 (11.62–13.46) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.16 (0.73), *P* < .05; Adjusted 12.98 (7.54), *P* = NS ▪ Time: Unadjusted -0.31 (0.39), *P* = NS; Adjusted -0.25 (0.40), *P* = NS ○ Physical appearance (N = 69), *P* < .001 ▪ Pre-irreversible gender-affirming treatment: 10.16 (9.37–10.95) ▪ Post- irreversible gender-affirming treatment: 12.81 (11.92–13.70) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 7.48 (0.72), *P* < .05; Adjusted 21.57 (5.20), *P* < .05 ▪ Time: Unadjusted 2.66 (0.42), *P* < .05; Adjusted 2.65 (0.42), *P* < .05 ○ Behavioral conduct (N = 70), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 15.81 (15.17–16.46) ▪ Post- irreversible gender-affirming treatment: 16.83 (16.23–17.43) ○ Close friendship (N = 70), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.87 (16.18–17.57) ▪ Post- irreversible gender-affirming treatment: 17.30 (16.57–18.03) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 16.44 (0.66), *P* < .05; Adjusted 21.39 (4.97), *P* < .05 ▪ Time: Unadjusted 0.43 (0.40), *P* = NS; Adjusted 0.49 (0.41), *P* = NS ○ Global self-worth (N = 68), *P* < .001 ▪ Pre-irreversible gender-affirming treatment: 12.01 (11.13–12.90) ▪ Post- irreversible gender-affirming treatment: 14.19 (13.32–15.06)

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 9.71 (0.87), *P* < .05; Adjusted 14.24 (5.53), *P* < .05 ▪ Time: Unadjusted 2.23 (0.54), *P* < .05; Adjusted 2.27 (0.55), *P* = NS • **Self-perception descriptive scores for trans women**, mean (95% CI) ○ Scholastic competence (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.29 (13.06–15.51) ▪ Post- irreversible gender-affirming treatment: 15.95 (14.61–17.29) ○ Social acceptance (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.91 (13.66–16.15) ▪ Post- irreversible gender-affirming treatment: 15.71 (14.64–16.79) ○ Athletic competence (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 11.91 (10.32–13.49) ▪ Post- irreversible gender-affirming treatment: 11.19 (9.41–12.97) ○ Physical appearance (N = 21), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 12.29 (10.65–13.92) ▪ Post- irreversible gender-affirming treatment: 14.95 (13.48–16.42) ○ Behavioral conduct (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.86 (16.04–17.68) ▪ Post- irreversible gender-affirming treatment: 16.71 (15.71–17.72) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 17.00 (0.85), *P* < .05; Adjusted 17.51 (7.99), *P* < .05 ▪ Time: Unadjusted -0.14 (0.52), *P* = NS; Adjusted -0.05 (0.57), *P* = NS ○ Close friendship (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 17.48 (16.46–18.49) ▪ Post- irreversible gender-affirming treatment: 17.67 (16.07–19.27) ○ Global self-worth (N = 21), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 13.57 (11.63–15.51) ▪ Post- irreversible gender-affirming treatment: 15.33 (13.99–16.68) • **Self-Perception Descriptive Scores for Trans men**, mean (95% CI) ○ Scholastic competence (N = 49), *P* = NS

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ Pre-irreversible gender-affirming treatment: 14.25 (13.33–15.16) ▪ Post- irreversible gender-affirming treatment: 14.53 (13.65–15.41) o Social acceptance (N = 49), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.78 (13.80–15.75) ▪ Post- irreversible gender-affirming treatment: 15.02 (14.03–16.01 o Athletic competence (N = 48), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 13.27 (12.01–14.53) ▪ Post- irreversible gender-affirming treatment: 13.13 (12.06–14.19) o Physical appearance (N = 48), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 9.23 (8.44–10.02) ▪ Post- irreversible gender-affirming treatment: 11.88 (10.85–12.90 o Behavioral conduct (N = 49), *P* = .003 ▪ Pre-irreversible gender-affirming treatment: 15.37 (14.53–16.20) ▪ Post- irreversible gender-affirming treatment: 16.88 (16.11–17.64) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.86 (0.80), *P* < .05; Adjusted 6.16 (5.06), *P* = NS ▪ Time: Unadjusted 1.51 (0.49), *P* < .05; Adjusted 1.51 (0.49), *P* < .05 o Close friendship (N = 49), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.61 (15.71–17.51) ▪ Post- irreversible gender-affirming treatment: 17.14 (16.32–17.97) o Global self-worth (N = 47), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 11.32 (10.39–12.24) ▪ Post- irreversible gender-affirming treatment: 13.68 (12.58–14.78)
Beckler-Hebly (2021)[72] [redacted] Germany	**Cohort 1: GnRH analogs (n = 11)**			• Outcomes were compared from intake appointment and then at follow up (6 months after the first referral and up to 4 years-average of 2 years.) • Psychological functioning measured using YSR/ASR and CGAS	**Cohort 1: GnRH analogs (n = 11)**
	N = 11 TGNB adolescents • **Eligibility**: baseline age of at least 11 YO, persistent GD, request for gender-affirming intervention in the absence of severe psychiatric issues	GnRH analogs (n = 11): for mean (SD) age, baseline was 15.56 years (1.85), follow-up age was 16.57 years (2.02), age at the time of the last medical treatment was 15.97 years (1.84); mean (SD) time since the last referral was 12.64 months (4.78); for onset, 91% were early onset, 9% were late onset; for gender, 72.7% were trans-male, 27.3% were trans-female; for	GnRH analogs		**Psychological functioning** • T YSR/ASR total problem score; mean (SD), 95% CI o Decreased from 62.27 (8.96), 95% CI (56.26, 68.29) at baseline to 61.91 (10.55), 95% CI (54.82, 69.00) at follow-up, *P* = NS • T YSR/ASR internalizing problems score; mean (SD), 95% CI

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Sampling method**: response rate 37% for all	additional psychotherapy, 91% had additional psychotherapy, 9% did not.		• Health related quality of life assessed using Kidscreen-27	○ Decreased from 63.64 (10.97), 95% CI (56.87, 70.40) at baseline to 61.55 (12.72), 95% CI (53.00, 70.09) at follow-up, *P* = NS • T YSR/ASR externalizing problem score; mean (SD), 95% CI ○ Decreased from 57.73 (10.05), 95% CI (50.98, 64.48) at baseline to 54.82 (11.37), 95% CI (47.18, 62.45) at follow-up, *P* = NS • CGAS global functioning score; mean (SD), 95% CI ○ Increased significantly from 67.27 (11.91), 95% CI (59.27, 75.27) at baseline to 81.82 (7.51), 95% CI (76.77, 86.86) at follow up. *P* < .05 [a] **Health-related quality of life** • T Kidscreen-27/SF-8 mental dimension; mean (SD), 95% CI ○ Increased from 39.04 (9.25), 95% CI (32.82, 45.25) at baseline to 43.17 (10.20), 95% CI (36.31, 50.01) at follow up, *P* = NS • T Kidscreen-27/SF-8 physical dimension; mean (SD), 95% CI ○ Increased from 43.43 (8.61), 95% CI (37.65, 49.22) at baseline to 49.57 (11.64), 95% CI (41.75, 57.39) at follow-up, *P* = NS
	Cohort 2: CSH and GnRH analogs (n = 32)				**Cohort 2: CSH and GnRH analogs (n = 32)**
	N = 32 TGNB adolescents • **Eligibility**: baseline age of at least 11 YO, persistent GD, request for gender-affirming intervention in the absence of severe psychiatric issues • **Sampling method**: response rate 37% for all	CSH and GnRH analogs (n = 32): for mean (SD) age, baseline was 15.47 years (1.04), follow-up age was 17.51 years (1.24), age at the time of the last medical treatment was 16.74 years (1.16); for onset, 84% were early onset, 16% were late onset; mean (SD) time since the last referral was 23.50 months (10.34); for gender, 87.5% were trans-male, 12.5% were trans-female; for additional psychotherapy, 81% had additional psychotherapy, 19% did not.	GnRH analogs and CSH		**Psychological functioning** • T YSR/ASR total problem score; mean (SD), 95% CI ○ There was a decrease from 61.56 (9.17), 95% CI (58.26, 64.87) at baseline to 60.09 (9.67), 95% CI (56.61, 63.58) at follow-up, *P* = NS • T YSR/ASR internalizing problems score; mean (SD), 95% CI ○ There was a significant decrease from 64.94 (11.18), 95% CI (60.91, 68.97) at baseline to 59.56 (10.34), 95% CI (55.83, 63.29) at follow-up. *P* < .05 [a] • T YSR/ASR externalizing problem score; mean (SD), 95% CI ○ There was a decrease from 54.13 (7.17), 95% CI (51.54, 56.71) at baseline to 52.03 (8.43), 95% CI (48.99, 55.07) at follow-up, *P* = NS • CGAS global functioning score; mean (SD), 95% CI ○ There was a significant increase from 73.13 (10.91), 95% CI (69.19, 77.06) at baseline to 85.63 (9.14), 95% CI (82.33, 88.92) at follow-up. *P* < .05 [a] **Health-related quality of life** • T Kidscreen-27/SF-8 mental dimension; mean (SD), 95% CI ○ There was a significant increase from 36.16 (6.78), 95% CI (33.72, 38.60) at baseline to 42.07 (10.74), 95% CI (8.20, 45.94) at follow-up. *P* < .05 [a]

[a] P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• T Kidscreen-27/SF-8 physical dimension; mean (SD), 95% CI ○ There was a significant increase from 39.12 (7.10), 95% CI (36.56, 41.68) at baseline to 49.36 (9.81), 95% CI (45.82, 52.90) at follow-up. *P* < .05 [a]
	Cohort 3: CSH and GA surgery (n = 11)				**Cohort 3: CSH and GA surgery (n = 11)**
	N = 11 TGNB adolescents • **Eligibility**: baseline age of at least 11 YO, persistent GD, request for gender-affirming intervention in the absence of severe psychiatric issues • **Sampling method**: response rate 37% for all	GA surgery and CSH (n = 11): for mean (SD) age, baseline was 15.96 years (1.02), follow-up age was 19.17 years (1.48), age at the time of the last medical treatment was 18.03 years (1.13); mean (SD) time since the last referral was 38.00 months (11.21); for onset, 91% were early onset, 9% were late onset; for gender, 90.9% were trans-male, 9.1% were trans-female; for additional psychotherapy, 73% had additional psychotherapy, 27% did not	CSH and one operation		**Psychological functioning** • T YSR/ASR total problem score; mean (SD), 95% CI ○ There was a decrease from 62.18 (8.78), 95% CI (56.28, 68.08) at baseline to 58.27 (8.72), 95% CI (52.42, 64.13) at follow-up, *P* = NS • T YSR/ASR internalizing problems score; mean (SD), 95% CI ○ There was a significant decrease from 65.73 (9.55), 95% CI (59.31, 72.14) at baseline to 55.36 (8.74), 95% CI (49.49, 61.24) at follow-up. *P* < .05 [a] • T YSR/ASR externalizing problem score; mean (SD), 95% CI ○ There was a significant decrease from 54.09 (7.80), 95% CI (48.85, 59.33) at baseline to 45.27 (10.87), 95% CI (37.97, 52.58) at follow-up. *P* < .05 [a] • CGAS global functioning score; mean (SD), 95% CI ○ There was a significant increase from 66.36 (14.33), 95% CI (56.73, 75.99) at baseline to 83.64 (8.09), 95% CI (78.20, 89.07) at follow-up. *P* < .05 [a] **Health-related quality of life** • T Kidscreen-27/SF-8 mental dimension; mean (SD), 95% CI ○ Increased from 37.88 (6.53), 95% CI (33.49, 42.27) at baseline to 43.44 (9.57), 95% CI (37.01, 49.87) at follow-up, *P* = NS • T Kidscreen-27/SF-8 physical dimension; mean (SD), 95% CI ○ Increased significantly from 39.88 (8.49), 95% CI (34.17, 45.59) at baseline to 53.87 (6.15), 95% CI (49.74, 58.00) at follow-up. *P* < .05 [a]
Carmichael (2021)[73] UK [redacted]	N = 44 TGNB adolescents • **Eligibility Criteria**: ○ Patients recruited from those referred to GIDS who were between 12-15 years and had commenced GnRH analog treatment.	Total sample median age at baseline was 13.6 (12.8,14.6), 89% white, all beyond stage 3 pubertal status. Median age at end of study was 16.1 (16.0,16.4). Birth registered males started at a median age of 13.4 (12.7,14.1) and birth registered females at 13.9 (13.5, 14.7) all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal	Suppression of puberty using GnRH analog triptorelin together with psychosocial support and therapy, from study entry until the end of the GnRH analog monotherapy pathway at age 16 or older. 3.75mg by IM injection given every 28 days during treatment period. 2 Participants given 11.25 mg every 10 weeks.	• Patients were measured at study entry, and then re-evaluated yearly at 12,24 and 36 month until they turned 16. • Measures of Psychological functioning were measured using the CBCL (parent report) and YSR (self-report.) • Reference data from both Australia and the Netherlands	**CBCL (parent report) and YSR** • **12 months scores mean (95%CI)** ○ Parent report CBCL ▪ Total Problems t-score showed a nonsignificant increase from 61.5(58.2, 64.7) at baseline for those followed up to 61.8(58.4, 65.1) at 12 months with a change of 0.3(-2.0, 2.6), *P* = NS ▪ Externalizing problems t-score showed a nonsignificant decrease from 55.7(52.1, 59.3) at baseline for those followed up to 55.4(51.8, 59.0) at 12 months, *P* = NS

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	○ Had been seen for at least 6 months and attended at least 4 interviews. ○ Psychological stability to withstand the stresses of medical treatment and ○ Displayed severe and persistent GD and actively requesting pubertal suppression ○ Able to give informed consent ○ Met physical/medical criteria of being in established puberty and having normal endocrine function and karyotype consistent with birth registered sex. • **Exclusions:** Inability to fully participate, BMI < 2nd percentile, serious psychiatric conditions, Inability to give consent, low spine or hip BMD • **Sampling Method:** Patients attending GIDS were provided with information and those wishing to find out more discussed with their clinician. Those likely deemed eligible were given detailed information and invited to a medical clinic for discussion. Young people needed to commit to regular medical and psychosocial follow up. Informed consent was obtained. 48 young people attended the clinics and 44 wished to participate. 8 young people were not yet eligible, but	function. No participants had evidence of disorders of sexual differentiation.		were used to calculate z-scores.	▪ Internalizing problems t-scores showed a nonsignificant increase from 61.8(58.3, 65.3) at baseline for those followed up to 62.9(59.5, 66.3) at 12 months, *P* = NS ○ Self-report YSR ▪ Total problems t-score showed a nonsignificant increase from baseline for those followed up from 57.6(54.5, 60.6) to 58.4(54.6, 62.2) at 12 months with a change of 0.8(-3.1, 4.8), *P* = NS ▪ Total problems z-score (ref: Netherlands) showed a nonsignificant increase from 0.97(0.62, 1.33) at baseline for those followed up to 0.99(0.55, 1.42) at 12 months, *P* = NS ▪ Total problems z-score (ref: Australia) showed no statistical change from 0.68(0.32, 1.03) at baseline for those followed up to 0.68(0.24, 1.12) at 12 months *P* = NS ▪ Externalizing problems t-score showed a nonsignificant increase from 52.3(49.2, 55.4) at baseline for those followed up to 52.5(48.7, 56.3) at 12 months *P* = NS ▪ Internalizing problems t-score showed a nonsignificant increase from 57.7(54.3, 61.0) at baseline for those followed up to 60.1(55.9, 64.3) at 12 months *P* = NS • **24 month scores mean (95% CI)** ○ Parent report CBCL ▪ Total Problems t-score showed a nonsignificant decrease from 61.2(56.5, 65.8) at baseline for those followed up to 60.2(54.6, 65.8) at 24 months with a change of -1.0(-4.0, 2.1), *P* = NS ▪ Externalizing problems t-score showed a nonsignificant increase from 55.4(49.9, 60.9) at baseline for those followed up to 55.2(48.9, 61.5) at 24 months, *P* = NS ▪ Internalizing problems t-score showed a nonsignificant decrease from 60.4(55.7, 65.1) at baseline for those followed up to 60.1(54.6, 65.6) at 24 months, *P* = NS ○ Self-report YSR ▪ Total problems t-score showed a nonsignificant increase from 55.1(50.9, 59.2) at baseline for those followed up to 56.5(50.6, 62.5) at 24 months with a change of 1.5(-3.4, 6.3) *P* = NS ▪ Total problems z-score (ref: Netherlands) showed a nonsignificant decrease from 0.66(0.17,1.15) at baseline for those followed up to 0.65(-0.05, 1.36) at 24 months. *P* = NS

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	were able to enter the study when sufficiently advanced in puberty. • **Subset Definition:** N = 44 TGNB adolescents age 12-15, including birth registered male (n = 25) and birth registered female (n = 19) adolescents.				▪ Total problems z-score (ref: Australia) showed a nonsignificant decrease from 0.39(-0.11,0.89) at baseline for those followed up to 0.37(-0.32, 1.07) at 24 months. *P* = NS ▪ Externalizing problems t-score showed a nonsignificant decrease from 53.1(48.5, 57.6) at baseline for those followed up to 52.3(45.3, 59.4) at 24 months. *P* = NS ▪ Internalizing problems t-score showed a nonsignificant increase from 53.9(49.9, 58.0) at baseline for those followed up to 55.9(50.8, 61.1) at 24 months. *P* = NS • **36 month scores mean (95%CI)** o Parent Report CBCL ▪ Total problems t-score showed a nonsignificant decrease from 62.4(55.1, 69.6) at baseline for those followed up to 61.1(52.3, 69.9) at 36 months with a change of -1.3(-6.6, 4.0). *P* = NS ▪ Externalizing problems t-score showed a nonsignificant decrease from 56.8(48.0, 65.6) at baseline for those followed up to 56.2(48.3, 64.1) at 36 months. *P* = NS ▪ Internalizing problems t-score showed a nonsignificant increase from 60.4(53.5, 67.2) at baseline for those followed up to 62.5(53.6, 71.5) at 36 months, *P* = NS • **There was no significant change in CBCL or YSR scores from baseline to any data collection point.**
Chen (2023)[75] USA- Gender clinics [redacted] from July 2016 through June 2019	**N = 315** • **Eligibility**: Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating CSH as part of their clinical care. For minors, parental consent was required to initiate treatment. • **Sampling Method:** Youth were recruited from 4 different sites at the start of CSH therapy. They were enrolled if they met inclusion criteria.	Participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) Higher percentage of those designated female at birth (64.8%) then male. Mostly non-Latinx or non-Latin white (58.1%)	CSH therapy	• Outcomes were measured at initiation of therapy, and then at 6,12,18 and 24 months. • **Positive Effect and Life Satisfaction** were assessed using measure from the NIH Toolbox—Emotion Battery.	• **Positive Effect:** Slope mean (95% CI) o There was a significant increase in T scores for positive affect showing an annual increase on a 100-point scale of 0.80 points (0.08 to 1.54) (unconditional model); 1.79 (0.14-3.43) (conditional model) after a period of 2 years of CSH treatment from baseline. • **Life Satisfaction:** Slope mean (95% CI) o There was a significant increase in T scores for life satisfaction showing an annual increase on a 100-point scale of 2.32 points (1.64 to 3.00) (unconditional model); 4.54 (2.66 to 6.43) (conditional model) after a period of 2 years of CSH treatment from baseline.

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Subset definition**: N = 315 TGNB adolescents, including: ○ FTM (n = 190,) MTF (n = 106) and NB (n = 19,) adolescents ○ Analytical sample n = 291 due to missing key variables at follow-up ○ Designated female at birth (n = 204,) and designated male at birth (n = 111) ○ Had early gender-affirming care-previously using GnRH analog (n = 24) ▪ youth designated female at birth with early gender-affirming care (n = 4) ▪ youth designated male at birth with early gender-affirming care (n = 20) ○ analytic sample (n = 291)				
Costa (2015)[77] [redacted]	**N = 201 TGNB adolescents** • **Eligibility**: diagnosed with gender dysphoria • **Sampling method**: all patients referred from 2010 and 2014 to the GIDS who completed diagnostic testing • **Subsets**: Of n = 201 of total population, n = 100 had delayed eligibility and only received psychological therapy, and n = 101 were immediately eligible for hormone therapy • Out of 101 immediately eligible population: ○ n = 101 at 6 months,	Full cohort: mean (SD) baseline age was 15.52 years (1.41), mean (SD) age at the start of GnRH analogs was 16.48 years (1.26); for living arrangement, 38.8% lived with both parents, 49.8% lived with one parent, 5.0% lived with other, 6.5% had no details; for education, 83.6% were in education, 9.5% were not in education, 7.0% had no details regarding education; for living in role, 58.2% completely did, 13.4% partly did; 21.4% did not, 7.0% had no details; for changing name, 53.2% did, 39.3% did not, 7.5% had no details	Puberty suppression and psychological support	Outcomes were assessed at baseline, then at: • **Time 1:** 6 months of psychological support for immediately eligible GD adolescents • **Time 2**: 12 months of psychological support with 6 months of puberty suppression for immediately eligible GD adolescents • **Time 3:** 18 months of psychological support with 12 months of puberty suppression for immediately eligible GD adolescents	**CGAS Scores for immediately eligible adolescents,** Mean (SD) There was a non-significant increase in scores between 58.72 (11.38) at baseline and 60.89 (12.17) at 6-month follow-up, *P* = NS • There was a significant increase in scores between baseline and 64.70 (12.17) at 12- month follow-up, *P* = .003 • There was a significant increase in scores between baseline and 67.40 (13.93) at 18- month follow-up, *P* < .001 • There was a non-significant increase in scores from 6 to 12 months, *P* = NS • There was a significant increase in scores from 6 month to 18 months, *P* = .001 • There was a non-significant increase in scores between 12 to 18 months, *P* = NS ○ Time 0 (baseline) CGAS, mean (SD) ▪ Immediately eligible GD adolescents (n = 101): 58.72 (11.38) ○ Time 1 (6 months) CGAS, mean (SD) ▪ Immediately eligible GD adolescents (n = 101): 60.89 (12.17)

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	○ n = 60 at 12 months ○ n = 35 at 18 months			CGAS used to assess adolescent's psychosocial functioning.	○ Time 2 (12 months) CGAS, mean (SD) ▪ Immediately eligible GD adolescents (n = 60): 64.70 (13.34) ○ Time 3 (18 months) CGAS, mean (SD) ▪ Immediately eligible GD adolescents (n = 35): 67.40 (13.93)
de Vries (2011)[57] [redacted]	**N = 70 TGNB youth** • **Eligibility**: adolescents with gender dysphoria eligible for medical intervention • **Sampling method**: first 70 patients consecutively enrolled from 2000 to 2008 • **Subset:** N = 70 TGNB youth, including N-37 natal females and N = 33 natal males	• **Full cohort:** mean (SD) age at baseline was 13.65 years (1.85); mean (SD) age at the start of GnRH analogs was 14.75 years (1.92); mean (SD) age at the start of CSH was 16.64 years (1.90); mean (SD) time between the start of GnRH analogs and CSH was 1.88 years (1.05); mean (SD) parental full-scale IQ was 98.2 (15.0); for parental marital status, 62.9% had both parents, 37.1% was other; for parents' education status, 10.6% had high, 66.7% had medium, 22.7% had low; for sexual attraction, 88.6% were attracted to their own natal sex, 8.6% were attracted to both sexes; 2.8% were attracted to other • **Natal male** (47%): mean (SD) age at baseline was 13.14 years (1.55); mean (SD) age at the start of GnRH analogs was 14.25 years (1.79); mean (SD) age at the start of CSH was 16.24 years (1.21); mean (SD) time between the start of GnRH analogs and CSH was 1.99 years (0.94); mean (SD) parental full-scale IQ was 97.1 (13.3); for parental marital status, 69.7% had both parents, 30.3% had other; for parents' education status, 3.3% had high, 76.7% had medium, 20.0% had low; for sexual attraction, 87.9% were attracted to their own natal sex, 6.1% were attracted to both sexes; 6.0% were attracted to other • **Natal female** (53%): mean (SD) age at baseline was 14.10 years (1.99); mean (SD) age at the start of GnRH analogs was 15.21 years (1.95); mean (SD) age at the start of CSH was 16.99 years (1.07); mean (SD) time	GnRH analogs (full cohort), N = 29 also started CSH	Participant data was collected before and after starting GnRH analogs • CGAS used to assess Psychosocial functioning • annoying situation. (Scale ranges from 1-4) • CBCL/ABCL and YSR/ASR used to assess behavioral and emotional problems using the total, internalizing and externalizing T scores as well as the clinical range scores for the indices (T score > 63)	**CBCL (n = 54)** • Total T-Score, mean (SD) ○ There was a significant decrease in scores from 60.70 (12.76) at baseline to 54.46 (11.23) at follow-up, *P* < .001 ○ Full cohort: T0- 60.70 (12.76), T1- 54.46 (11.23) ○ Female at birth: T0- 61.73 (13.60), T1- 57.73 (10.82) ○ Male at birth: T0- 60.00 (9.51), T1- 52.17 (9.81) • Internalizing T-Score, mean (SD) ○ There was a significant decrease in scores from 61.00 (12.21) at baseline to 54.46 (10.22) at follow-up, *P* < .001 ○ Full cohort: T0- 61.00 (12.21), T1- 54.46 (10.22) ○ Female at birth: T0- 61.80 (14.12), T1- 56.30 (10.33) ○ Male at birth: T0- 60.00 (9.51), T1- 52.17 (9.81) • Externalizing T-Score, mean (SD) ○ There was a significant decrease in scores from 58.04 (12.99) at baseline to 53.81 (11.86) at follow-up, *P* < .001 ○ Full cohort: T0- 58.04 (12.99), T1- 53.81 (11.86) ○ Female at birth: T0- 60.70 (12.64) , T1- 57.87 (11.66) ○ Male at birth: T0- 54.71 (12.91), T1- 48.75 (10.22) **YSR (n = 54)** • Total T-Score, mean (SD) ○ There was a significant decrease in scores from 55.46 (11.56), at baseline to 50.00 (10.56) at follow-up, *P* < .001 ○ Full cohort: T0- 55.46 (11.56), T1- 50.00 (10.56) ○ Female at birth: T0- 57.10 (10.87), T1- 51.86 (10.11) ○ Male at birth: T0- 53.56 (12.26), T1- 47.84 (10.86) • Internalizing T-Score, mean (SD)

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
		between the start of GnRH analogs and CSH was 1.78 years (1.16); mean (SD) parental full-scale IQ was 99.2 (15.2); for parental marital status, 56.8% had both parents, 43.2% had other; for parents' education status, 16.7% had high, 58.3% had medium, 25.0% had low; for sexual attraction, 89.2% were attracted to their own natal sex, 10.8% were attracted to both sexes; 0% were attracted to other			○ There was a significant decrease in scores from 56.04 (12.49) at baseline to 49.78 (11.63) at follow-up, *P* < .001 ○ Full cohort: T0- 56.04 (12.49), T1- 49.78 (11.63) ○ Female at birth: T0- 56.17 (13.25), T1- 50.24 (11.28) ○ Male at birth: T0- 55.88 (11.81), T1- 49.24 (12.24) • Externalizing T-Score, mean (SD); P-Value (for T0-T1) = 0.009 ○ There was a significant decrease in scores from 53.30 (11.87) at baseline to 49.98 (9.35) at follow-up, *P* = .009 ○ Full cohort: T0- 53.30 (11.87), T1- 49.98 (9.35) ○ Female at birth: T0- 57.24 (10.59), T1- 52.97 (8.51) ○ Male at birth: T0- 48.72 (11.83), T1- 46.52 (9.23) **CGAS (n = 41), mean (SD)** • There was a significant decrease in scores from 70.24 (10.12) at baseline to 73.90 (9.63) at follow-up, *P* = .005 • Full cohort: T0- 70.24 (10.12), T1- 73.90 (9.63) • Female at birth: T0- 67.25 (11.06), T1- 70.30 (9.44) • Male at birth: T0-73.10 (8.44), T1- 77.33 (8.69)
de Vries (2014)[79] [redacted]	**N = 55 TGNB youth** • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011 • **Subset:** N = 55 TGNB adolescents, with N = 22 MTF and N = 33 FTM)	Full cohort: the mean age (SD) at assessment pretreatment was 13.6 (1.9) (range: 11.1–17.0), the mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5), the mean age (SD) at the start of CSH was 16.7 (1.1) (range: 13.9–19.0), the mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3), the mean age (SD) at assessment post treatment was 20.7 (1.0) (range: 19.5–22.8); the mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)	CSH and GRS	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS) • CGAS used to assess Psychosocial functioning • CBCL/ABCL and YSR/ASR used to assess behavioral and emotional problems using the total, internalizing and externalizing T scores as well as the clinical range scores for the indices (T score > 63) General linear models examined the repeated measures with an analysis of variance-based model.	• **CGAS (Psychosocial functioning) (n = 32), mean (SD)** ○ Scores significantly increased from 71.13 (10.46) at intake to 79.94 (11.56) at post treatment, *P* < .001 ○ T0- 71.13 (10.46), T1- 74.81 (9.86), T2- 79.94 (11.56) ○ Significant linear effect (time) *P* < 0.001, Quadratic effect (time) *P* = NS • **CBCL /ABCL (Behavioral and emotional problems) (n = 40)** ○ Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 60.20 (12.66) at intake to 48.10 (9.30) at post treatment, *P* < .001 ▪ T0- 60.20 (12.66), T1- 54.70 (11.58), T2- 48.10 (9.30) ▪ Significant linear effect (time) *P* < .001, quadratic effect (time) *P* = NS ○ Internalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 60.83 (12.36) at intake to 50.45 (10.04) at post treatment, *P* < .001 ▪ T0- 60.83 (12.36), T1- 54.42 (10.58), T2- 50.45 (10.04)]

[a] P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				A linear effect signifies an overall change across T0 to T2. Quadratic effect signifies change was not continuous.	▪ Significant linear effect (time) *P* < 0.001, quadratic effect (time) *P* = 0.42 ○ Externalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 57.85 (13.73) at intake to 47.85 (8.59) at post treatment, *P* < .001 ▪ T0- 57.85 (13.73), T1- 53.85 (12.77), T2- 47.85 (8.59) ▪ Significant linear effect (time) *P* < .001, quadratic effect (time) *P* = NS • **YSR/ ASR (Behavior and emotional problems) (n = 43)** ○ Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 54.72 (12.08) at intake to 48.53 (9.46) at post treatment, *P* < .005 ▪ T0- 54.72 (12.08), T1- 49.16 (11.16), T2- 48.53 (9.46) ▪ Significant linear effect (time) *P* < .005, quadratic effect (time) *P* = NS ○ Internalizing T-Score, mean (SD); ▪ Scores showed a significant decrease from 55.47 (13.08) at intake to 50.07 (11.15) at post treatment, *P* < .03 ▪ T0- 55.47 (13.08), T1- 48.65 (12.33), T2- 50.07 (11.15) ▪ Significant linear effect (time) *P* < .03, Significant quadratic effect (time) *P* < .008 ○ Externalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 52.77 (12.47) at intake to 49.44 (9.37) at post treatment with a P value of 0.14 ▪ T0- 52.77 (12.47), T1- 49.44 (9.59), T2- 49.44 (9.37) ▪ linear effect (time) *P* = NS, quadratic effect (time) *P* = NS
	N = 22 MTF TGNB youth • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	**MTF**: for ages, the mean age (SD) at assessment pretreatment was 13.6 (1.8), the mean age (SD) at the start of GnRH analogs was 14.8 (2.0), the mean age (SD) at the start of CSH was 16.5 (1.3), the mean age (SD) at the start of GRS was 19.6 (0.9), the mean age (SD) at assessment post treatment was 21.0 (1.1); the mean full scale intelligence (SD) was 97.8 (14.2)	CSH and GRS		• **CGAS (Psychosocial functioning) MTF (n = 12), mean (SD)** ○ Scores significantly increased from 74.33 (7.53) at intake to 82.40 (8.28) at post treatment, *P* < .001 ○ T0-74.33 (7.53), T1- 78.20 (9.56), T2- 82.40 (8.28) • **CBCL /ABCL (Behavior and emotional problems) MTF (n = 15)** ○ Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 57.40 (12.76), at intake to 48.13 (12.58) at post treatment *P* < .002 ▪ T0- 57.40 (12.76), T1- 49.67 (12.29), T2- 48.13 (12.58) ○ Internalizing T-Score, mean (SD)

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ Scores showed a significant decrease from 59.40 (10.03), at intake to T2- 48.73 (12.61)]at post treatment ,*P* < .001 ▪ T0- 59.40 (10.03), T1- 50.93 (11.15), T2- 48.73 (12.61) ○ Externalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 52.53 (14.11), at intake to 46.33 (10.95) at post treatment, *P* = NS ▪ T0- 52.53 (14.11), T1- 47.87 (12.07), T2- 46.33 (10.95) • **YSR/ ASR (Behavior and emotional problems) MTF (n = 17)** ○ Total T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 50.65 (12.19), at intake to 47.24 (12.28) at post treatment, *P* = NS ▪ T0- 50.65 (12.19), T1- 45.94 (12.24), T2- 47.24 (12.28) ○ Internalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 54.00 (12.31), at intake to 48.12 (12.54) at post treatment, *P* < .04 ▪ T0- 54.00 (12.31), T1- 47.59 (14.26), T2- 48.12 (12.54) ○ Externalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 46.00 (11.58), at intake to 50.24 (11.18)]at post treatment, *P* = NS ▪ T0- 46.00 (11.58), T1- 44.71 (9.53), T2- 50.24 (11.18)
	N = 33 FTM TGNB youth • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	**FTM**: for ages, the mean age (SD) at assessment pretreatment was 13.7 (2.0), the mean age (SD) at the start of GnRH analogs was 14.9 (1.9), the mean age (SD) at the start of CSH was 16.8 (1.0), the mean age (SD) at the start of GRS was 19.0 (0.8), the mean age (SD) at assessment post treatment was 20.5 (0.8); the mean full scale intelligence (SD) was 100.4 (14.3)	CSH and GRS		• **CGAS (Psychosocial functioning) FTM (n = 17), mean (SD)** ○ Scores significantly increased from 67.65 (11.87), at intake to 76.29 (14.48)]at post treatment, *P* < .02 ○ T0- 67.65 (11.87), T1- 70.65 (9.89), T2- 76.29 (14.48) • **CBCL /ABCL (Behavior and emotional problems) FTM (n = 25)** ○ Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 61.88 (12.56), at intake to 48.08 (6.95)]at post treatment, *P* < .001 ▪ T0- 61.88 (12.56), T1- 57.72 (10.23), T2- 48.08 (6.95) ○ Internalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 61.68 (13.70), at intake to T2- 51.48 (8.25) at post treatment, *P* < .001 ▪ T0- 61.68 (13.70), T1- 56.52 (9.86), T2- 51.48 (8.25)

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Externalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 61.04 (12.71), at intake to 48.76 (6.89) at post treatment, *P* < .001 ▪ T0- 61.04 (12.71), T1-57.44 (12.01), T2- 48.76 (6.89) • **YSR/ ASR (Behavior and emotional problems) FTM (n = 26)** ○ Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 57.38 (11.47), at intake to 49.38 (7.21) at post treatment, *P* < .01 ▪ T0- 57.38 (11.47), T1- 51.27 (10.08), T2- 49.38 (7.21) ○ Internalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 56.42 (13.86), at intake to 51.35 (10.19)at post treatment, *P* = NS ▪ T0- 56.42 (13.86), T1- 49.35 (11.13), T2- 51.35 (10.19) ○ Externalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 57.16 (11.14), at intake to 48.92 (8.18) at post treatment, *P* = NS ▪ T0- 57.16 (11.14), T1- 52.54 (8.43), T2- 48.92 (8.18)
Kaltiala (2020)[138] Finland [redacted]	**N = 52** • **Eligibility** Criteria: The study comprises a retrospective chart review of adolescents referred to one of the two gender identity service facilities between 2011-2017, before age 18, who had been diagnosed with transsexualism and proceeded to cross-sex hormonal treatments and who had completed a follow-up of approximately a year after starting on cross-sex hormones (real-life phase). • **Sampling Method:** Between 2011 and 2017, 57 adolescents at the gender identity facility had been diagnosed with F64.0,	Mean age of 18.1 (1.1) years at diagnosis, range 15.2-19.9 years	CSH	• Participants were assessed at an initial gender identity assessment appointment before starting hormone therapy, and then about a year after treatment (called the "real-life phase") • Psychosocial indicators data for adolescent development were collected retrospectivity from charts with specific criteria	**Psychosocial indicators of adolescent development:** • There was a significant decline in the proportion of participants living with parent(s)/guardians from initial assessment to 12 month follow up appointment from 73% (38/52) to 40% (21/50), *P* < .001 • There was a significant decline in the proportion of those functioning age-appropriately in peer relationships from initial assessment to 12 month follow up appointment from 89% (46/52) to 81% (42/52), *P* < .001 ○ Of those adolescents with age-appropriate peer contacts during assessment (46/52), 91% (42/46) continued to have age-appropriate peer contacts during the real-life phase while 9% (4/46) no longer had these. ○ Of those with difficulties in peer contacts (6/52), all continued to have difficulties in this field. (*P* < .001, using cross tabulations with chi square statistics/Fisher's exact test) • There was a nonsignificant decline in the proportion of participants progressing normatively in school/ work from initial assessment to 12 month follow up appointment from 64% (33/52) to 60% (31/52), *P* = NS ○ Of those who progressed age-appropriately at school/working life during assessment (33/52), 85% (28/33) continued to do so during the real-life phase,

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	transsexualism, and had been offered an opportunity to start hormonal sex reassignment. One of them did not want any treatment, two withdrew and two had started hormonal treatments but had not yet completed the real-life phase at the end of 2017. Thus, 52 patients were included in the study. • **Subset definition**: N = 52 patients in study. N = 11 birth assigned males. N = 41 birth assigned females				but 15% (5/33) did not. Of those with problems at school (work) (19/52), 84% (16/19) continued to have problems, but 16% (3/19) ceased to have problems in this field. (*P* < .001 using cross tabulations with chi square statistics/Fisher's exact test) • There was a nonsignificant decline in the proportion of participants that had been dating or had steady relationships from initial assessment to 12 month follow up appointment from 62% (32/50) to 58% (30/52), *P* = NS ○ Of those who had experiences of dating/steady relationships during the assessment (32/50), 66% (21/32) had dating/ steady relationships during the real-life phase, and 34% (11/32) did not. Of those who had not had any dating/steady relationships by the end of the gender identity assessment, 44% (8/18) had and 56% (10/18) did not have these during the real-life phase. (*P* = NS using cross tabulations with chi square statistics/Fisher's exact test) • There was no significant change in the proportion of participants who were age-appropriately able to dealt with matters outside of the home from initial assessment to 12 month follow up appointment staying at 81% (42/52, *P* = NS) ○ Of those who had had age-appropriate skills in dealing with matters outside home (42/52), 88% (37/42) continued to be able to do so but 12% (5/42) functioned below the age-appropriate level during the real-life phase. Of those who had had difficulties in dealing with matters outside home (10/52), half (5/10) continued to do so, but half (5/10) no longer had problems in this field (*P* < .02 using cross tabulations with chi square statistics/Fisher's exact test).
Lavender (2023)[142] At an endocrine clinic in the UK between 2014 and 2018	**N = 38 TGNB adolescents** • **Eligibility**: younger than 15 years and at Tanner stage 2+, referred by the GIDS for GnRH analog treatment and CSH treatment at *16 years (and with a minimum of around 1 year on GnRH analogs) • **Sampling method**: Young people referred to endocrinology were sent questionnaires at baseline, after 1 year on GnRH analogs, and after 1 year on CSH treatment. Before August 2020, questionnaires were sent by post to the young people and	• **Full cohort (N = 38):** Most of participants are white (N = 29); mean (SD) age at first endocrine clinic was 13.47 (0.94); mean (SD) age at starting GnRH analogs was 14.01 (0.81); mean (SD) age at starting CSH was 16.10 (0.29); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD) time between start GnRH analogs and CSH was 2.09 (0.85) • **Assigned female young people group (N = 28):** Most are white (N = 22); mean (SD) age at first endocrine clinic was 13.74 (0.68); mean (SD) age at starting GnRH analogs was 14.19 (0.66); mean (SD) age at starting CSH was 16.06 (0.22); mean (SD) time between first endocrine clinic and GnRH analogs was 0.55 (0.36); mean (SD)	GnRH analogs and CSH	• Baseline was assessed at point of referral to endocrinology. Assessed after approximately 1 year on GnRH analogs, and then after approximately 1 year on CSH • General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change	• **YSR: Mean (95% CI)** ○ There was no significant difference in total and internalizing YSR scores across time points, although a general improvement over time was evident, except for a significant decrease in Externalizing problem T-scores from 53.91 (48.26-59.56) at baseline to 49.38 (44.96-53.79) 1 year after CSH, *P* < .04 • **CBCL: Mean (95% CI)** ○ Internalizing T-scores demonstrated a significant reduction across time F (1.27, 20.31) = 4.45, *P* < .04. Specifically, there was a reduction in mean internalizing scores from 62.77 (55.87-69.71) at baseline to 41.89 (23.19-60.59) at 1 year after GnRH analogs that was statistically significant (F(1, 16) = 5.50, *P* = 0.03). There was a non-significant increase after 1 year on CSH relative to baseline. ○ Externalizing T-scores also reduced over time, with reductions approaching significance. Mean scores indicated a general reduction after 1 year on GnRH analogs with a slight increase in reported externalizing behaviors after 1 year on CSH in the CBCL caregiver reports.

[a] *P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)*

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.2. Longitudinal pre-post studies evaluating psychosocial outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	their caregivers, including a cover letter detailing the purpose of questionnaires and the right to opt out. From August 2020, questionnaire administration moved to an online platform with email links sent to young people and caregivers (Qualtrics, Provo, UT). • **Subset definition**: Assigned female at birth N = 28 and Assigned male at birth N = 10	time between start GnRH analogs and CSH was 2.03 (0.79) • **Assigned male young people group (N = 10):** Most are white (N = 7); mean (SD) age at first endocrine clinic was 12.74 (1.20); mean (SD) age at starting GnRH analogs was 13.51 (0.99); mean (SD) age at starting CSH was 16.25 (0.42); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD) time between start GnRH analogs and CSH was 2.10 (0.86)		was not continuous with time as within-subject factor. • Psychological and behavioral functions were measured using the YSR and CBCL	

López de Lara (2020)[62]
[redacted] Spain: Pediatric endocrinology clinic [redacted]
	N=23 TGNB youth
	• **Eligibility**: adolescents aged 14 to 18 yo, absence of psychiatric comorbidity, Tanner state 2 or higher, understanding of risks and benefits of CSH
	Sampling method: requested volunteers
		Transgender adolescents:
		• mean age: 16 years (range 14-18)
		• assigned sex at birth:
		  ○ 69% female
		  ○ 31% male
		• 91% Caucasian and Spanish descent
		• 52% parents with a university education
		• 30.4% had previously used mental health services
		• sexual orientation
		  ○ 65% heterosexual,
		  ○ 13% homosexual
		• 21% bisexual
			CSH (oral estradiol, intramuscular testosterone)	Participants were assessed at baseline and 1 year after CSHT
				• Behavior problems: assessed using SDQ
					• **Behavior Problems**, mean (SD)
					  ○ Strengths and Difficulties Questionnaire (SDQ): There was a significant decrease in prosocial, emotional symptoms, conduct problems, peer problems and total difficulties scores from baseline to one year, *P* < 0.001
					  ○ Total difficulties, mean (SD), *P* < 0.001
					  T0: 14.7 (3.3)
					  T1: 10.3 (2.9)
					  ▪ Prosocial, mean (SD), *P* < 0.001
					  T0: 8 (1.6)
					  T1: 9 (1.2)
					  ▪ Emotional symptoms, mean (SD), *P* < 0.001
					  T0: 5.2 (1.6)
					  T1: 3.4 (1.2)
					  ▪ Conduct problems, mean (SD), *P* < 0.001
					  T0: 2.7 (0.8)
					  T1: 1.8 (1)
					  ▪ Hyperactivity, mean (SD), *P* < 0.001
					  T0: 4 (1.9)
					  T1: 2.6 (1.8)
					  ▪ Peer problems, mean (SD), *P* = NS
					  T0: 2.6 (1.3)
					  T1: 2.3 (0.8)
					• There was an increase in normal (0-15 points) SDQ scores from baseline (n=14; 61%) to one year (n=22; 95.6%), decrease in borderline scores (16-19 points) from baseline (n=8; 34.7%) to one year (n=1; 4.3%) and a decrease from abnormal scores (20-40 scores) from n=1 (4.3%) at baseline to none (0%) at one year.

[a] P values are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Becker-Hebly 2021)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Abbreviations: ABCL, Adult Behavior Checklist; ASR, adult self-report; CBCL, Children's behavior checklist; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; CGAS, Children's Global Assessment Scale; CI, confidence interval; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; ; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; GWBS, General Well-being Scale; ITS, interrupted time series; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; QLES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SHS, Subjective Happiness Scale; SWLS, Satisfaction With Life Scale; TGNB, transgender, non-binary, or gender-diverse; YSR, youth self-report

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Alvares (2022)[132] [redacted]	**N = 15 TGNB women** **Eligibility Criteria**: Women were included if they met the criteria for a gender dysphoria diagnosis according to the DSM-IV and V and/or ICD-10 guidelines, began androgen blockade after 12 years of age, regularly used estrogen in the last year, were between 25-45 years old, and had a BMI of 18.0-34.9 kg/m². They were excluded if they had current or previous illnesses that could interfere with strength or aerobic tests, or had chronic disease or chronic use of medications. **Sampling Method:** All participants were patients at the above setting. No additional information is given.	• 11/15 TGNB women were non-gonadectomized and taking estrogen and cyproterone acetate • 4/15 TGNB women were gonadectomized and taking estrogen only. • None of them used GnRH analogs at any time. • Average (SD) age at time of study: 34.2 (5.2) years • Median age at start of CSHT: 17 (range 12-35) years • Average (SD) duration of CSHT: 14.4 (3.5) years	**Estrogen treatment: n=15 (100%)** • Estradiol valerate: ○ n=1 patient at 1 mg/day ○ n=4 patients at 2 mg/day • Conjugated estrogens: ○ n=4 patients at 0.625 mg/day ○ n=3 patients at 1.25 mg/day • 17-beta estradiol gel: ○ n=1 patient at 0.5 mg/day ○ n=1 patient at 1 mg/day ○ n=1 patient at 1.5 mg/day **Antiandrogen treatment: n=11 (73.3%)** • Cyproterone acetate: ○ n=11 patients at 50 mg/day **Prior gonadectomy:** n=4 patients **Average duration of CSHT:** 14.4 (SD3.5) years	• Testosterone levels were measured using electrochemoimmunoassay 12 months before the start of the study and at the time of the study • Blood test collected on the day of the study, immediately before bioimpedance, ergospirometry, and strength tests Investigators used median TT of the past 12 months to determine values at T0	Total testosterone (TT): • There was no difference in testosterone levels between the measurements 12 months before the study and at the time of the study, *P* = NS
Beking (2020)[129] [redacted]	**N =** 21 transgender boys • **Eligibility criteria**: received puberty suppression and testosterone, no continuous psychotropic medication use, no psychiatric or neurologic disorder • Sampling method: recruitment/invitation	• Mean age = 16.1 years, SD = 0.7	• **Session 1** (baseline): had received 3.75 mg Triptorelin (Decapeptyl-CR®) subcutaneously or intramuscularly every 4 weeks (mean duration = 1.6 years, SD = 1.0) • **Session 2** (follow-up): had been receiving testosterone treatment since session 1 (mean duration = 9.8 months, SD = 2.9, range 5.6–14.8 months)	• fMRI data was collected as participants engaged in a face-matching task that has been shown to engage the amygdala at baseline and a follow-up appointment (mean 9.8 ± 2.9 months.)	• Testosterone and change in lateralization were not significantly associated. • Changes between session 1 and 2: ○ Δ in left amygdala activation: increase, t = 5.3, pFWE = .024 ○ Δ in right cerebellar activation: decrease, pFWE < .05 ○ Δ in bilateral fusiform gyrus activation: increase, pFWE < .05 ○ Δ in emotional face processing: no change, pFWE > .05
Boogers (2022)[66] [redacted]	**N = 161 TGNB girls** **Eligibility:** initiated GnRH analog treatment before age 18 years,	• **Median age at start of puberty suppression (yr, range):** ○ Regular dose: 13.5 (13.2 to 14.5) ○ High dose: 13.1 (12.1 to 13.6)	• Puberty suppression: Triptorelin (Decapeptyl-CR (Ferring) 3.75 mg every 4 weeks or Pamorelin (Ipsen)	• Height and weight were evaluated at the start of PS and then every 3-6 months.	**Puberty Suppression only** • Overall: Growth and bone maturation decelerate during PS, but accelerate again when starting CSHT • **Growth Velocity**

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	received estrogen therapy, and had reached adult height **Sampling method:** 176 from the 5350 birth-assigned males in the ACOG database met inclusion criteria; 15 were excluded due to missing data and temporary treatment continuation; 88 of the remaining had growth potential and were considered as part of the pubertal group; **Subset:** of N = 161 TGNB girls: • Pubertal group (N = 88) ○ N = 47 regular dose estradiol treatment ○ N = 22 high dose estradiol treatment ○ N = 11 ethinyl estradiol treatment ○ N = 8 combined treatment • N = 73 post-pubertal	○ Ethinyl estradiol: 12.4 (12.1 to 14.0) ○ Post-pubertal: 16.8 (16.1 to 17.3) • **Mean height at start of puberty suppression (cm, SD):** ○ Regular dose: 165.8 (8.4) ○ High dose: 163.4 (7.2) ○ Ethinyl estradiol: 160.8 (6.3) ○ Post-pubertal: 176.7 (6.9) • Mean duration of puberty suppression: 2.4 (0.8)	11.25 mg every 10-12 weeks) to suppress puberty. • From age 15 to 16 years, CSHT was initiated	Bone age was determined at start g PS and CSHT and repeated yearly to every 2 years until (near) adult height was reached Measures included: • Growth velocity • Adult height • Height SDS was calculated according to Dutch Male reference data. • Bone age was determined through X-rays of the left hand	○ There was a significant Δ between year 1 and year 2 (mean, 95% CI): -1.9 cm, 95% CI (-2.4 cm, -1.4 cm) ○ Year 1 (mean ± SD): 5.3 cm/year ± 2.2 ○ Year 2 (mean ± SD): 3.5 cm/year ± 1.3 • **Height SDS** ○ Significant Δ in height SDS per year (mean, 95% CI): -0.37/year, 95% CI (-0.47, -0.27) • **Bone Age** ○ Significant Δ BA per year (mean, 95% CI): -0.5 years/year, 95% CI (-0.8, -0.2) ○ Significant Δ BA (mean ± SD) at the start of PS (baseline) vs. start of CSHT: -1.6 years ± 0.8 (implicit) • **PAH** ○ Significant Δ in PAH (mean, 95% CI) at the start of CSHT vs start of PS: 1.5 cm, 95% CI (0.5 cm, 2.6 cm)
			Regular dose 17β-estradiol: starting dose of 5 µg/kg/d, which was increased every 6 months by 5 µg/kg/d up to an adult dose of 2 mg/d		• **Height** ○ Significant Δ in height (cm) from the start of CSHT to adult height (mean, 95% CI): 5.9 cm, 95% CI (5.7 cm, 6.2 cm) ○ Significant Δ in height (SDS) from the start of CSHT to adult height (mean, 95% CI): 0.17 cm, 95% CI (0.04 cm, 0.29 cm)
			High dose, growth reductive 17β-estradiol: dose increased up to 6 mg per day for 10 weeks		• **Height** ○ Significant Δ in height (cm) from the start of CSHT to adult height (mean, 95% CI): 9.9 cm, 95% CI (9.6 cm, 10.2 cm) ○ Significant Δ in height (SDS) from the start of CSHT to adult height (mean, 95% CI): 0.30 cm, 95% CI (0.01 cm, 0.58 cm) ○ Subgroup: those with a BA ≤ 14 years at the start of CSHT (n = 17) ▪ Non-significant growth reduction (mean, 95% CI) from the start of CSHT to adult height: 0.7 cm, 95% CI (-1.7 cm, 3.2 cm) ○ Subgroup: those with a PAH ≥ 180 cm at the start of CSHT (n = 15) ▪ Non-significant growth reduction (mean, 95% CI) from the start of CSHT to adult height: 0.9 cm, 95% CI (-1.4 cm, 3.2 cm)
			Growth reductive Ethinyl estradiol: 100 or 200 ug per day		• **Height** ○ Significant Δ in height (cm) from the start of CSHT to adult height (mean, 95% CI): 7.6 cm, 95% CI (7.1 cm, 8.0 cm) ○ Non-significant Δ in height (SDS) from the start of CSHT to adult height (mean, 95% CI): 0.05 cm, 95% CI, –0.23 cm to 0.33 cm) ○ Subgroup: those with a BA ≤ 14 years at the start of CSHT (n = 6)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ Non-significant growth reduction (mean, 95% CI) from the start of CSHT to adult height: 2.7 cm, 95% CI (-0.7, 6.2 cm) ○ Subgroup: those with a PAH ≥ 180 cm at the start of CSHT (n = 5 ▪ Non- significant growth reduction (mean, 95% CI) from the start of CSHT to adult height: 0.9 cm, 95% CI (-1.4 cm, 3.2 cm)
			Post-pubertal group		• **Height** (n = 34) ○ Δ between adult height and PAH at the start of PS (mean ± SD): 0.5 ± 1.0 cm
Ghelani (2020)[58] [redacted] between 2013 and 2015	**N = 36 TGNB adolescents** • **Eligibility**: not clearly stated • **Sampling method**: Patients were verified to be phenotypically and chromosomally normal through physical examination and karyotype analysis. 36 subjects whose data were complete were included in this study. Others were only excluded if they had an incomplete set of body composition data or if any other confounding factor was identified from routine clinic questioning about lifestyle that could affect the results (n = 4). Examples included patients that had excessive weight gain due to body-building activities and excessive weight loss when diagnosed with anorexia. • **Subset definition**: 11 transgender girls (birth-registered males identifying as female) and 25 transgender boys (birth-registered females identifying as male)	The mean age for full cohort was 16.5 (15.8–17.2) years. The mean age for transgender boys was 16.6 years (1 SD = ±0.69 years) and for transgender girls was 16.4 years (1 SD = ±0.66 years), P value = 0.50. The mean age of menarche in the transgender boys was 11.9 years (1 SD = ±1.10 years). All transgender girls were in late puberty (Tanner stages G4 and 5). There was no significant difference in age, weight and BMI between the two sexes. Transgender girls were significantly taller than transgender boys as expected for a late pubertal cohort, 167.7 (161.8–173.6) cm vs. 162.8 (156.4–169.2) cm, P value = 0.03.	**GnRH analog treatment:** Triptorelin (Gonapeptyl Depot 3.75 mg or Decapeptyl SR 11.25 mg) was administered subcutaneously for at least 1 year	Patients were measured at baseline and then at 6months and 12 months of GnRH analog treatment • Body composition (lean mass, height, weight, BMI): Data was taken from this routine clinic monitoring of patients and subsequently anonymized. Whole-body impedance at 50 kHz (Z, in Ω) was measured using a Tanita Body Composition Analyzer, Model type/Number BC-418MA III. The conventional whole-body impedance index (height2/Z) was calculated and used as an indicator of lean mass. Standard deviation scores (SDSs) for lean mass were calculated using recent UK body composition reference data. Height, weight and BMI SDS were derived from UK90 data.	• **Lean mass:** ○ The fall in lean mass SDS from baseline to 12 months is significant in transgender girls (*P* < .002). ○ Although lean mass SDS was decreasing from baseline to 12 months for full cohort, it is not statistically significant (*P* = NS). • **Height:** ○ The fall in height SDS from baseline to 12 months is significant in transgender girls (*P* = .012). ○ Although height SDS was decreasing from baseline to 12 months for full cohort, it is not statistically significant (*P* = NS). • **Weight:** ○ Changes in weight SDS in both transgender girls and transgender boys were not statistically significant, *P* = NS. • **BMI:** ○ Over the whole 12-month treatment period, the average BMI SDS in transgender girls decreased by 0.07. ○ In the transgender boys there was a fall in BMI SDS between 0 and 6 months but overall by 12 months there was an increase of 0.1 indicating a small but insignificant upward trend. ○ Changes in BMI SDS in both transgender girls and transgender boys were not statistically significant, *P* = NS.
Hannema (2017)[59] [redacted]	**N = 28 TGNB girls** • **Eligibility**: gender dysphoric adolescents seen at clinic. GD was diagnosed using DSM-IV,	• Average age was 16 with a range from 13.9 to 18.9. • 28 participants completed one year of treatment. 21 completed 2 years, and 16 completed 3 years. All were trans girls	Initial treatment was IM triptorelin 3.75 mg every 4 weeks. Oral estradiol was added around the age of 16 years. Two were treated with 200 ug ethinyestradiol and	• Data was collected before treatment as a baseline, then at 1 year of treatment. The whole cohort participated in the one year follow-up, measurements were then	• **Tanner Breast Stage:** ○ At baseline, there was no breast development. ○ Breast development began in all participants within 1 year, with 15 of 18 individuals starting within 3 months of treatment. ○ After 1 year on treatment, the median Tanner stage was 3 (range 2-5)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
[redacted]	had been treat with estrogen > 12 months • Sampling method: adolescents at the clinic were invited to participant in study.		four were treated with 6 mg estradiol.	taken at years 2 and 3 with dropout occurring. • Pubertal development was measured in several ways: Tanner stage, waist circumference, hip circumference and waist/hip ratio and testicular volume. Tanner stage is a scoring system used to measure pubertal development, in this case for breast development and testicular volume. Standard deviation scores were measured using Dutch reference data. • Bone age, which is a measurement of skeletal and biological maturity, was determined via a radiograph of the left hand. • Height, height SDS, sitting height and sitting height SDS were measured. SDS values were calculated using Dutch reference data • Anthropometric data was used to determine BMI, • Fat mass, fat percentage and lean body mass percentages were measured using dual energy X-ray absorptiometry	○ After 2 years on treatment, the median Tanner stage was 4 (range 2-5) ○ At 3 years, 1 individual had tanner stage 2, 1 had stage 3, 3 had stage 4, and 9 had stage 5 breast development, with those at stage 2 and 3 taking the longest to reach the adult dose of medication. • **Waist circumference (cm):** Mean ± SD ○ There were no significant changes to waist circumference from baseline (T0) to measurements at 1 (T1), 2 (T2) or 3 (T3) years ○ T0: 73.9 ±7.3; T1: 73.1 ± 9.0; T2: 72.8 ± 8.1; T3: 73.7 ±9.5 ○ **WC SDS compared to Female:** Mean ± SD ▪ There was a significant decrease from 0.72 ± 0.89 at baseline to 0.42 ± 1.10 after 1 year, *P* < .05 ▪ There was a nonsignificant decrease from baseline to 0.27 ± 1.04 after 2 years ▪ There was a nonsignificant decrease from 0.67 at baseline to 0.22 ± 1.29 after 3 years (*P* = NS) ○ **WC SDS compared to male:** ▪ There was a significant decrease from 0.07 ± 1.10 at baseline to 0.42 ± 1.41 after 1 year (*P* < .01) ▪ There was a significant decrease from baseline to -0.75 ±1.38 after 2 years (*P* < .01) ▪ There was a significant decrease from baseline to -0.9 ±1.70 after 3 years (*P* < .01) • **Hip circumference (cm)**: Mean ± SD ○ There was a nonsignificant increase from 93.9 ± 7.8 cm at baseline to 95.1 ± 8.8cm at year 1 (*P* = NS) ○ There was a significant increase from 93.5 ± 8.2 cm at baseline to 97.5 ± 9.0 cm at year 2 (*P* = 0.003) ○ There was a significant increase from baseline to 97.4 ± 7.9 cm at year 3 (*P* < .05) ○ **HC SDS compared to Female:** ▪ There was no significant change from 0.38 ± 0.96 at baseline to 0.37 ±1.07 at year 1, 0.51 ± 1.09 at year 2 or, 0.42 ± 0.98 at year 3. ○ **HC SDS compared to male:** ▪ There was no significant change from 0.60 ± 1.16 at baseline to 0.54 ± 1.30 at year 1, 0.70 ± 1.34 at year 2 or 0.64 ± 1.26 at year 3 • **Waist to Hip ratio:** Mean ± SD

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ There was a significant decrease in WHR from 0.79 ± 0.04 at baseline, to 0.76 ± 0.05 after one year. (*P* < .001) ○ There was a significant decrease in WHR ratio from baseline, to 0.75 ± 0.05 after 2 years. (*P* < .001) ○ There was a significant decrease in WHR ratio from baseline, to 0.75 ± 0.06 after 3 years. (*P* < .001) ○ **WHR SDS compared to Female:** ▪ There was a significant decrease from 0.49 ± 0.68 at baseline to 0.18 ± 0.85 at year 1. (*P* < .01) ▪ There was a significant decrease from baseline to -0.16 ± 0.86 at year 2 (*P* < .001) ▪ There was a significant decrease from baseline to -0.04 ±1.01 at year 3 (*P* = .002) ○ **WHR SDS compared to Male:** ▪ There was a significant decrease from -0.74 ± 0.86 at baseline to -1.19 ± 1.09 at year 1. (*P* < .01) ▪ There was a significant decrease from baseline to -1.71 ± 1.06 at year 2 (*P* < .001) ▪ There was a significant decrease from baseline to -1.48 ± 1.29 at year 3 (*P* < .001) • **Testicular volume (mL):** Mean ± SD ○ Testicular volume slightly decreased during the first year of treatment (*P* = .02), and did not significantly change thereafter. ○ T0: 8 (3-25), T1: 8 (3-23), T2: 10 (3-18), T3: 6.5 (4-11) • **Bone age:** ○ Bone age advances by a median of 1 year during the first year of treatment, 1.5 during the second year and 1 year during the third year. 25 participants in the study reached a bone age > 15 years, indicating they were near or at their adult height. ○ T0: 14.3 (13-18), T1: 15.5 (13.5-18), T2: 17 (15-19), T3: 18 (16-19) • **Sitting Height/Height:** Mean ± SD ○ There was no significant change in height from baseline: 0.509 ±0.013, to year 1: 0.509 ± 0.014, year 2: 0.513 ± 0.016 or year 3: 0.518 ± 0.158 ○ **Sitting Height/Height SDS Female comparison:** ▪ There was no significant change from baseline: -0.91 ± 0.82 to year 1: -0.98 ± 0.92, year 2: -0.75 ± 1.0, pr year 3: -0.68 ± 0.99 ○ **Sitting Height/Height SDS Male comparison:**

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ There was no significant change from baseline: 0.15 ± 0.89, to year 1: -0.27 ± 0.94, year 2: -0.07 ± 1.06, or year 3: 0.21 ± 1.12 • **Height (cm):** Mean ± SD ○ There was a significant increase in height from 178 ± 6.9 cm at baseline to 181.3 ± 7.1 cm at year 1 (*P* < .001), ○ There was a significant increase in height from baseline to 181.8 ± 8.4 at year 2 (*P* < .001) ○ There was a significant increase in height from baseline to 180.0 ± 9.4 (*P* < .01) ○ **Height SDS Female:** ▪ There was a significant increase from 1.48 ±1.11at baseline to 1.85 1.14 at year 1 (*P* < .001) ▪ There was a significant increase from baseline to 1.84 ± 1.32 at year 2 (*P* < .001) ▪ There was a significant increase from baseline to 1.53 ± 1.50 (*P* < .05) ○ **Height SDS Male:** ▪ There was a significant increase from -0.08 ±1.15 at baseline to 0.05 ±1.12 at year 1 (*P* < .05), ▪ There was no significant change from baseline to year 2 (-0.12 ± 1.24) or year 3 (-0.49 ± 1.36) • **BMI:** Mean ± SD ○ There was no significant change from 20.8 ± 3.0 kg/m² at baseline to 21.0 ± 3.3 kg/m² at year 1 or 21.3 ± 3.7 kg/m² at year 2. ○ There was a significant increase from baseline, 21.5 ± 3.2 kg/m² to 21.5 ± 3.3 kg/m² at year 3 (*P* = .01) ○ **BMI SDS Female:** ▪ There were no significant change from baseline to any measurement period ▪ T0: 0.16 ± 1.21, T1: 0.05 ± 1.28, T2: 0.02 ± 1.35, T3: -0.00 ± 1.35 ○ **BMI SDS Male:** ▪ There was a nonsignificant decline from baseline to all measurement periods ▪ T0: 0.34 ±1.32, T1: 0.12 ±1.40, T2: -0.03 ± 1.44, T: -0.14 ± 1.47 • **Fat Mass** ○ There was no significant change from baseline to year 1 or 2, but there was a significant increase from 17.2 ± 8.1 kg at baseline to 20.5 ± 9.1 kg at year 3 (*P* = .007) • **Lean Body mass %:** ○ There was no significant change from baseline to any measurement period

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ T0: 71 ± 6.5, T1: 72.8 ± 8.2, T2: 72.7 ± 8.9, T3: 70.9 ± 7.6 • **Fat Percentage:** ○ There was no significant change from baseline to any measurement period ○ T0: 26 ± 7.0, T1:24 ± 8.7, T2: 24 ± 9.3, T3: 25.9 ± 8.1
Jarin (2017)[136] Preexisting databases	**N = 116 TGNB adolescents** • **Eligibility**: Outpatient data from adolescents aged 14 to 25 years diagnosed with GD (International Classification of Diseases, Ninth Revision codes 302.85 and 302.50) and receiving cross-sex hormone therapy from 2008 to 2014 were included • **Sampling method**: Clinic and outpatient records were retrospectively reviewed • **Subset definition**: 72 affirmed male subjects and 44 affirmed female subjects	• The mean age of the affirmed male and female subjects was 16 and 18 years, respectively. • Depression was the most common medical comorbidity, with 35 subjects (30%) reportedly undergoing treatment for depression during hormone use. • Ten (23%) affirmed female subjects were undergoing medical therapy for HIV; no concurrent HIV was reported among the affirmed male subjects. • The longest follow-up time noted was 35 months. Baseline BMI, blood pressure, and metabolic values were within normal limits for all participants. • Seven affirmed male subjects reported undergoing puberty suppression with gonadotropin releasing hormone analogs before treatment, and 2 reported hormone use outside the practice of their medical providers (ie, street hormones). In affirmed male cohort, mean baseline total cholesterol levels were within normal limits at 151 mg/dL, with a corresponding baseline LDL level of 84 mg/dL. • Previous puberty suppression with gonadotropin-releasing hormone analogs was noted in 2 affirmed female subjects, whereas 5 subjects reported exogenous street hormone use.	Affirmed male subjects taking testosterone and affirmed female subjects taking estrogen with or without testosterone blockers (ie, spironolactone)	• Data was collected at baseline (or immediately before initiation of therapy,) at 1-3 months after initiation, at 4-6 months after initiation, and at 6 months and beyond. • Anthropometric measurements height/weight, BMI were compared.	**BMI:** • For affirmed male subjects, testosterone therapy was associated with significantly increasing BMI, changing from a mean baseline BMI of 26.0 kg/m² to 27.3 kg/m² after 6 months ($P < .0001$). • For affirmed female cohort, mean baseline BMI was 23.7 kg/m² and remained stable during treatment.
Klaver (2018)[83]	**N = 192 TGNB adolescents** • **Eligibility Criteria**: All persons who started hormonal treatment before 18 years of age, started the Dutch treatment protocol, had	**Baseline Characteristics:** • **MTF** participants started GnRH analogs at a mean age of 14.5 + 1.8 yrs. and CHT at a mean age of 16.4 + 1.1 yrs. They were mostly Caucasian.	The treatment protocol, referred to as the Dutch protocol, was followed. • **At a minimum age of 12 years and stage B2 (breast) for girls and Tanner stage G3 (genital)**	• Participants were assessed at the start of GnRH analog therapy, after the addition of CHT therapy, and at an appointment near 22 years of age (range 20.5-23.5)	**MTF subset findings: mean (95% CI)** • Waist circumference showed a significant increase from 71 cm (69-73) at start of GnRH to 76 cm (71-82) at 22 yo follow-up, with a change of 8 cm (5-10) ,$P < .001$ • Hip circumference showed a significant increase from 89 cm (87-91) at start of GnRH to 106 cm (102-110) at 22 yo follow-up, with a change of 17 cm (13-21), $P < .001$

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	undergone whole-body dual-energy x-ray absorptiometry (DXA) during treatment, and according to their age had their medical checkups in young adulthood (> 20.5 years) were eligible for this study. • **Sampling method**: Medical records were retrospectively reviewed for all adolescents diagnosed with gender dysphoria from 1998 until December 2015. All patients who met criteria were included in the study. Despite missing data, selection bias was not found. • **Subset definition**: N = 192 TGNB adolescents, MTF (N = 71) and FTM (N = 121) adolescents	• **FTM** participants started GnRH analogs at a mean age of 15.3 + 2.0 yrs. and CHT at a mean age of 16.9 + 0.9 yrs.	**for boys,** subcutaneous GnRH analogs 3.75 mg for 4 weeks was started. • **From 16 years of age,** CHT was added with increasing doses to initiate pubertal development. ○ Transgender women were prescribed oral 17b-estradiol starting at 5 mg per kilogram of body weight per day, which was increased by 5 mg/kg per day every 6 months until the maintenance dose of 2 mg/day was reached. ○ Transgender men used initially mixed testosterone esters (Sustanon; Organon Pharmaceuticals, Oss, The Netherlands) intramuscularly starting at 25 mg per square meter of body surface area every 2 weeks, which was increased by 25 mg/m² every 6 months until the maintenance dose of 250 mg every 3 to 4 weeks was achieved. • **When GnRH analog was started after 16 years of age, CHT was added after 3 to 6 months** with a start dosage of 17b-estradiol 1 mg/day or intramuscular Sustanon 75 mg/week. After 6 months, this was increased to 17b-estradiol 2 mg/day in transgender women and Sustanon 250 mg every 3 to 4 weeks in transgender men. • **From 18 years,** patients were eligible for gonadectomy, after	• Whole-body and regional body fat, LBM, and total mass were measured using DXA.	• Waist to hip ratio showed a significant decline from 0.81 (0.79-0.82) at start of GnRH to 0.77 (0.75-0.79) at 22 yo follow-up, with a change of -0.04 (-0.05 to -0.02), *P* < .001 • There was a decrease of the WHR of 0.02 during GnRH analogs alone and a further decrease of 0.02 after the addition of CHT. • The percentage of body fat in the android region significantly increased from 23% (21-25) at start of GnRH to 32% (28-36) with a change of 9% (6-12), *P* < .001 • The percentage of body fat in the gynoid region significantly increased from 29% (27-30) at start of GnRH to 40% (38-42) with a change of 11% (9-12), *P* < .001 • The percentage of total body fat significantly increased from 25% (23-26) at start of GnRH to 34% (32-36) with a change of 9% (8-11), *P* < .001 • There was an increase of percentage of total body fat of 6% (4-7) during GnRH analogs alone and a further increase of 3% (1-5) after the addition of CHT. • The percentage of Lean body mass significantly decreased from 75% (74-77) at start of GnRH to 66% (64-68) with a change of -9% (8-11), *P* < .001 • There was a decrease of the percentage of lean body mass of 6% during GnRH analogs alone and an additional decrease of 3% after the addition of CHT. • WHR and body composition changed towards the affirmed sex **FTM subset Findings: Mean (95% CI)** • Waist circumference showed a significant increase from 71 cm (69-73) at start of GnRH to 77 cm (75-79) at 22 yo follow-up, with a change of 6 cm (4-8), *P* < .001 • Hip circumference showed a significant increase from 92 cm (90-93) at start of GnRH to 96 cm (94-99) with a change of 5 cm (2-7) at 22 yo follow-up, *P* < .001 • Waist to hip ratio showed a significant increase from 0.77 (0.76-0.78) at start of GnRH to 0.80 (0.78-0.82) with a change of 0.03 (0.01 to 0.04) at 22 yo follow-up, *P* < .001 • There was a decrease in the WHR of 0.01 (-0.02-0) on GnRH analogs alone, and an increase of 0.04 (0.02-0.05) after the addition of CHT • The percentage of body fat in the android region showed no significant change from 29% (27-30) at start of GnRH to 30% (28-32) with a change of 1% (0-3), *P* = .18 • The percentage of body fat in the gynoid region significantly decreased from 36% (35-37) at start of GnRH to 31% (30-33) with a change of -5% (-6 to -3), *P* < .001) • The percentage of total body fat significantly decreased from 30% (29-31) at start of GnRH to 27% (26-28) with a change of -3% (-4 to -2), *P* < .001 • There was an increase of total body fat percentage of 3% (2-4) on GnRH analogs alone, and a decrease of 6% (-8 to-4) after the addition of CHT

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
			which treatment with GnRH analogs ceased.		• The percentage of Lean body mass significantly increased from 70% (69-71) at start of GnRH to 73% (72-74) with a change of 3% (2-4), *P* < .001 • There was a decrease of lean body mass percentage of 3% (-4 to -2) on GnRH analogs alone, and an increase of 6% (4-8) after the addition of CHT • WHR and body composition changed towards the affirmed sex
Klaver (2020)[139] [redacted]the Netherlands) from 1998 to December 2015	**N = 192 TGNB subjects** • **Eligibility**: subjects were included (1) if they had started treatment with GnRH analogs before the age of 18, (2) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogs or CSH treatment or within 1.5 years before or after the 22nd birthday), and (3) if, on the basis of their age, they were likely to have had at least 1 medical consultation in young adulthood (> 20.5 years • **Sampling method**: Medical records of all adolescents diagnosed with gender dysphoria at this medical center were retrospectively reviewed. • Subset: n = 71 trans women and n = 121 trans men	• All transgender subjects started GnRH analog treatment at a mean age of 15 and CSH treatment at a mean age of 17. • White participants accounts for 98% of subjects in trans women group and 94% of subjects in trans men group. • In trans women group, duration of GnRH analogs monotherapy [median (IQR)] = 2.1 (1.0–2.7), duration of GnRH analogs + CSH [median (IQR)] = 3.1 (2.5–3.6) and duration CSH monotherapy [median (IQR)] = 2.2 (1.1–3.1); • In trans men group, duration of GnRH analog monotherapy [median (IQR)] = 1.0 (0.5–2.9), duration of GnRH analogs + CSH [median (IQR)] = 2.3 (1.8–2.8) and duration CSH monotherapy [median (IQR)] = 2.9 (1.7–3.4	• GnRH analog treatment with a subsequent addition of CSHs. The Dutch protocol was followed.	• Measurements were taken at the start of GnRH analog treatment, and then followed up at the addition of CSH and again at age 22y (range 20.5-23.5) • BMI: Calculated as weight in kilograms divided by height in meters squared.	**BMI** • Trans women ○ There was a significant increase in BMI during GnRH analog treatment alone. The mean change (95% CI) was +1.1 kg/m² (0.7 to 1.5), *P* < .001 ○ There was a significant increase in BMI between start of CSH treatment and 22 y. Mean change (95% CI) was +1.9 kg/m² (0.6 to 3.2), *P* < .005. • Trans men ○ There was a significant increase in BMI during GnRH analog treatment alone. The mean change (95% CI) was +0.9 kg/m² (0.5 to 1.3), *P* < .001; ○ There was a significant increase in BMI between start of CSH treatment and 22 y. The mean change (95% CI) was +1.4 kg/m² (0.8 to 2.0), *P* < .001.
Klink (2015)[140] Unspecified tertiary referral center in [redacted]the Netherlands	**N = 34** TGNB adolescents • **Eligibility Criteria:** Study subjects were included when they were at least 21 years of age, gonadectomy had taken place in the period from June 1998 to August 2012, and data on BMD at start of GnRH analog treatment, at start of CSH therapy, and at the age of 22 years were available. The 34 eligible subjects and their	• Median age of trans women was 14.9 ± 1.9 at start of GnRH analogs, 16.6 ± 1.4 at start of CSH and 22.1 ± 0.9 at 22 year follow up • Median age for trans men was 15.0 ± 2.0 at start of GnRH analogs, 16.4 (2.3) at start of CSH and 21.9 ± 0.5 at 22 year follow up • Median duration of GnRH analog monotherapy in trans women and trans men was 1.3 years (range, 0.5–3.8) and 1.5 years (range, 0.25–5.2), respectively.	• GnRH analog monotherapy (median duration in natal boys with GD [trans women] and natal girls with GD [trans men] 1.3 and 1.5 y, respectively) followed by CSH (median duration in trans women and trans men, 5.8 and 5.4 y, respectively) with discontinuation of GnRH analogs after gonadectomy.	• Baseline Data was collected at start of GnRH analogs, start of CSH therapy and at follow-up near age 22 • Height (in cm) and weight (in kg) were taken and BMI calculated	**Trans women** (n = 15) • **Height** ○ There was a significant increase in height, from 174.6 ± 8.9 cm at start of GnRH analogs to 179.9 [17.1]cm at start of CSH, *P* = 0.01, and from 179.9 [17.1]cm at start of CSH to 181.0 ±9.3 cm at age 22y, *P* = .001 ○ There was a significant decrease in height SDS from 0.14 ± 1.3 at start of GnRH analogs to -0.97 ± 1.3 at start of CSH, *P* = .001. There was a nonsignificant increase from start of CSH to -0.42 ±1.3 at age 22y • **Weight**

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	parents or legal representatives gave written consent for follow-up at start of treatment. • **Sampling Method:** Patients that met criteria were included • **Subset:** of the total population (N = 34) there were (n = 15) trans women and (n = 19) trans men	• Median duration of CSH therapy was 5.8 years (range, 3.0–8.0) and 5.4 years (range, 2.8–7.8), respectively. • The median duration of combined GnRH analog and CSH therapies was 3.1 years (range, 2.1– 4.5) and 2.2 years (range, 1.4 – 3.1), respectively.	• Treatment protocol: Triptorelin (Decapeptyl-CR, Fer- ring) 3.75 mg every 4 weeks s.c. was started in patients diagnosed with gender identity disorder (DMS IV-TR) in the age range from 11.4 –18.3 years. In the age range from 15.6 –19 years trans- women were prescribed incremental dosing of 17-β-estradiol orally and trans men were given in mixed T esters (Sustanon 250 mg/ml, MSD) every 2–4 weeks in incremental dosages. At a minimum age of 18 years, after gonadectomy, GnRH analog treatment was terminated and CSH therapy continued. During the entire treatment patients were advised on calcium intake and weight- bearing physical exercise		○ There was a significant increase in weight, from 64.8 ± 10.4kg at start of GnRH analogs to 67.0 ± 10.2kg at start of CSH, *P* = .004 and from start of CSH to 74.6 ± 14.5 kg at age 22y, *P* = 0.01 • **BMI** ○ There was a significant increase in BMI, from 20.3 ± 2.3 kg/m² at start of GnRH analogs to 21.2 ± 2.8 kg/m² at start of CSH, *P* = .01. There was a nonsignificant increase to 22.7 ± 4.4 kg/m² at age 22y ○ There was a nonsignificant decrease in BMI-SD from 0.17 ± 0.90 at start of GnRH analogs to 0.07 ± 1.11 at CSH and from start of CSH to 0.62 ± 2.1 at age 22y. **Trans men** (n = 19) • **Height** ○ There was a significant increase in height from 165.2 ± 9.1 cm at start of GnRH analogs to 168.4 ± 8.3 cm at start of CSH, *P* = .03 and from start of CSH to 170.6 ± 7.9cm, *P* = .0001 ○ There was no significant change in height-SDS from -0.06 ±1.2 at start of GnRH analogs to -0.1 ±1.3 at start of CSH and -0.1 ±1.2 at 22y. • **Weight** ○ There was a significant increase in weight from 57.6 ±12.1 kg at start of GnRH analog therapy to 64.1 ± 11.5 kg at start of CSH, *P* = 0.01. ○ There was a nonsignificant increase to 68.2 ± 9.8kg at age 22y from start of CSH • **BMI** ○ There was a significant increase in BMI, from 20.9 ± 3.2 kg/m² at start of GnRH analogs to 22.9 ± 3.7 kg/m² at start of CSH. ○ There was a non-significant increase to 23.4 ±2.6 at 22y from start of CSH. ○ There was a non-significant increase in BMI-SDS from 0.3 ±1.0 at start of GnRH analogs to 0.5 ± 1.2 at start of CSH and from start of CSH to 0.96 ± 1.2 at age 22y
Laurenzano (2021)[84] A US gender/endocrine (doesn't specify) clinic [redacted] California	**N = 119 TGNB individuals assigned female at birth** • **Eligibility**: Younger than 21 years when starting T and received T for a minimum of 6 months, assessed by mental health professional to make sure they were ready to start T and met diagnostic criteria for GD.	Average age at presentation to clinic was 16 years. Average age of starting SC-T was 16.5 years. 110 patients were transgender males, 3 were nonbinary, 6 patients were classified as "other." 99 patients had no menstrual suppression before starting T, 12 used GnRH analogs and 8 used contraceptive. Average BMI was 24.	Subcutaneous testosterone injections starting at 50 to 100 mg/month in two injections.	Patients were assessed before starting testosterone as a baseline, and then followed up at most recent testosterone lab check • Body mass index (BMI), which is a value derived from the height and mass of each patient was calculated. BMI z-score, which compares BMI to a person of similar age and gender. Values for the z-score	• **BMI (mean scores)** ○ BMI significantly increased from baseline 24.85 to 25.71 kg/m² at follow (*P* < 0.001) ○ There was no significant change of BMI z-score (baseline was 0.56, follow up z-score was 0.5, *P* = NS) ▪ BMI z-score at follow up was only available for 95 patients, as 24 patients aged out. The baseline BMI z score given is for the 95 patients. • **Overall change in free and total T and estradiol: (mean levels)** ○ There was a significant increase in Total T from 31.6 to 432.2 dg/dL (*P* < .001),

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Sampling method**: Patients were selected if they met criteria and were a patient of the clinic.			were taken from the CDC for age 2-20 cisgender females. • Hormone levels were assessed for total and free testosterone and estradiol	○ There was a significant increase Free T from 3.7 to 86.2 pg/mL (*P* < .001), ○ There was a significant decrease in Estradiol from 78.9 to 49.1 pg/mL (*P* < .001) • **Change in free and total T:** significant in each dosing group ○ SC-T < 160 mg: ▪ Total T: 29.2 baseline to 328.8 ng/dL (*P* < .001) ▪ Free T 3.8 to 53.9 pg/mL (*P* < .001) ▪ Estradiol: 81.3 to 52.9 pg/mL (*P* = NS) ○ SC-T 160 to 240 mg: ▪ Total T: 31.6 to 456.8 ng/dL (*P* < .001) ▪ Free T: 3.6 to 91.9 pg/mL (*P* < .001) ▪ Estradiol: 79.6 to 48.4 pg/mL (*P* < .001) ○ SC-T > 240 mg: ▪ Total T 37.8 to 522.6 ng/dL (*P* < .001) ▪ Free T 4.5 to 124.6 pg/mL (*P* < .001) ▪ Estradiol 68.6 to 47.3 pg/mL (*P* = NS)
Navabi (2021)[92] Endocrine diversity clinic [redacted] from January 2006 to April 2017	**N = 119 transgender males (for this subset)** • **Eligibility**: patients < 18 years old starting/on GnRH analog treatment with one baseline DEXA measurement • **Sampling method**: all patients from January 2006 to April 2017 were reviewed, and about 86.9% were included as they had a baseline DEXA measurement	Mean LBM z-score (SD) being -1.03 (1.22); mean TBF (SD) was 37.14% (10.46) with the mean TBF z-score (SD) being 1.68 (0.96); mean BMI (SD) was 24.04 kg/m² (5.17) with the mean BMI z-score (SD) being 0.89 (1.25)	GnRH analogs	• Participants were assessed at GnRH analog initiation and then at a follow-up appointment at least 18 months after start of therapy. • Anthropometrics were retrieved from medical records and *z* scores calculated from 2014 WHO growth charts for Canada	**Body composition changes, (n = 80) Mean (95% CI)** • significant increase in BMI with a mean post-pre difference of 1.36 kg/m² (0.75 to 1.97), *P* < .001 • non-significant increase in the BMI z-score, with a mean post-pre difference of 0.15 (0.01 to 0.29), *P* = NS • no change in TT-FMR, mean post-pre difference: 0.00 (-0.01 to 0.01), *P* = NS • no change in LT-FMR, mean post-pre difference: 0.00 (-0.01 to 0.00), *P* = NS • no change in ET-FMR, mean post-pre difference: 0.00 (-0.02 to 0.02), *P* = NS • significant increase in Android fat %, with a mean post-pre difference: 2.75% (1.21 to 4.28), *P* < .001 • significant increase in Gynoid fat % with a mean post-pre difference: 1.83% (0.77 to 2.88), *P* < .001 • significant increase in TBF in kg with a mean post-pre difference: 2.19 (0.75 to 3.63), *P* = .001 • significant increase in TBF in %, with a mean post-pre difference: 2.21 (0.99 to 3.43), *P* < .001 • non-significant increase in TBF z-score in %, with mean post-pre difference: 0.13 (0.00 to 0.25), *P* = NS • significant increase in LBM in kg, with a mean post-pre difference: 1.05 (0.45 to 1.64), *P* < .001

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• non-significant decrease in LBM z-score, with a mean post-pre difference: -0.02 (-0.16 to 0.12), *P* = NS
	N = 51 transgender females (for this subset) • **Eligibility**: patients < 18 years old starting/on GnRH analog treatment with one baseline DEXA measurement • **Sampling method**: all patients from January 2006 to April 2017 were reviewed, and about 86.9% were included as they had a baseline DEXA measurement	Mean LBM (SD) was 45.74 kg (9.98) with the mean LBM z-score (SD) being -1.19 (1.45); mean TBF (SD) was 24.45% (12.48) with the mean TBF z-score (SD) being 1.42 (1.02); mean BMI (SD) was 23.22 kg/m² (6.33) with the mean BMI z-score (SD) being 0.62 (1.67)	GnRH analogs	• Participants were assessed at GnRH analog initiation and then at a follow-up appointment at least 18 months after start of therapy. • Anthropometrics were retrieved from medical records and z scores calculated from 2014 WHO growth charts for Canada.	**Body composition changes** • non-significant increase in BMI, with a mean post-pre difference: 0.57 kg/m² (-0.46 to 1.60), *P* = NS • non-significant decrease in BMI z-score, with a mean post-pre difference: -0.10 (-0.38 to 0.17), *P* = NS • non-significant decrease in TT-FMR, with a mean post-pre difference: -0.02 (-0.03 to 0.00), *P* = .010 • significant increase in LT-FMR, with a mean post-pre difference: 0.01 (0.00 to 0.02), *P* = .013 • significant increase in ET-FMR, with a mean post-pre difference: 0.08 (0.02 to 0.13), *P* = .004 • significant increase in Android fat %, with a mean post-pre difference: 4.18 (1.09 to 7.28), *P* = .002 • significant increase in Gynoid fat %, with a mean post-pre difference: 7.17 (4.64 to 9.69), *P* < .001 • significant increase in TBF in kg, with a mean post-pre difference: 4.41 (2.22 to 6.60), *P* < .001 • significant increase in TBF in %, with a mean post-pre difference: 5.36 (2.83 to 7.88), *P* < .001 • significant increase in TBF z-score in %, with a mean post-pre difference: 1.05 (0.79 to 1.32), *P* < .001 • Significant decrease in LBM in kg, with a mean post-pre difference: -1.58 (-3.0 to -0.15), *P* = .006 • Significant decrease in LBM z-score, with a mean post-pre difference: -0.73 (-0.95 to -0.5), *P* < .001 • Body changes, especially fat redistribution, were in keeping with youth affirmed gender
Neyman (2019)[64] Pediatric endocrine clinic at [redacted]	**N = 23 MTF (data is from 13 patients)** • **Eligibility**: MTF patients that were treated with bicalutamide at the clinic. Patients were excluded if they received an additional therapy (estrogen or spironolactone)	Median age 16.63 years. All but one patient was Caucasian.	Bicalutamide 50 mg	• Patients were assessed before starting therapy as a baseline and then at next clinic visit after starting therapy. Median time is 6.3 months. Range of 8 to 2.17 months. For patients that had a second visit, the average time to the second visit was 12.6 months.	• All patients started with Tanner Stage I breast development. At the follow up 7 patients had Tanner Stage III breasts, two patients had mixed Tanner Stages, 1 patient has Tanner stage II and two patients had Tanner stage II breasts. One patient had Tanner Stage V. • Five patients had a second visit recorded, in which two patients progressed to the next Tanner stage, while three remained at the same Tanner stage.

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Sampling method**: patients were selected from clinic if they met inclusion criteria.			• Breast development measured by Tanner stage, which is an objective classification of puberty stage.	
Olson-Kennedy (2018)[143] Center for Trans Youth Health and Development [redacted]	**N = 101 participants**, data for 59 participants • **Eligibility:** Participants were eligible if they were between the ages of 12 and 24, had gender dysphoria, had a desire to undergo phenotypic gender transitions, were naive to cross sex hormones or less than three months of previous hormone use, ability to read and comprehend English. • **Sampling method:** Patients were selected for the study if they fit the eligibility criteria. Patients from February 2011 to June 2013 were screened for participation. • **Subset:** o **n =** 25 transfeminine o n = 34 transmasculine	• Mean age 18 years (range 12 years to 23 years) • 22% had started hormones younger than 16 years.	• Transfeminine: testosterone blocking agent (spironolactone or GnRH analog) and feminizing medication (17 B estradiol). Some also have the addition of progesterone. seven youth did not use puberty blockers. • Transmasculine- testosterone cypionate SQ, with doses ranging from 12.5 to 75 mg weekly. Two patients were on GnRH analogs.	• Measurements were taken at baseline and then at a 24-month follow-up • BMI was calculated with height and weight taken at appointments • Mean hormone levels for Testosterone and estradiol	**BMI (kg/m²)** • **Transfeminine (n = 24)** o There was no significant change from 24.60 (4.73) at baseline to 24.86 (5.34) at 24-month follow-up, *P* = NS • **Transmasculine (n = 35)** o There was no significant change from 27.27 (6.17) at baseline to 27.99 (5.53) at 24-month follow-up, *P* = NS **Testosterone and Estradiol levels** • **Transfeminine** o There was a significant drop in free and total Testosterone levels, no significant change in estradiol and prolactin levels. ▪ Testosterone free (pg/mL) n = 24: T0 = 80.90 (49.83), T1 = 28.54 (43.17) *P* < .001 ▪ Testosterone total (ng/dL) n = 24: T0 = 425.88 (233.82), T1 = 169.0 (217.61) *P* < .001 ▪ Estradiol (pg/mL) n = 23: T0 = 26.16 (14.55), T1 = 286.04 (92.04) *P* = NS ▪ Prolactin (ng/mL) n = 13: T0 = 8.27 (5.98), T1 = 11.99 (5.44) *P* = NS • **Transmasculine** o There was a significant increase in free and total Testosterone levels, no significant change in estradiol levels ▪ Testosterone free (pg/mL) n = 35: T0 = 5.79 (7.71), T1 = 117.43 (80.51) *P* < .001 ▪ Testosterone total (ng/dL)n = 35: T0 = 41.17 (45.31), T1 = 533.26 (331.31 *P* < .001 ▪ Estradiol (pg/mL): T0 = 81.93 (81.95), T1 = 50.79 (43.21) *P* = NS
Olson-Kennedy (2021)[93] Preexisting patients at the Center for Trans Youth Health and Development at [redacted] as well as patients enrolled in the Trans Youth Care study, which was a multisite	**N = 66 participants** • **Eligibility**: histrelin implant at Tanner stage 2 or 3 used to treat gender dysphoria. They had to have hormone levels measured before implantation. • **Sampling method**: data was taken from patient charts of	• Average age is 11.3 years. There were 51 (77.3%) participants in Tanner stage 2, and 15 participants (22.7%) in Tanner stage 3. 46 (69.7%) participants had a Supprelin implant and 20 (30.3%) had a Vantas implant. 32 (48%) were transfeminine and 32(52%) were transmasculine.	Histrelin implant which was either Vantas or Supprelin. N = 66 patients, 46 (69.7%) participants had a Supprelin implant and 20 (30.3%) had a Vantas implant.	• Baseline taken before histrelin implant. To be eligible, hormone levels had to be taken before implantation. Follow-up levels were taken 2-12 months following implantation. • Hormone levels	• **SupprelinLA:** o Significant decrease in all hormone levels (*P* < .001) ▪ LH (mIU/mL: 0.62 (T0) to 0.2 (T1) ▪ FSH (mIU/mL): 2 (T0) to 0.63(T1) ▪ Estradiol (pg/mL): 7(T0) to 2 (T1) ▪ Testosterone (ng/dL): 19.5 (T0) to 9 (T1) • **Vantas:**

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
observational study conduct at major hospitals [redacted]	eligible patients from CHLA clinic and Trans Youth Care study. • **Subset**: Supprelin implant and Vantas implant	• Other demographic information can be found in Table I.1 of source		○ LH(mIU/mL), FSH (mIU/mL) ○ either Estradiol for transmasculine participants or total testosterone for transfeminine participants.	○ Significant decrease in all hormone levels (P < .001) ▪ LH (mIU/mL: (T0) to 0.21 (T1) ▪ FSH (mIU/mL): 3.63 (T0) to 0.5 (T1) ▪ Estradiol (pg/mL) :35.5 (T0) to 3 (T1) ▪ Testosterone (ng/dL): 57.5 (T0) to 7 (T1)
Perl (2020)[144] Israeli Pediatric Gender Dysphoria Clinic [redacted] between 2013 and 2018	**N = 15 TGNB adolescents** • **Eligibility**: All transgender male adolescents who were treated solely with GnRH analogs for ≥ 2 months • **Sampling method**: The medical files of 48 transgender male adolescents who had sought medical attention due to GD at the clinic were reviewed	• Mean age at initiation of pubertal suppression was 14.4 ± 1.0 years. • GnRH analogs were administered for a mean period of 3 ± 1 months. • All 15 transgender males had clinical and laboratory evidence of Tanner stage 4/5 puberty. Their weight status at the initiation of GnRH analog treatment was normal (mean BMI-SDS 0.2 ± 0.9), as were their BP levels and percentiles (mean SBP 115 ±7mmHg [71 ±19 percentile] and mean DBP: 64 ±10mm Hg [56 ±26 percentile]). • Testosterone treatment was initiated in 9 of the 15 transgender male adolescents at a mean age of 15.1 ± 0.9 years. • The mean treatment period of testosterone was 4 ± 2 months	Pubertal suppression therapy consisted of a depot preparation of the GnRH analog D-Trp-6-LHRH (Decapeptyl; Ferring Pharmaceuticals Ltd., Malmo¨, Sweden) at a dose of 3.75mg administered by intramuscular injection every 4 weeks. Gender-affirming hormone therapy consisted of intramuscular testosterone enanthate 250 mg/mL (Testoviron Depot; Bayer Israel Ltd.) at a starting dose of 50–100 mg administered by intramuscular injection every 4 weeks.	• Participants were evaluated within 1-4 weeks of starting GnRH analogs as a baseline, and then evaluated within 1-4 weeks of the addition of testosterone injections. • BMI: Changes in weight status were measured by body mass index standard deviation score.	**BMI**: • BMI-SDS did not increase significantly during GnRH analog therapy, P = NS . • After the addition of testosterone, BMI-SDS did not change significantly.
Perl (2021)[145] Israeli Pediatric Gender Dysphoria Clinic [redacted] between 2013 and 2018	**Population: N = 19 TGNB female adolescents (AMAB)** • **Eligibility Criteria:** Files were reviewed retrospectively among TGNB female adolescent that sought medical attention due to GD at site who had been treated solely with GnRH analogs for ≥ 2 months and had BP data in file • **Sampling Method:** 86 files were reviewed at facility and then files were excluded that did not meet the study criteria. • **Subset Definition:** Of the N = 19 TGNB female adolescents, N = 15 received estradiol	• The mean age at initiation of pubertal suppression was 15.7 ± 1.6 years. • All 19 transgender females had clinical and laboratory evidence of Tanner stage 4/5 puberty. • Weight status at the initiation of GnRH analog treatment was as follows: mean BMI-SDS −0.21 ± 1.42. Three participants were underweight with BMI-SDS < −2. • Mean SBP was 116 ± 8 mm Hg (55 ± 29 percentile) with three participants having systolic pre- hypertension. • Mean DBP was 70 ± 9 mm Hg (64 ± 27 percentile), with three participants having diastolic prehypertension (one participant had both systolic and diastolic prehypertension).	Pubertal suppression: an intramuscular injection of depot-preparation GnRH analog D-Trp-6-LHRH (Decapeptyl, Ferring Pharmaceuticals Ltd., Malmo, Sweden) at a dose of 3.75 mg was administered every 4 weeks.	• Patients data was reviewed before pubertal suppression (GnRH analog treatment) and then at a Follow-up appointment after GnRH analog administration (mean period of 9 ± 6 months) • Data was reviewed for anthropometric measurements.	**Weight** Mean ± SD • Weight status (BMI-SDS) did not change significantly during GnRH analog therapy (from -0.21 ± 1.42 at baseline to -0.25 ±1.29 at follow-up, P = NS)
			Gender-affirming hormone therapy: consisted of oral tab beta estradiol 1 or 2 mg (Estrofem, Novo Nordisk LTD, Israel) at a starting dose of 1 mg daily for 6 months. Dose was increased to 2 mg after 6 months, and continued to be increased every 4–6 months	• Patients data was reviewed before the addition of CSH, and then again at a follow-up appointment after administration. Median treatment period of 18.5 months (range 3-63 months)	**Weight** Mean ± SD • Weight status (BMI-SDS) did not change significantly with the addition of CSH from -0.24 ± 1.30 at baseline to -0.33 ± 1.32 at follow-up, P = NS)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	therapy after GnRH analogs alone	• Four (21%) adolescents re- ported smoking, with one having prehypertension, none reported alcohol consumption or drug abuse. • Four (21%) reported a diagnosis of anxiety, all with normal BP.	for serum estradiol to not exceed the peak physiologic range of 367–734 pmol/L	• Data was reviewed for anthropometric measurements.	
Schagen (2016)[148] [redacted] the Netherlands) from 1998 through 2009	**N:116 TGNB adolescents** • **Eligibility**: being treated by the VU University Medical Centre's treatment protocol with sufficient background data • **Sampling method:** All eligible patients with data were included in study • **Subset:** of total group (N = 116) ○ N = 49 MTF ○ N = 67 FTM	• Median (range) age of transgender females was 13.6 (11.6-17.9) • Median (range) age of transgender males was 14.2 (11.1-18.6)	Triptorelin (GnRH analog)	• Baseline measurements were taken at the start of GnRH analogs, and then 1 year after GnRH analogs. • When data was available, comparisons were also made at year 2 and 3 • Measurements of body composition and pubertal development were taken ○ Height and weight were gathered and then SDS scores calculated using Dutch reference data. BMI SDS was calculated using reference data from Cole et al. ○ Fat mass, fat percentage and lean body mass percentage were measured with dual-energy X-ray absorptiometry • Testicular volume was determined in transgender females	**Transgender Females** **Body Composition** • **Height** (n = 36), mean (SD) ○ There was a significant increase after height in the first year of GnRH analogs from 167.8 cm (7.5) to 172.3 cm (6.5); *P* < .001 • **Height SDS**, mean (SD) ○ There was a significant decrease after the first year on GnRH analogs (n = 36) of .23 ± 0.23 from 0.20 (1.0) to -0.04 (1.0); *P* < .001 ○ There was a significant decrease after the second year on GnRH analogs (n = 21) of 0.28 ± -.14, *P* < .001 ○ There was no significant change in the third year on GnRH analogs (n = 3) • **Weight** (n = 36), mean (SD); ○ There was a significant increase after the first year on GnRH analogs from 57.4 kg (11.1) to 63.3 kg (11.9); *P* < .001 • **BMI** (n = 36), mean (SD) ○ There was a significant increase after the first year of GnRH analogs from 20.3 kg/m² (3.0), to 21.2 kg/m² (3.2); *P* < .001 • **BMI SDS**, mean (SD) ○ There was no significant change after the first year on GnRH analogs (n = 36) from 0.82 (1.1) to 0.89 (1.2) ○ There was a significant increase after the second year on GnRH analogs (n = 21) of 0.13 ±0.21 (*P* = .009) • **Fat percentage** (n = 26), mean (SD) ○ There was a significant increase after the first year on GnRH analogs from 22.4% (6.9) to 26.8% (6.6); *P* < .001 • **Lean body mass percentage** (n = 26), mean (SD) ○ There was a significant decrease after the first year on GnRH analogs from 74.6% (6.4) to 70.9% (7.3); *P* < .001 • **Testicular volume** (n = 33), mean ± SD ○ There was a significant decrease after the first year on GnRH analogs (n = 33) from 13.9 ± 5.5mL to 8.6 ± 4.7 ml, *P* < .001

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ There was no significant change after the second year of treatment (n = 17) from 8.2 ± 4.4 mL at 12 months to 8.4 ± 3.7 mL at 24 months, *P* = NS **Transgender Males** **Body Composition** • **Height** (n = 41), mean (SD) ○ There was a significant increase in height in the first year of GnRH analogs from 161.4 cm (8.4) to.5 cm (7.9), *P* < .001 • **Height SDS**, (mean (SD); ○ There was a significant decrease of 0.15 ± 0.23 after the first year on GnRH analogs (n = 41) from -0.10 (1.1), T1: -0.25 (1.1), *P* < .001 ○ There was a significant decrease after the second year on treatment (n = 22) of 0.13 ± 0.24, *P* = .02 ○ There was no significant change after the third year of treatment (n = 10) • **Weight** (n = 41), mean (SD) ○ There was a significant increase after the first year of GnRH analogs from 55.1 kg (14.7) to 59.5 kg (14.4), *P* < .001 • **BMI** (n = 41), mean (SD) ○ There was a significant increase after the first year of treatment from 21.0 kg/m² (4.5) to 22.1 kg/m² (4.6); *P* < .001 • **BMI SDS** (n = 41), mean (SD ○ There was a significant increase of 0.17 ± 0.41 after the first year of treatment (n = 41) from 0.68 (1.2) to 0.84 (1.2); *P* = .01 ○ There was no significant change after year two or three of treatment • **Fat percentage** (n = 27), mean (SD) ○ There was a significant increase after the first year of treatment from 25.0% (6.9) to 29.5% (7.3); *P* < .001 • **Lean body mass percentage** (n = 27), mean (SD) ○ There was a significant decrease after the first year of treatment from 71.5% (6.7) to 67.7% (6.7); *P* < .001
Schagen (2018)[147] [redacted] between 1998 and 2009.	**N = 127 adolescents** • **Eligibility:** adolescents with DSM-IV criteria for gender identity disorder and met the criteria for treatment according to the Endocrine Society.	• Trans girls: Mean age at start of GnRH analogs: 14, Weight- 57.4 kg, BMI- 20.2, Tanner stage- 4, length of GnRH analog treatment- 22.8 • Trans boys: Mean age at GnRH analog start- 14.3 years, weight- 56.8 kg, BMI- 21 kg, Tanner stage- 4, length of GnRH analog treatment- 24.5 mo	Intramuscular injections of GnRH analogs triptorelin (3.75 mg) at 0, 2 and 4 weeks followed by injections every 4 weeks. Length of treatment was dependent on when they were eligible for CSH therapy.	• Measurements were collected at baseline, before the beginning of therapy, and then every 6 months during 2 years of GnRH analog therapy only. • DHEAS and androstenedione levels were collected	**DHEAS** • Trans boys: ○ There was a significant increase from 4.21 ± 0.30 mmol/L at baseline to 5.67 ± 0.44 mmol/L, 2 years into GnRH analog therapy, *P* < .001. • Trans girls: ○ There was a nonsignificant increase from baseline to 2 years into GnRH analog therapy, *P* = NS

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Sampling method:** there was no exclusion criteria. Since it is a prospective study, it can be assumed that those that met the inclusion criteria were included. • **Subset:** Of N = 127, n = 54 trans girls and n = 73 trans boys.				**Androstenedione** • Trans boys: o There was a significant decrease in the first year of treatment from 5.74 ± 0.24 nmo/L at baseline to 3.86 ± 0.28 nmol/L at the first year, *P* = .01 o Levels stabilized during the second year of treatment • Trans girls: o There was no significant change in levels during GnRH analog treatment
			Patients were switch from GnRH analogs to CSH around the age of 16 years Trans girls: daily oral 17-beta estradiol starting at 5 ug/kg/d. dose increase by 5 ug/kg/d every 6 months until the maintenance dose of 2 mg/d was reached. Trans boys: 25 mg/m² of testosterone ester IM every 2 weeks. Doses increased by 25 mg/m² until the maintenance dose of 125 mg per 2 weeks was reached. Those treated with GnRH analogs after the age of 16 had an accelerated protocol where CSH were started 3 to 6 months after GnRH analogs	• Measurements were collected before CSH treatment and then compared to 2 years after CSH treatment. • DHEAS and androstenedione levels were collected	**DHEA** • DHEAS levels did not significantly change in trans boys or trans girls. **Androstenedione** • Trans boys: o Androstenedione levels rose non-significantly in the first year of testosterone treatment (*P* = NS) and then stabilized. • Trans girls: o Levels did not significantly change during CSH treatment.
Stoffers (2019)[149] At a clinic between November 2010 (when the clinic first started) and August 2018 (does not mention the details of this clinic)	**N = 62 TGNB adolescents** • **Eligibility**: diagnosed with gender dysphoria who had started GnRH analog treatment and had subsequently received testosterone treatment for more than 6 months (or had had their 6-month visit, which was sometimes scheduled just before 6 months of treatment) • **Sampling method**: Individuals were assessed by mental health professionals to confirm the diagnosis of gender dysphoria to	• Full cohort (N = 62): All had been treated with a GnRH analog (Decapeptyl-CR; 3.75 mg every 4 weeks s.c.) for a median duration of 8 months (range 3-39) before they began testosterone treatment at a median age of 17.2 years (range 14.9-18.4) (Table I.1). • Median duration of follow-up during testosterone treatment was 12 months (range 5-33). No one discontinued testosterone therapy. • Age, median (range), at start of GnRH analogs was 16.5 (11.8-18.0) years and duration, median (range), of GnRH analog	Testosterone	• Participants were assessed at the start of GnRH analog therapy and then every 6 months during 24 months of testosterone treatment. • Growth (height, BMI): Height was measured using a wall-mounted stadiometer, and weight was measured using a digital floor scale. Height SDS were calculated using Dutch reference data and BMI SDS were calculated using reference data from Cole et al.	**Amenorrhea**: • All adolescents experienced amenorrhea during treatment except for 3 individuals. One of these individuals was noncompliant with the GnRH analog and testosterone for a period, which could explain the menstrual bleeding. Another had administered the GnRH analog a few days late, but the cause was unclear for the third individual, who had mild bleeding for 1 to 2 days. **Growth**: • Most adolescents had completed linear growth before the start of treatment; only 5 individuals grew more than 2 cm during the follow-up period. • BMI significantly increased during the first 6 months from 22.4 ± 3.4 kg/m² to 23.2 ± 3.0 kg/m² (n = 46; *P* < .001), but BMI SDS did not change.

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	exclude psychological, medical, or social problems that might interfere with treatment; and to determine if they were able to consent to treatment	therapy was 8 (3-39) months. Smoker, n (%), accounts for 10 (16%).			
Tack (2017)[150] The multidisciplinary child-gender team [redacted] from 2008 through October 2016	**N = 27 TGNB adolescent girls (AMAB)** • **Eligibility**: All trans-girls who received CA for at least 6 months from 2008 through October 2016 • **Sampling method**: Intake visits were aimed at excluding a disorder of sexual development underlying GD and at determining the pubertal (Tanner) stage by a physical examination performed by a pediatric endocrinologist. Follow-up visits were scheduled every 6 months. • **Subset definition**: All of participants (N = 27) had received CA and incremental doses of estrogen in a subset (n = 21) were added for at least 6 months after initiation of CA.	• Mean age at start of CA and CA + E was 16 years 6 months and 17 years 7 months, respectively. • Mean treatment duration for CA was 12 months and that for CA + E was 16 months. • For side effects at "baseline", 12/21 (57.1%) participants had breast tenderness, 6/21 (28.6%) had emotionality, 5/21 (23.8%) had changes in hunger, 3/21 (14.3%) had fatigue, 3/21 (14.3%) had flushes and 15/21 (71.4%) had decreased shaving need. B • Breast development for Tanner stages B3 was in 14/21 (66.7%) and for Tanner stages B4 was in 2/21 (9.5%) participants.	• Cyproterone acetate (CA) (50 mg/d) was started in trans-girls. • After at least 6 months, 17b-estradiol (E) was added if the adolescent was at least 16 years old and had a persistent desire to proceed with the gender change process. E doses were increased at every visit until a maximum of 2 mg was reached (0.5 mg/d at start, 0.75 mg/d after 6 months, 1 mg/d after 1 year, 1.5 mg/d after 18 months, 2 mg/d after 2 years).	• Measurements was taken at baseline-at the start of adding E to those who had already received CA • Measurements were then taken at 6 and 12 month follow-ups after taking the combination therapy. • Cardiovascular-related anthropometrics (weight, BMI): Body weight (wearing only underwear) was measured at each visit, and BMI was calculated	**Weight, BMI and Height** • No clinically important changes in body weight and BMI were observed throughout the CA + E treatment. • After 6 months of CA + E vs start of CA + E, ○ mean weight change in kg (SD) was +0.48 (3.12), *P* = NS ○ mean BMI change in kg/m² (SD) was +0.08 (1.03), *P* = NS ○ There was a significant increase in mean height in cm (SD), with a mean change of +0.3 (0.41), *P* < .009 • After 12 months of CA + E vs start of CA + E, ○ mean weight change in kg (SD) was +2.41 (4.45), *P* = NS ○ There was a significant increase mean BMI in kg/m² (SD), with a mean change of +0.66 (1.40) *P* < .017. ○ There was a significant increase in height in cm (SD) with a mean change of +0.4 (0.58), *P* < .020
van der Loos (2021)[69] [redacted]	**N = 322 TGNB adolescents** • **Eligibility**: minimum duration of 6 months of GnRH analogs monotherapy; started therapy before 18 years of age, DEXA scan was available within a 6-month range before or after the start of GnRH analogs (baseline), the start of CSH, and/or after greater than equal to 2 years since the start of CSH • **Sampling method:** all patients who visited the gender clinic in	Age at start of GnRH analogs: Median (interquartile range) • Trans women early puberty: 13.1 (12.5;13.5), mid puberty: 13.4 (12.9;14.9), late puberty: 15.5 (14.3;16.6) • Trans men early puberty: 11.9 (11.8;12.0), mid puberty: 12.5 (12.1;13.0) and late puberty: 15.7 (14.6;16.8) Age at start of CSH: Median (interquartile range) • Trans women early puberty: 15.7 (15.3;16.0), mid puberty: 16.0 (15.8;16.6) late puberty: 16.4 (16;17.4)	• Adolescents diagnosed with GD were started with subcutaneous triptorelin (GnRH analog) 3.75 mg every 4 weeks or 11.25 mg every 12 weeks. The criterion for commencement was having a Tanner breast stage 2 or more for trans boys or Tanner genital stage 2–3 or more for trans girls, commonly around the age of 12 years. • Around the age of 16 years, CSH was added in incremental	• Data was collected at the start of GnRH analog therapy, at the start of CSH therapy, and then ≥ 2 years after CSH therapy • The outcome was 2 geometric parameters: subperiosteal width and endocortical diameter. They were obtained by running an HAS option on previously produced DXA images of the non-dominant proximal femur.	**Transgender women/Early puberty** **Subperiosteal width**; mean difference (95% CI) • Significant Δ between the start of GnRH analogs and the start of CSH: 0.38, 95% CI (0.16, 0.60) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.44, 95% CI (0.23, 0.65) • Non-significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.006, 95% CI (-0.15, 0.27) • **Endocortical diameter**; mean difference (95% CI) • Significant Δ between the start of GnRH analogs and the start of CSH: 0.39, 95% CI (0.16, 0.61)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	between 1972 and December 2018 • **Subset:** ○ Transgender male (n = 216) ▪ early puberty (n = 8) ▪ mid-puberty (n = 22) ▪ late puberty (n = 186) ○ Transgender female (n = 106) ▪ early puberty (n = 32) ▪ mid-puberty (n = 30) ○ late puberty (n = 44)	• Trans men early puberty: 15.9 (15.7;15.9), mid puberty15.9 (15.4;16.0) and late puberty: 16.5 (16.0;17.5)	dosages to induce novel puberty. ○ Trans girls were prescribed oral 17-beta-estradiol, usually starting at 5 µg/kg body weight. This was increased up to a daily maintenance dose of 2 to 4 mg. ○ Trans boys were usually prescribed an ester mixture of 25 mg/m² body surface area intramuscular testosterone. Dosage was increased up to a maintenance of 250 mg every 3 to 4 weeks. • Eligibility for gonadectomy was determined at the age of 18 years after receiving at least 1 year of CSH. Further, GnRH analogs were discontinued after gonadectomy.		• Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.38, 95% CI (0.17, 0.60) • Non-significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.00, 95% CI (-0.21, 0.21) **Transgender women/Mid puberty** **Subperiosteal width**; mean difference (95% CI) • Significant Δ between the start of GnRH analogs and the start of CSH: 0.33, 95% CI (0.15, 0.50) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.57, 95% CI (0.39, 0.75) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.25, 95% CI (0.11, 0.38) **Endocortical diameter**; mean difference (95% CI) • Significant Δ between the start of GnRH analogs and the start of CSH: 0.34, 95% CI (0.17, 0.51) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.55, 95% CI (0.37, 0.72) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.21, 95% CI (0.08, 0.34) **Transgender women/Late puberty** **Subperiosteal width**; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.06, 95% CI (-0.08; 0.20) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27, 95% CI (0.16; 0.39) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.21, 95% CI (0.09, 0.34) **Endocortical diameter**; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.08, 95% CI (−0.06; 0.22) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27, 95% CI (0.15, 0.40) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.19, 95% CI (0.06, 0.33) **Transgender men/Early puberty** **Subperiosteal width**; mean difference (95% CI)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• Significant Δ between the start of GnRH analogs and the start of CSH: 0.63, 95% CI (0.58, 0.68) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.79, 95% CI (0.72, 0.85) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.15, 95% CI (0.12, 0.19) **Endocortical diameter**; mean difference (95% CI) • Significant Δ between the start of GnRH analogs and the start of CSH: 0.62, 95% CI (0.57, 0.67) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.73, 95% CI (0.67, 0.79) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.11, 95% CI (0.08, 0.14) **Transgender men/Mid puberty** **Subperiosteal width**; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.10, 95% CI (−0.09, 0.29) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.31, 95% CI (0.11, 0.50) • Significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.21, 95% CI (0.03, 0.38) **Endocortical diameter**; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.09, 95% CI (-0.11, 0.30) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27, 95% CI (0.06, 0.48) • Non-significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.18, 95% CI (-0.01, 0.36) **Transgender men/Late puberty** **Subperiosteal width**; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.07, 95% CI (−0.03, 0.18) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.15, 95% CI (0.04, 0.26) • Non-significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.07, 95% CI (−0.04, 0.18)

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					Endocortical diameter; mean difference (95% CI) • Non-significant Δ between the start of GnRH analogs and the start of CSH: 0.10, 95% CI (−0.01, 0.21) • Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.17, 95% CI (0.05, 0.28) • Non-significant Δ between the start of CSH and after ≥ 2 years of CSH: 0.07, 95% CI (−0.04, 0.17)
Willemsen (2023)[127] Gender identity clinic [redacted]	**N = 61** FTM treated with GnRH analogs with growth potential (BA of 14 or less; or menarche for less than 1 year before start of PS) • **Eligibility:** FTM individuals were eligible if they started PS before 16 years of age, received testosterone therapy for at least 6 months, and had reached the age of 18 at the time that the study was conducted. They were excluded if they had not reached adult height (defined as skeletal age of 14 years or older, or had a growth velocity of less than 2 centimeters per year). • **Sampling Method:** Data was retrospectively collected as part of the Amsterdam Cohort of Gender Dysphoria (ACOG) study, and includes the complete population of patients seen at the clinic. It was gathered from 1972 - December 2018.	• Mean age was 12.7 ± 1.0 years at the start of PS. • BA was 12.4 ± 1.0 years at the start of PS. • Height at start of PS: 157.3 ± 8.5 cm • BA was 12.4 ± 1.0 years at the start of PS.	PS	Outcomes were measured every 3-6 months during puberty suppression until start of CSHT • **Height** was assessed every 3-6 months from start of PS, using a wall-mounted stadiometer • **Female height SDS** was calculated according to Dutch reference data • **Midparental height** was calculated using (paternal height + maternal height)/2 - 6.5 • **BA** was determined by evaluating X-rays of the left hand • Predicted adult height was calculated	**Height:** • During the puberty suppressive phase, height increased significantly by 8.6 cm (95% CI, 7.5-9.6) to 166.9 ± 7.0 cm at start of CSHT. **Female height SDS:** • Female height SDS showed a non-significant decrease of −0.2 ± 1.0 (decrease of −0.2; 95% CI, −0.5 to 0.1) **PAH:** • PAH increased significantly by 2.4 cm (95% CI, 1.3-3.4) between start PS and start CSHT. **BA - CA (bone age - chronological age):** • At start of CSHT, the difference between BA and CA further increased to −2.2 ± 1.2 years from -3 ± 0.9 at baseline (change since start of PS −1.9 years; 95% CI, −2.2 to −1.6). **IGF-1 levels:** • During the puberty suppression phase, IGF-1 levels did not significantly change (statistics not given)
			CSHT	• Outcomes were measured every 3-6 months from the start of CSHT to adulthood • **Height** was assessed every 3-6 months from start of PS, using a wall-mounted stadiometer • **Female height SDS** was calculated according to Dutch reference data • **Midparental height** was calculated using (paternal height + maternal height)/2 - 6.5	**Height**: • From the start of CSHT, height significantly increased by 5.0 cm (95% CI, 4.3-5.8) to an adult height of 172.0 ± 6.9 (female height SDS +0.2 ± 1.1, male height SDS −1.7 ± 1.0) **Female height SDS:** • Female height SDS increased significantly by 0.3 SDS from the start of CSHT to adult height (95% CI, 0.2-0.5) **BA - CA:** • remained stable in the first 18 months of CSHT, after which BA progressively increased (no statistics given) **PAH:**

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				• BA was determined by evaluating X-rays of the left hand • Predicted adult height was calculated	• adult height was close to PAH at the start of CSHT (difference, 0.2 ± 2.3 cm; 95% CI, −0.5 to 0.9) • A younger BA (12 or less years) at the start of CSHT was associated with an adult height above PAH (1.2 cm/year, 95% CI = 0.5, 2.0) **Midparental height:** • A younger BA at the start of PS had an adult height above midparental height • m = 1.3 cm/year (95% CI = -0.4, 3.0) **IGF-1 levels:** • IGF-1 levels slightly increased by 3.6 nmol/L (95% CI = 0.9, 6.4) after the initiation of testosterone and remained stable thereafter.
			PS and CSHT	• Outcomes were measured every 3-6 months from the start of PS to adulthood • **Height** was assessed every 3-6 months from start of PS, using a wall-mounted stadiometer • **Female height SDS** was calculated according to Dutch reference data • **Midparental height** was calculated using (paternal height + maternal height)/2 - 6.5 • **BA** was determined by evaluating X-rays of the left hand • **Predicted adult height** was calculated	**Height SDS:** • There was no significant change in height SDS 0.1 (95% CI = -0.2, 0.4) **PAH:** • Adult height was 3.0 ± 3.6 cm above PAH at start of PS (95% CI, 2.0-3.9) • A younger BA (12 or less years) at the start of PS was associated with adult height further above PAH (1.2 cm/year, 95% CI = 0.3, 2.1) **BMI SDS:** • Per 1 SDS decrease in BMI, adult height was above PAH at start of PS (0.4 cm, 95% CI = 0.0, 0.8) **Midparental height:** • Adult height was 3.9 ± 6.0 cm above midparental height at start of PS (95% CI, 2.4-5.4) • A younger BA (years not defined) at the start of PS was associated with adult height further above midparental (1.3 cm/year, 95% CI = -0.4, 3.0)
	N = 85 FTM treated with GnRH analogs and CSHT with little to no growth potential (BA over 14, or menarche for 1 year or more before start of PS) Same eligibility, sampling method above	• Mean age was 15.1 ± 0.9 years at the start of PS. • BA was 15.7 ± 1.1 years at the start of PS. • Height at start of PS: 166.4 ± 6.7 • PAH at start of PS: 167.3 ± 6.8	PS and CSHT	Outcomes were measured every 3-6 months from the start of PS to adulthood • **Height** was assessed every 3-6 months from start of PS, using a wall-mounted stadiometer • **Female height SDS** was calculated according to Dutch reference data	**Height:** • From the start of PS, height increased by 2.5 cm (95% CI, 2.1-3.0) to an adult height of 169.0 ± 6.8 cm **Height SDS scores:** • female height SDS −0.3 ± 1.1 • male height SDS −2.1 ± 1.0 **Midparental height (n = 57):** • Adult height was 3.0 ± 4.7 cm above midparental height at start of PS

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.3. Longitudinal pre-post studies evaluating body change outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				• **Midparental height** was calculated using (paternal height + maternal height)/2 - 6.5 • **BA** was determined by evaluating X-rays of the left hand • **Predicted adult height** was calculated	**PAH (n = 37)** • Adult height was 3.0 ± 4.7 cm above PAH at start PS

Abbreviations: BA, bone age; BMI, body mass index; BP, blood pressure; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; ET-FMR, extremities/trunk fat mass ratio; GAHT, gender-affirming hormone therapy; GD, gender dysphoria; LBM, lean body mass; LT-FMR, legs/total fat mass ratio; N/A, not applicable; N/R, not reported; PAH, predicted adult height; PS, puberty suppression; SD, standard deviation; T, testosterone; TBF, total body fat; TGNB, transgender, non-binary, or gender-diverse; TT-FMR, Trunk/total fat mass ratio

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Chen (2023)[75] USA- Gender clinics [redacted] from July 2016 through June 2019	**N = 315 TGNB youth** • **Eligibility**: Participants were recruited from the gender clinics from July 2016-June 2019. This cohort was initiating CSH as part of their clinical care. For minors, parental consent was required to initiate treatment. • **Sampling Method:** Youth were recruited from 4 different sites at the start of CSH therapy. They were enrolled if they met inclusion criteria. • **Subset definition**: N = 315 TGNB adolescents, including: ○ FTM (n = 190,) MTF (n = 106) and NB (n = 19,) adolescents ○ Analytical sample n = 291 due to missing key variables at follow-up ○ Designated female at birth (n = 204,) and designated male at birth (n = 111) ○ Had early gender-affirming care-previously using GnRH analog (n = 24) ▪ youth designated female at birth with early gender-affirming care (n = 4) ▪ youth designated male at birth with early gender-affirming care (n = 20) ○ analytic sample (n = 291)	Participants were 12 to 20 years of age (mean [±SD], 16 ±1.9 years.) Higher percentage of those designated female at birth (64.8%) then male. Mostly non-Latinx or non-Latin white (58.1%)	CSH therapy	• Outcomes were measured at initiation of therapy, and then at 6,12,18 and 24 months. • **Appearance congruence** was captured through the 9-item appearance congruence subscale of the Transgender Congruence Scale.	• **Appearance congruence**: Slope mean (95% CI) ○ Scores for appearance congruence significantly increased showing an annual increase on a 5-point scale of 0.48 points (0.42 to 0.54) (unconditional model); 0.51 (0.07-0.96) (conditional model) after a period of 2 years of CSH treatment from baseline.
de Vries (2010)[78] [redacted]	**N = 27** TGNB adolescents • **Eligibility**: not clearly stated • **Sampling method**: 140 of 196 consecutively referred adolescents were considered	• Full cohort (N = 27): • Age, mean (SD) ○ assessment of pre-treatment: 13.5 (1.8) with a range of 11.2–17.0.	Puberty suppression or cross-sex hormone treatment	• Outcomes were measured twice; first, shortly after the participant's initial attendance at the gender identity clinic (pre-treatment) and second, at least one year after their	**Gender dysphoria: (N = 21)** • The mean (SD) of the UGDS score was 54.5 (5.4) for pre-treatment and 15.4 (3.1) for post treatment, with a significant improvement was seen in the UGDS ($P < .001$) between pretreatment and post treatment.

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	eligible for medical intervention between 2000 and 2008 at the clinic. Of this cohort, 29 adolescents who were age 16 years or older were prescribed CSH only, and 111 adolescents were prescribed GnRH analogs to suppress puberty. Subsequently, 70 of the 111 started CSH treatment between the years 2003 and 2009. The first 30 young adults who had become age 18 and had GRS between 2004 and 2009 were invited to participate at least one year after their last operation. GRS was vaginoplasty for MTFs and hysterectomy for FTMs, because after these surgeries transsexuals can legally change their gender. One person (MTF) refused to participate and two (one FTM and one MTF) failed to send back their questionnaires. This resulted in 27 participants, 11 MTFs and 16 FTMs. • **Subset definition**: Out of total sample (N = 27), there were n = 11 MTFs and n = 16 FTMs	○ start of GnRH analogs: 14.6 (1.7) with a range of 11.5–17.9. ○ start of CSH: 16.6 (1.1) with a range of 13.9–18.6. ○ assessment of post treatment: 20.9 (1.0) with a range of 19.7–22.8. • The mean (SD) full-scale intelligence was 98.2 (15.0) with a range of 70–131. • MTFs group (N = 11): • Age, mean (SD) ○ assessment of pre-treatment: 13.9 (.8). ○ start of GnRH analogs: 15.0 (0.6). ○ start of CSH: 16.7 (1.4). ○ assessment of post treatment: 21.3 (1.1). • The mean (SD) full-scale intelligence was 94.4(12.3). • FTMs group (N = 16): • Age, mean (SD) age ○ assessment of pre-treatment: 13.2 (1.8). ○ start of GnRH analogs: 14.4 (0.3). ○ start of CSH: 16.6 (0.9). ○ assessment of post treatment was 20.7 (0.8). • The mean (SD) full-scale intelligence was 103.5 (15.2).		gender reassignment surgery (post treatment.) • Gender dysphoria: the UGDS was used to measure adolescents' gender dysphoria. • Body satisfaction: The BIS was administered to measure body satisfaction.	**Body satisfaction: (N = 22)** • The mean (SD) of the BIS primary sex characteristics was 4.2 (0.5) for pre-treatment and 2.4 (0.6) for post treatment, with a significant improvement ($P < .001$) between pretreatment and post treatment. • The mean (SD) of the BIS secondary sex characteristics was 2.6 (0.6) for pre-treatment and 2.3 (0.5) for post treatment, with a significant improvement ($P < .05$) between pretreatment and post treatment. • The mean (SD) of the BIS neutral body characteristics was 2.4 (0.6) for pre-treatment and 2.3 (0.5) for post treatment, with an non-significant improvement (P = NS between pretreatment and post treatment.
de Vries (2011)[57] [redacted]	**N = 70 TGNB youth** • **Eligibility**: adolescents with gender dysphoria eligible for medical intervention • **Sampling method**: first 70 patients consecutively enrolled from 2000 to 2008 • **Subset:** N = 70 TGNB youth, including N-37 natal females and N = 33 natal males	• **Full cohort:** mean (SD) age at baseline was 13.65 years (1.85); mean (SD) age at the start of GnRH analogs was 14.75 years (1.92); mean (SD) age at the start of CSH was 16.64 years (1.90); mean (SD) time between the start of GnRH analogs and CSH was 1.88 years (1.05); mean (SD) parental full-scale IQ was 98.2 (15.0); for parental marital status, 62.9% had both parents, 37.1% was other; for parents' education status, 10.6% had high, 66.7%	GnRH analogs (full cohort), N = 29 also started CSH	Participant data was collected before and after starting GnRH analogs • UGDS was used to measure GD • BIS used to measure dissatisfaction with body characteristics	**UGDS (n = 41), mean (SD)** • There was a no statistical change in GD symptoms, P = NS • Full cohort: 0- 53.20 (7.91), T1- 53.9 (17.42) **BIS (n = 57) mean (SD);** • Primary sex characteristics ○ There was no significant change in body dissatisfaction, P = NS ○ Full cohort: T0- 4.10 (0.56), T1- 3.98 (0.71) ○ Female at birth: T0- 4.16 (0.52), T1- 4.17 (0.58)

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
		had medium, 22.7% had low; for sexual attraction, 88.6% were attracted to their own natal sex, 8.6% were attracted to both sexes; 2.8% were attracted to other • **Natal male** (47%): mean (SD) age at baseline was 13.14 years (1.55); mean (SD) age at the start of GnRH analogs was 14.25 years (1.79); mean (SD) age at the start of CSH was 16.24 years (1.21); mean (SD) time between the start of GnRH analogs and CSH was 1.99 years (0.94); mean (SD) parental full-scale IQ was 97.1 (13.3); for parental marital status, 69.7% had both parents, 30.3% had other; for parents' education status, 3.3% had high, 76.7% had medium, 20.0% had low; for sexual attraction, 87.9% were attracted to their own natal sex, 6.1% were attracted to both sexes; 6.0% were attracted to other • **Natal female** (53%): mean (SD) age at baseline was 14.10 years (1.99); mean (SD) age at the start of GnRH analogs was 15.21 years (1.95); mean (SD) age at the start of CSH was 16.99 years (1.07); mean (SD) time between the start of GnRH analogs and CSH was 1.78 years (1.16); mean (SD) parental full-scale IQ was 99.2 (15.2); for parental marital status, 56.8% had both parents, 43.2% had other; for parents' education status, 16.7% had high, 58.3% had medium, 25.0% had low; for sexual attraction, 89.2% were attracted to their own natal sex, 10.8% were attracted to both sexes; 0% were attracted to other			○ Male at birth: T0- 4.02 (0.61), T1- 3.74 (0.78) • Secondary sex characteristics, ○ There was no significant change in body dissatisfaction, *P* = NS ○ Full cohort: T0- 2.74 (0.65), T1- 2.82 (0.68) ○ Female at birth: T0- 2.81 (0.76), T1- 3.18 (0.42) ○ Male at birth: T0- 2.66 (0.50), T1- 2.39 (0.69) • Neutral sex characteristics ○ There was no significant change in body dissatisfaction, *P* = NS ○ Full cohort: T0- 2.41 (0.63), T1- 2.47 (0.56) ○ Female at birth: T0- 2.24 (0.62), T1- 2.61 (0.50) ○ Male at birth: T0- 2.60 (0.58), T1- 2.32 (0.59)
de Vries (2014)[79] [redacted]	**N = 55 TGNB youth** • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression	Full cohort: the mean age (SD) at assessment pretreatment was 13.6 (1.9) (range: 11.1–17.0), the mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5), the mean age (SD) at the start of CSH was 16.7 (1.1) (range: 13.9–19.0), the mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3), the mean age (SD) at assessment post	CSH and GRS	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS) • CGAS used to assess Psychosocial functioning	• **UGDS (GD) (n = 33), mean (SD)** ○ Scores showed a significant decrease from 53.51 (8.29) at intake to 15.81 (2.78) at post treatment, *P* < .001 ○ [T0- 53.51 (8.29), T1- 54.39 (7.70), T2- 15.81 (2.78)] ○ Significant linear effect (time) *P* < .001, Significant quadratic effect (time) *P* < .001 ○ GD persisted from T0-T1 but then decreased significantly

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	and continued with GRS between 2004 and 2011 • **Subset:** N = 55 TGNB adolescents, with N = 22 MTF and N = 33 FTM)	treatment was 20.7 (1.0) (range: 19.5–22.8); the mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)		• BDI used to assess depressive symptoms • TPI administered to assess the tendency to respond with anger to a threatening or annoying situation. (Scale ranges from 1-4) • STAI administered to assess the tendency to respond with anxiety to a threatening or annoying situation. (Scale ranges from 1-4) • CBCL/ABCL and YSR/ASR used to assess behavioral and emotional problems using the total, internalizing and externalizing T scores as well as the clinical range scores for the indices (T score > 63) • UGDS was used to measure GD • BIS used to measure dissatisfaction with body characteristics General linear models examined the repeated measures with an analysis of variance-based model. A linear effect signifies an overall change across T0 to T2. Quadratic effect signifies change was not continuous.	• **BIS (body image) (n = 45)** ○ Primary sex characteristics, mean (SD) ▪ There was a significant decrease in body dissatisfaction of primary sex characteristics from 4.13 (0.59) at intake to 2.59 (0.82) post treatment, *P* < .001 ▪ T0- 4.13 (0.59), T1- 4.05 (0.60), T2- 2.59 (0.82) ▪ Significant linear effect (time) *P* < 0.001, significant quadratic effect (time) *P* < .001 ○ Secondary sex characteristics, mean (SD) ▪ There was a significant decrease in body dissatisfaction of secondary sex characteristics from 2.73 (0.72) at intake to 2.27 (0.56) post treatment, *P* < .001 ▪ T0- 2.73 (0.72), T1- 2.86 (0.67), T2- 2.27 (0.56) ▪ significant linear effect (time) *P* < .001, significant quadratic effect (time) *P* < .001 ○ Neutral body characteristics, mean (SD) ▪ There was a non-significant decrease in body dissatisfaction of neutral body characteristics, *P* = NS ▪ T0- 2.35 (0.68), T1- 2.49 (0.53), T2- 2.23 (0.49) ▪ linear effect (time) *P* = .29 , significant quadratic effect (time) *P* = .01
	N = 22 MTF TGNB youth • **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	**MTF**: for ages, the mean age (SD) at assessment pretreatment was 13.6 (1.8), the mean age (SD) at the start of GnRH analogs was 14.8 (2.0), the mean age (SD) at the start of CSH was 16.5 (1.3), the mean age (SD) at the start of GRS was 19.6 (0.9), the mean age (SD) at assessment post treatment was 21.0 (1.1); the mean full scale intelligence (SD) was 97.8 (14.2)	CSH and GRS		• **UGDS MTF (n = 11), mean (SD)** ○ Scores showed a significant decrease from 47.07 (11.05), at intake to 17.27 (2.57) at post treatment, *P* < .001 ○ T0- 47.07 (11.05), T1- 48.95 (10.80), T2- 17.27 (2.57) • **BIS (n = 17) mean (SD);** ○ There was a significant decrease in body dissatisfaction of primary sex characteristics from 4.03 (0.68) at intake to 2.07 (0.74) at post treatment, *P* < .001 ○ There was a significant decrease in body dissatisfaction of secondary sex characteristics from 2.63 (0.60) at intake to 1.93 (0.63) posttreatment with a *P* < .001 ○ There was a significant decrease in body dissatisfaction in neutral body characteristics from 2.57 (0.70) at intake to 2.09 (0.56) at post treatment with a *P* = .014
	N = 33 FTM TGNB youth	**FTM**: for ages, the mean age (SD) at assessment pretreatment was 13.7 (2.0), the mean age (SD) at the start of GnRH analogs	CSH and GRS		• **UGDS FTM (n = 22), mean (SD)**

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Eligibility**: adolescents with GD prescribed puberty suppression between 2004 and 2011 • **Sampling method**: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011	was 14.9 (1.9), the mean age (SD) at the start of CSH was 16.8 (1.0), the mean age (SD) at the start of GRS was 19.0 (0.8), the mean age (SD) at assessment post treatment was 20.5 (0.8); the mean full scale intelligence (SD) was 100.4 (14.3)			○ Scores showed a significant decrease from 56.74 (3.74) at intake to 15.08 (2.64) at post treatment, *P* < .001 ○ T0- 56.74 (3.74), T1- 57.11 (3.40), T2- 15.08 (2.64) • **BIS (n = 28) mean (SD)** ○ There was a significant decrease in body dissatisfaction of primary sex characteristics from 4.18 (0.53) at intake to 2.89 (0.71) at post treatment, *P* < .001 ○ There was a significant decrease in body dissatisfaction of secondary sex characteristics from 2.80 (0.72), at intake to 2.48 (0.40) at post treatment with a *P* = .05 ○ There was a non-significant increase in body dissatisfaction with neutral body characteristics, from 2.21 (0.64 at intake to 2.32 (0.44) at post treatment with a *P* = NS
Lavender (2023)[142] At an endocrine clinic in the UK between 2014 and 2018	**N = 38 TGNB adolescents** • **Eligibility**: younger than 15 years and at Tanner stage 2+, referred by the GIDS for GnRH analog treatment and CSH treatment at *16 years (and with a minimum of around 1 year on GnRH analogs) • **Sampling method**: Young people referred to endocrinology were sent questionnaires at baseline, after 1 year on GnRH analogs, and after 1 year on CSH treatment. Before August 2020, questionnaires were sent by post to the young people and their caregivers, including a cover letter detailing the purpose of questionnaires and the right to opt out. From August 2020, questionnaire administration moved to an online platform with email links sent to young people and caregivers (Qualtrics, Provo, UT).	• **Full cohort (N = 38):** Most of participants are white (N = 29); mean (SD) age at first endocrine clinic was 13.47 (0.94); mean (SD) age at starting GnRH analogs was 14.01 (0.81); mean (SD) age at starting CSH was 16.10 (0.29); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD) time between start GnRH analogs and CSH was 2.09 (0.85) • **Assigned female young people group (N = 28):** Most are white (N = 22); mean (SD) age at first endocrine clinic was 13.74 (0.68); mean (SD) age at starting GnRH analogs was 14.19 (0.66); mean (SD) age at starting CSH was 16.06 (0.22); mean (SD) time between first endocrine clinic and GnRH analogs was 0.55 (0.36); mean (SD) time between start GnRH analogs and CSH was 2.03 (0.79) • **Assigned male young people group (N = 10):** Most are white (N = 7); mean (SD) age at first endocrine clinic was 12.74 (1.20); mean (SD) age at starting GnRH analogs was 13.51 (0.99); mean (SD) age at starting CSH was 16.25 (0.42); mean (SD) time between first endocrine clinic and GnRH analogs was 0.57 (0.38); mean (SD)	GnRH analogs and CSH	• Baseline was assessed at point of referral to endocrinology. Assessed after approximately 1 year on GnRH analogs, and then after approximately 1 year on CSH • General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous with time as within-subject factor. • Body image and satisfaction was measured using the BIS • Gender dysphoria was measured using the UGDS	• **BIS: Mean (95% CI)** ○ There was no significant change in overall BIS scores, but there was a statistically significant reduction of dissatisfaction with primary sexual characteristics over time observed and from 4.71 (4.39-5.02) at baseline to 4.11 (3.75-4.48) 1 year after CSH, *P* < .02 • **UGDS: Mean (95% CI)** ○ Mean scores of GD were significantly reduced over time from 4.70 (4.45-4.94) at baseline to 3.97 (3.49-4.46), *P* < .02

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.4. Longitudinal pre-post studies evaluating body image outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Subset definition**: Assigned female at birth N = 28 and Assigned male at birth N = 10	time between start GnRH analogs and CSH was 2.10 (0.86)			

López de Lara (2020)[62]
[redacted] Spain: [redacted]
	N=23 TGNB youth
	• **Eligibility**: adolescents aged 14 to 18 yo, absence of psychiatric comorbidity, Tanner state 2 or higher, understanding of risks and benefits of CSH
	Sampling method: requested volunteers
		Transgender adolescents:
		• mean age: 16 years (range 14-18)
		• assigned sex at birth:
		  ○ 69% female
		  ○ 31% male
		• 91% Caucasian and Spanish descent
		• 52% parents with a university education
		• 30.4% had previously used mental health services
		• sexual orientation
		  ○ 65% heterosexual,
		  ○ 13% homosexual
		• 21% bisexual
			CSH (oral estradiol, intramuscular testosterone)	Participants were assessed at baseline and 1 year after CSHT
				• Gender Dysphoria: assessed using UGDS
					• Gender Dysphoria
					• UGDS: Every TGNB participant had gender dysphoria at baseline, and none had gender dysphoria at one year with a significant decrease in UGDS scores from 57.1 (4.1) at to 14.7 (3.2).

*See **Appendix I.H** for a complete description of referenced mental health assessment tools.*

Table abbreviations: BIS, body image survey; CI, confidence interval; CSH, cross-sex hormones; CSHT, cross-sex hormone therapy; FTM, assigned female at birth transitioning to male; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone analogs; GRS, gender reassignment surgery; MTF, assigned male at birth transitioning to female; N/A, not applicable; N/R, not reported; PB, puberty blockers; SD, standard deviation; TGNB, transgender, non-binary, or gender-diverse; UGDS, Utrecht Gender Dysphoria Scale

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Carmichael (2021)[73] UK [redacted]	**N = 44 TGNB adolescents** • **Eligibility Criteria**: ○ Patients recruited from those referred to GIDS who were between 12-15 years and had commenced GnRH analog treatment. ○ Had been seen for at least 6 months and attended at least 4 interviews. ○ Psychological stability to withstand the stresses of medical treatment and ○ Displayed severe and persistent GD and actively requesting pubertal suppression ○ Able to give informed consent ○ Met physical/medical Criteria of being in established puberty and having normal endocrine function and karyotype consistent with birth registered sex. • **Exclusions**: Inability to fully participate, BMI < 2nd percentile, serious psychiatric conditions, Inability to give consent, low spine or hip BMD • **Sampling method**: Patients attending GIDS were provided with information and those wishing to find out more discussed with their clinician. Those likely deemed eligible were given detailed information and invited to a medical clinic for discussion. Young people needed to commit to regular	Total sample median age at baseline was 13.6 (12.8,14.6), 89% white, all beyond stage 3 pubertal status. Median age at end of study was 16.1 (16.0,16.4). Birth registered males started at a median age of 13.4 (12.7,14.1) and birth registered females at 13.9 (13.5, 14.7) all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal function. No participants had evidence of disorders of sexual differentiation.	Suppression of puberty using GnRH analog triptorelin together with psychosocial support and therapy, from study entry until the end of the GnRH analog monotherapy pathway at age 16 or older. 3.75mg by IM injection given every 28 days during treatment period. 2 Participants given 11.25 mg every 10 weeks.	• Patients were measured at study entry, and then re-evaluated yearly at 12,24 and 36 month until they turned 16. • Bone mineral content (BMC) and bone mineral density (BMD) in the lumbar (L1-L4) spine and hip was measured by dual energy X-ray absorptiometry (DEXA) scans. BMD z-scores for age and birth-registered sex were calculated and adjusted for height (HAZ.) • Numbers were lower for hip than for spine as some hip scans were not done for technical reasons.	**12 month outcomes Mean (95%CI)** • Lumbar BMC showed a nonsignificant increase from 39.6 (35.8,43.4) at baseline for those followed up to 41.2 (38.2, 44.2) at 12 months with a change of 1.6 (0.2, 3.1) *P* < .03 • Lumbar BMD showed a nonsignificant increase from 0.76 (0.71, 0.80) at baseline for those followed up to 0.77 (0.72, 0.81) at 12 months with a change of 0.01 (-0.00, 0.03), *P* = NS • Hip BMC showed a nonsignificant increase from 25.5 (23.4, 27.6) at baseline for those followed up to 26.1 (24.4, 27.9) at 12 months with a change of 0.7 (-0.2, 1.5), *P* = NS • Hip BMD showed a nonsignificant increase from 0.81 (0.75, 0.87) at baseline for those followed up to 0.82 (0.78, 0.86) at 12 months with a change of 0.01 (-0.02, 0.05), *P* = NS • BMD spine z-score showed a nonsignificant increase from -0.3 (-0.7, 0.1) at baseline for those followed up to -1.0 (-1.3, -0.7) at 12 months. *P* = NS • BMD HAZ spine z-scores showed a nonsignificant increase from -0.4 (-0.8, -0.1) at baseline for those followed up to -1.0 (-1.3, -0.6) at 12 months. *P* = NS • BMD hip z-scores showed a nonsignificant increase from -0.5 (-0.9, -0.1) at baseline for those followed up to -1.0 (-1.3, -0.6) at 12 months. *P* = NS • BMD HAZ hip z-scores showed a nonsignificant decrease from -0.6 (-1.0, -0.2) at baseline for those followed up to -0.9 (-1.3, -0.5) at 12 months. *P* = NS **24 Months outcomes Mean (95%CI)** • Lumbar BMC showed a significant increase from 34.1 (30.3, 37.9) at baseline for those followed up to 40.1 (36.7, 43.5) at 24 months with a change of 6.0 (4.0, 7.9) *P* < .0001 • Lumbar BMD showed significant increase from 0.68 (0.63, 0.74) at baseline for those followed up to 0.73 (0.68, 0.78) at 24 months with a change of 0.05 (0.03, 0.07) *P* = .0001 • Hip BMC showed a significant increase from 23.9 (21.2, 26.6) at baseline for those followed up to 26.3 (24.1, 28.6) at 24 months with a change of 2.4 (0.7, 4.1) *P* = .008[a] • Hip BMD showed a nonsignificant increase from 0.76 (0.68, 0.85) at baseline for those followed up to 0.79 (0.74, 0.84) at 24 months with a change of 0.03 (-0.04, 0.10) *P* = NS • BMD spine z-score showed a significant decrease from -0.5 (-1.1, 0.0) at baseline for those followed up to -1.5 (-2.1, -0.8) at 12 months. *P* < .05 b

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	medical and psychosocial follow up. Informed consent was obtained. 48 young people attended the clinics and 44 wished to participate. 8 young people were not yet eligible, but were able to enter the study when sufficiently advanced in puberty. • **Subset definition**: N = 44 TGNB adolescents age 12-15, including birth registered male (N = 25) and birth registered female (N = 19) adolescents.				• BMD HAZ spine z-scores showed a significant decrease from -0.7 (-1.2, -0.1) at baseline for those followed up to -1.3 (-1.9, -0.7) at 24 months. $P < .05$ [b] • BMD hip z-scores showed a significant decrease from -0.5 (-1.1, -0.1) at baseline for those followed up to -1.4 (-2.0, -0.9) at 24 months. $P < .05$ [b] • BMD HAZ hip z-scores showed a significant decrease from -0.5 (-1.1, 0.1) at baseline for those followed up to -1.2 (-1.7, -0.6) at 24 months. $P < .05$ [b] **36 Months outcomes Mean (95%CI)** • Lumbar BMC showed a significant increase from 37.05 (31.0, 43.1) at baseline for those followed up to 42.4 (37.4, 47.4) at 36 months with a change of 5.3 (2.8, 7.8) $P = .0007$ • Lumbar BMD (g/cm²) showed a nonsignificant increase from 0.72 (0.65, 0.80) at baseline for those followed up to 0.76 (0.70, 0.82) at 36 months with a change of 0.03 (0.0, 0.07) $P = .05$ • Hip BMC showed a nonsignificant increase from 26.1 (22.1, 30.0) at baseline for those followed up to 26.8 (21.2, 32.3) at 36 months with a change of 0.7 (-3.8, 5.2) P = NS • Hip BMD (g/cm²) showed a nonsignificant decrease from 0.82 (0.73, 0.91) at baseline for those followed up to 0.81 (0.74, 0.88) at 36 months with a change of -0.009 (-0.05, 0.03) P = NS • BMD spine z-score showed a significant decrease from -0.2 (-1.0, 0.6) at baseline for those followed up to -1.5 (-2.2, -0.8) at 36 months. $P < .05$ [b] • BMD HAZ spine z-scores showed a significant decrease from -0.4 (-1.2, 0.3) at baseline for those followed up to -1.3 (-2.2, -0.5) at 36 months. $P < .05$ [b] • BMD hip z-scores showed a significant decrease from -0.3 (-1.3, 0.6) at baseline for those followed up to -1.1 (-1.8, -0.5) at 36 months. $P < .05$ [b] • BMD HAZ hip z-scores showed a nonsignificant decrease from -0.5 (-1.5, 0.5) at baseline for those followed up to -1.0 (-1.8, -0.2) at 36 months. P = NS
Joseph (2019)[137] Early intervention program national endocrine clinic at [redacted] between 2011 and 2016	**N = 70 TGNB adolescents** • **Eligibility**: not clearly stated • **Sampling method**: not clearly stated • **Subset definition**: 31 subjects had three scans, baseline and 2 subsequent years on GnRH analog treatment, and 70 (an additional 39) had two scans,	• **Full cohort:** All subjects by definition had entered puberty to consider blockade. All but two of the transgender boys were post-menarchal. Fifty-seven percent of the transgender girls were in early puberty (G2–3 and testicular volume > 4 mL) and 43% were in late puberty (G4–5). • **Transgender girls (N = 10):** Mean age (SD) for scan 1 was 13.0 (1.1), for scan 2 was 14.5 (1.2) and for scan 3 was 15.8 (1.3). Mean Height (SD) for scan 1 was 160.3	GnRH analog treatment	• Participants had a baseline scan (scan-1) at the start of treatment. They then had scan 2 and scan 3 each subsequent year on GnRH analog treatment • **Body health measure (BMD, BMAD):** BMD for lumbar spine and femoral neck (hip) was reported as absolute areal values (g/cm²) and as Z-scores	**Completed 3 scans:** • <u>Overall:</u> ○ Among those who had three scans (N = 31), Z-scores in both transgender boys and transgender girls at each site and both showed a significant drop after 1 year, thereafter levelling off, but there was no change in BMD for the lumbar spine or hip, or lumbar spine BMAD absolute values over the course of the 3 years • <u>Transgender girl scores (n = 10) mean (SD)</u> ○ Hip BMD, kg/m²

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	baseline and after 1 year on GnRH analog treatment. • For those who had two scans. ○ n = 31 transgender girls (birth-registered males identifying as female) and ○ n = 39 transgender boys (birth-registered females identifying as male).	(5.4), for scan 2 was 163.4 (5.7) and for scan 3 was 165.1 (5.7). Mean weight (SD) for scan 1 was 66.4 (14.6), for scan 2 was 6.1 (19.4) and for scan 3 was 82.9 (30.5). Mean BMI (SD) for scan 1 was 25.8 (5.3), for scan 2 was 28.2 (7.1) and for scan 3 was 30.5 (8.6). • **Transgender boys (N = 21):** Mean age (SD) for scan 1 was 12.9 (3.0), for scan 2 was 14.3 (3.3) and for scan 3 was 15.6 (3.5). Mean Height (SD) for scan 1 was 159.0 (35.8), for scan 2 was 165.3 (36.7) and for scan 3 was 168.7 (37.5). Mean weight (SD) for scan 1 was 49.8 (17.1), for scan 2 was 54.4 (17.5) and for scan 3 was 59.5 (19.6). Mean BMI (SD) for scan 1 was 19.4 (5.9), for scan 2 was 20.7 (7.9) and for scan 3 was 20.9 (6.6).		for birth sex and age. Only the BMD values and Z-scores were produced by the internal software associated with this commercially available equipment. As this areal measurement does not allow for the growth of an adolescent or their ethnicity, BMAD volumetric values in g/cm3 and Z-scores were calculated from the formulae proposed by Crabtree et al. from the ALPHABET study using UK norms for Caucasian subjects. Hip BMAD Z-scores were not calculated as there were no reference ranges provided as per the International Society for Clinical Densitometry	▪ Nonsignificant change between S1-S2 (*P* = 0.338), S1-S3 (*P* = NS) and S2-S3 (*P* = 0.944) ▪ S1: 0.920 (0.116) S2: 0.913 (0.099) S3: 0.910 (0.125) ○ Hip Z-score ▪ Significant decrease between S1-S2 (*P* = 0.002). S1-S3 (*P* = .002), and non-significant decrease from S2-S3 (*P* = NS) ▪ S1: 0.45 (0.781) S2: –0.344 (0.752) S3: –0.600 (1.059) ○ Spine BMD, kg/m² ▪ Non-significant change at all time points : S1-S2 (*P* = 0.952) S1-S3 (*P* = NS) S2-S3 (*P* = 0.202) ▪ S1: 0.867 (0.141) S2: 0.866 (0.126) S3: 0.878 (0.130) ○ Spine BMD Z-score ▪ Significant decrease from S1-S2(*P* = 0.001) and S1-S3(*P* = 0.000) but no significant change from S2-S3 (*P* = NS) ▪ S1: 0.130 (0.972) –S2: 0.650 (1.182) S3: –0.890 (1.075) ○ Spine BMAD, g/cm3 ▪ Nonsignificant change between S1-S2(*P* = 0.588), S1-S3(*P* = 0.865) and S2-S3 *P* = NS) ▪ S1: 0.240 (0.027) S2: 0.238 (0.029) S3: 0.240 (0.030) ○ Spine BMAD Z-score ▪ Significant decrease between S1-S2 (*P* = 0.000) and S1-S3 (*P* = 0.000) Non-significant decrease from S2-S3 (*P* = NS) ▪ S1: 0.486 (0.809) S2: –0.097 (1.00) S3: –0.279 (0.93) • <u>Transgender boy scores, (n = 21)</u> ○ Hip BMD, kg/m² ▪ Nonsignificant change between S1-S2 (*P* = 0.913), S1-S3 (*P* = NS) and S2-S3 (*P* = NS) ▪ S1: 0.766 (0.215) S2: 0.774 (0.203) S3: 0.773 (0.197) ○ Hip Z-score ▪ Significant decrease between S1-S2 (*P* = 0.000) and S1-S3 (*P* = .001) and non-significant decrease from S2-S3 (*P* = NS) ▪ S1: –1.075 (1.145) S2: –1.633 (0.899) S3: –1.779 (0.816) ○ Spine BMD, kg/m² ▪ Nonsignificant increase between S1-S2 (*P* = NS) ,S1-S3 *P* = NS) and S2-S3 (*P* = .056) (but approaching significance)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ S1: 0.695 (0.220) S2: 0.711 (0.205) S3: 0.731 (0.209) ○ Spine BMD Z-score ▪ Significant decrease between S1-S2 (*P* = 0.000), S1-S3 (*P* = .000) and S2-S3 (*P* = .035) ▪ S1: –0.715 (1.406) S2: –1.610 (1.462) S3: –2.000 (1.384) ○ Spine BMAD, g/cm3 ▪ Nonsignificant change between S1-S2 (*P* = NS), S1-S3 (*P* = 0.433) and S2-S3 (*P* = NS) ▪ S1: 0.195 (0.058) S2: 0.195 (0.054) S3: 0.198 (0.055) ○ Spine BMAD Z-score ▪ Significant decrease between S1-S2 (*P* = 0.000) and S1-S3 (*P* = .001) Non-significant decrease S2-S3 (*P* = NS) ▪ S1: –0.361 (1.439) S2: –1.007 (1.347) S3: –0.913 (1.318) **Completed 2 scans (n = 70)** • <u>Overall:</u> ○ Among those who had two scans (N = 70), BMD and BMAD Z-scores showed a fall of similar magnitude in this larger cohort with similar transgender boy/transgender girl baseline differences although BMD Z-scores were higher in this larger group, and there was no significant change in absolute BMD in the spine or hip values, nor lumbar spine BMAD over this first treatment year (a small ,but non-significant, increase). • <u>Transgender girls, (n = 31)</u> ○ Nonsignificant increase in Hip BMD, kg/m² from 0.894 (0.118) at S1 to 0.905 (0.104) at S2, *P* = NS ○ Significant decrease in Hip Z-score from 0.157 (0.905) at S1 to –0.340 (0.816) at S2 *P* = .002 ○ No significant change in Spine BMD, kg/m 2 from 0.860 (0.154) at S1 to 0.859 (0.129) at S2, *P* = NS ○ Significant decrease in spine BMD Z-score from –0.016 (1.106) at S1 to –0.461 (1.121) at S2, *P* = .003 ○ No significant change in Spine BMAD, g/cm3 from 0.235 (0.030)at S1 to 0.233 (0.029) at S2, *P* = NS ○ Significant decrease in Spine BMAD Z-score from 0.859 (0.154) at S1 to –0.228 (1.027) at S2, *P* = .000 • <u>Transgender boys, (n = 39)</u>

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ No significant change in Hip BMD, kg/m² from 0.772 (0.137) at S1 to 0.785 (0.120) at S2, *P* = NS ○ Significant decrease in Hip Z-score –0.863 from (1.215) at S1 to –1.440 (1.075) at S2, *P* = .000 ○ Significant increase in Spine BMD, kg/m² from 0.694 (0.149) at S1 to 0.718 (0.124) at S2, *P* = .006 ○ Significant decrease in Spine Z-score from –0.395 (1.428) at S1 to –1.276 (1.410) at S2, *P* = .000 ○ Nonsignificant increase in Spine BMAD, g/cm3 from 0.196 (0.035) at S1 to 0.201 (0.033) at S2, *P* = NS ○ Significant decrease in Spine BMAD Z-score from –0.186 (1.230) at S1 to –0.541 (1.396) at S2, *P* = .006
Klink (2015)[140] Unspecified tertiary referral center in [redacted] the Netherlands	**N = 34** TGNB adolescents • **Eligibility Criteria:** Study subjects were included when they were at least 21 years of age, gonadectomy had taken place in the period from June 1998 to August 2012, and data on BMD at start of GnRH analog treatment, at start of CSH therapy, and at the age of 22 years were available. The 34 eligible subjects and their parents or legal representatives gave written consent for follow-up at start of treatment. • **Sampling Method:** Patients that met criteria were included • **Subset:** of the total population (N = 34) there were (n = 15) trans women and (N = 19) trans men	• Median age of trans women was 14.9 ± 1.9 at start of GnRH analogs, 16.6 ± 1.4 at start of CSH and 22.1 ± 0.9 at 22 year follow up • Median age for trans men was 15.0 ± 2.0 at start of GnRH analogs, 16.4 (2.3) at start of CSH and 21.9 ± 0.5 at 22 year follow up • Median duration of GnRH analogs monotherapy in trans women and trans men was 1.3 years (range, 0.5–3.8) and 1.5 years (range, 0.25–5.2), respectively. • Median duration of CSH therapy was 5.8 years (range, 3.0–8.0) and 5.4 years (range, 2.8–7.8), respectively. • The median duration of combined GnRH analog and CSH therapies was 3.1 years (range, 2.1– 4.5) and 2.2 years (range, 1.4 – 3.1), respectively.	• GnRH analog monotherapy (median duration in natal boys with GD [trans women] and natal girls with GD [trans men] 1.3 and 1.5 y, respectively) followed by CSH (median duration in trans women and trans men, 5.8 and 5.4 y, respectively) with discontinuation of GnRH analogs after gonadectomy. • Treatment protocol: Triptorelin (Decapeptyl-CR, Fer- ring) 3.75 mg every 4 weeks s.c. was started in patients diagnosed with gender identity disorder (DMS IV-TR) in the age range from 11.4 –18.3 years. In the age range from 15.6 –19 years trans- women were prescribed incremental dosing of 17-beta-estradiol orally and trans men were given in mixed T esters (Sustanon 250 mg/ml, MSD) every 2–4 weeks in incremental dosages. At a minimum age of 18 years, after gonadectomy, GnRH analog treatment was terminated and	• Baseline Data was collected at start of GnRH analogs, start of CSH therapy and at follow-up near age 22 • BMAD and aBMD with accompanying z-scores of lumbar spine and femoral region were measured. aBMD of the LS and FN was measure by dual energy X-ray absorptiometry. Z-scores were calculated using UK reference population.	**BMAD and BMD** • **Trans women** Mean ±SD or median [interquartile range] ○ GnRH analog monotherapy ▪ There was no significant change in absolute LS and FN BMAD or aBMD during GnRH analog monotherapy ▪ There was a non-significant decrease in LS BMAD and aBMD z-scores during GnRH analog monotherapy (-.44 ± 1.10 to -.90 ± 0.80 and -.77 ± 0.89 to -1.01 ± 0.98 respectively) ▪ There was a non-significant decrease in FN BMAD and aBMD z-scores during GnRH analog monotherapy (-.93 ± 1.22 to -1.57 ± 1.74 and -.66 ± 0.77 to -.95 ± 0.63 respectively) ○ Start of CSH therapy to age 22 ▪ There was a significant increase from the start of CSH to age 22 for absolute LS BMAD (0.22 g/cm3 ± 0.03 to 0.23 g/cm3 ± 003, *P* = .003,) but the z-score change was not significant and lower than at the start of treatment. ▪ LS and FN aBMD scores showed a significant increase from the start of CSH to age 22 (0.84 g/cm3 ± 0.11 to 0.93 g/cm3 ± 0.10, *P* < .001 and 0.87 g/cm3 ± 0.08 to 0.94 g/cm3 ± 0.11, *P* = .009 respectively); however, the z-score showed no significant change. ▪ There was a nonsignificant increase in bone age from 15.5 ± 1.9y at start of GnRH analogs to 15.9 ± 1.8y at start of CSH ○ Start of GnRH analogs to age 22 ▪ There was a significant increase in LS aBMD from start of GnRH analogs to age 22 (0.84 g/cm3 ± 0.13 to 0.93 g/cm3 ± 0.10, *P* = 0.06,) but the corresponding z-score had significantly declined from the start of treatment from -0.77 ± 0.89 to -1.36 ± 0.83 at age 22, *P* = .003

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
			CSH therapy continued. During the entire treatment patients were advised on calcium intake and weight- bearing physical exercise		▪ LS and FN BMAD and FN aBMD showed no significant change from start of GnRH analogs to age 22 • **Trans men** Mean ±SD or median [interquartile range] ○ GnRH analog monotherapy ▪ LS and FN BMAD scores showed no significant change during GnRH analog monotherapy, but LS BMAD z-scores significantly decreased from -.28 ± 0.90 to -0.50 ± 0.81, *P* = .004 ▪ There was a significant decrease in LS aBMD and their corresponding z-scores during GnRH analog monotherapy. LS aBMD decreased from 0.95 g/cm3 ±0.12 to 0.91 g/cm3 ± 0.10, *P* = .006, and the z-scores decreased from 0.17 ± 1.18 to -0.72 ± 0.99, *P* < .001 ▪ There was a significant decrease in FN aBMD and their corresponding z-scores during GnRH analog monotherapy. FN aBMD decreased from 0.92 g/cm3 ± 0.10 to 0.88 g/cm3 ± 0.09, *P* = .005, and the z-scores decreased from 0.36 ± 0.88 to -0.35 ± 0.79, *P* = .001 ▪ There was a significant increase in bone age from 15.0y [4.4] at start of GnRH analogs to 16.3y [3.25] at start of CSH, *P* = .002 ○ Start of CSH therapy to 22 ▪ LS BMAD significantly increased from 0.24 g/cm3 ± 0.02 at the start of CSH to 0.25 g/cm3 ± 0.28 at the age 22, *P* = .001. The corresponding z-scores also significantly increased from -0.50 ± 0.81 to -0.033 ± 0.95, *P* = .002 ▪ There was a significant increase in absolute LS aBMD, from 0.91 ± 0.10 at the start of CSH to 0.99 ± 0.13 at age 22, (*P* < .001) but there was no significant change in the corresponding z-score. ▪ There was a significant increase in FN BMAD from 0.31 ± 0.04 at start of CSH therapy to 0.33 ± 0.05 at age 22, (*P* = .01), and aBMD from 0.88 ± 0.09 at start of CSH therapy to ± 0.95 ± 0.10 at age 22 (*P* < .001) ○ From start of GnRH analogs to age 22 ▪ There was no significant change in LS BMAD and their corresponding z-score or absolute aBMD. ▪ There was also no significant change in FN BMAD and it's corresponding z-score or aBMD and its corresponding z-score. ▪ The only significant change was a decrease in the LS aBMD z-score from 0.17 ± 1.18 to -0.33 ± 1.12, *P* = .02 ○ Overall ▪ Both absolute LS and FN aBMD and the respective z scores significantly decreased during GnRH analog monotherapy and subsequently increased between start of CSH therapy and age 22 years.

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ At age 22 years, LS aBMD z scores were lower compared with start GnRH analogs but this was not significant. Scores significantly declined from start of GnRH analogs to start of CSH, but then improved from the start of CSH to age 22
Navabi (2021)[92] Endocrine diversity clinic [redacted] from January 2006 to April 2017	**N = 119 transgender males (for this subset)** • **Eligibility**: patients < 18 years old starting/on GnRH analog treatment with one baseline DEXA measurement • **Sampling method**: all patients from January 2006 to April 2017 were reviewed, and about 86.9% were included as they had a baseline DEXA measurement	• For LS, the mean aBMD (SD) was 1.13 g/cm² (0.17) with the mean aBMD z-score (SD) being 0.04 (1.10), mean BMAD (SD) was 0.37 g/cm3 (0.46) with the mean BMAD z-score being -0.10 (1.00); • For LTH, mean aBMD score (SD) was 1.00 g/cm² (0.15) with the mean aBMD z-score (SD) being 0.10 (1.06); mean BMC (SD) was 2.40 (0.54) kg with the mean BMC z-score (SD) being 0.05 (1.30)	GnRH analogs	Participants were assessed at GnRH analog initiation and then at a follow-up appointment at least 18 months after start of therapy. DXA results were used to retrieve aBMD of LS, LTH, and TBLH. Volumetric BMD was calculated with z scores calculated using available reference for age-matched birth-assigned gender BMAD and SD .	**BMD changes (n = 80) Mean (95% CI)** • Significant decrease in LS aBMD z-score, with a mean post-pre difference of -0.74 (-0.85 to- 0.63), *P* < .001 • Significant decrease in LS BMAD z-score, with a mean post-pre difference of -0.59 (-0.74 to -0.45), *P* < .001 • Significant decrease in LTH aBMD z-score, with a mean post-pre difference of -0.33 (-0.40 to -0.26), *P* < .001 • Significant decrease in TBLH aBMD z-score, with a mean post-pre difference: -0.34 (-0.43 to -0.25), *P* < .001 • Non-significant change in BMC in kg, with a mean post-pre difference: 0.006 (-0.03 to 0.04), *P* = NS • Significant decrease in BMC z-score, with a mean post-pre difference: -0.39 (-0.51 to -0.28), *P* < .001
	N = 51 transgender females (for this subset) • **Eligibility**: patients < 18 years old starting/on GnRH analog treatment with one baseline DEXA measurement • **Sampling method**: all patients from January 2006 to April 2017 were reviewed, and about 86.9% were included as they had a baseline DEXA measurement				**BMD changes** • Significant decrease in LS aBMD z-score, with a mean post-pre difference of -0.33 (-0.46 to -0.19, *P* < .001 • Significant decrease in LS BMAD z-score, with a mean post-pre difference of -0.37 (-0.61 to -0.14), *P* < .003 • Significant decrease in LTH aBMD z-score, with a mean post-pre difference of -0.46 (-0.60 to -0.31), *P* < .001 • Significant decrease in TBLH aBMD z-score, with a mean post-pre difference: -0.34 (-0.48 to -0.21), *P* < .001 • Significant increase in BMC in kg, with a mean post-pre difference: 0.15 (0.10 to 0.20), *P* < .001 • Non-significant decrease in BMC z-score, with a mean post-pre difference: : -0.12 (-0.26 to 0.02), *P* = NS
Schagen (2020)[94] Setting: N/R	**N = 121 patients** • **Eligibility**: adolescents with DSM-IV **Criteria** for gender identity disorder and eligible for medical treatment per existing guidelines.	• Mean age at the start of GnRH analogs: ○ Transgender females: 14.1 (1.7) ○ Transgender males: 14.5 (2.0) • Mean age at the start of CSH (yrs., SD) ○ Transgender females: 16.2 (1.2)	Receiving GnRH analog treatment: Triptorelin-CR injections. The first 2 injections were given at 2 week intervals followed by injections every 4 weeks.	Patients data was collected at baseline (before GnRH analog administration) and 24 months after starting GnRH analogs • aBMD is a measurement obtained from a DXA scan to estimate peak bone mass. It is	**BMD (g/cm²) and BMAD (g/cm³)** mean • There was a significant decrease in aBMD LS measurements and z-scores for aBMD LS in all subsets • There was a significant decrease in aBMD and whole body BMD measurements and z-scores in all subsets except for aBMD and whole body BMD measurements for late transgender girls

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	• **Sampling method**: study does not mention how patients were sampled • **Subsets**: Out of N = 121 patients starting GnRH analogs, there were (n = 51) transgender females and (n = 70) transgender males ○ Early puberty group: Transgender females (n = 15) and Transgender males (n = 14) ○ Late puberty group: Transgender females (n = 36) Transgender males (n = 56) ○ Received CSH in addition to GnRH analogs: transgender females (n = 36) and transgender males (n = 42)	○ Transgender males: 16.9 (1.1) • Duration of GnRH analogs use before starting CSH (yrs., SD), P value NS: ○ Transgender females: 2.0 (0.94) ○ Transgender males: 1.8 (1.11)		calculated as bone mineral content divided by scanned area. In this study, they looked at aBMD for lumbar spine (LS), hip, and whole body. • Z-Score: compared patient's bone density to the average values of their same age and gender. In this study, the National Health and Nutrition Examination Surveys values were used for the aBMD. For BMAD, z-scores were calculated from an English reference population using LMS data. • BMAD: bone mineral apparent density, also referred to as volumetric body density. They used this measure, as bone density may change in youth as they grow. They calculated BMAD for LS and hip. • Serum bone markers: osteocalcin, P1NP, P3NP and 1CTP levels which were taken from blood samples. Osteocalcin was measured by an immunometric assay. 1CTP, P1NP and P3NP was measured using a radioimmunoassay.	• There was no significant change in BMAD LS except for early transgender girls, however, there was a significant decrease in BMAD LS z-scores across all subsets. • There was a significant decrease in BMAD hip measurements and z-scores in all subsets except for BMAD hip measurements and z-scores for early transgender girls • Z-scores decreased in all subsets for all measures except BMAD hip in early transgender girls • **aBMD LS:** ○ Transgender girls early: 0.73 to 0.75 ($P < .05$) Transgender girls late: 0.79 to 0.82 ($P < .05$) ○ Transgender boys early: 0.75 to 0.8 ($P < .05$) Transgender boys late: 0.95 to 0.92 ($P < .05$) • **Z-score for aBMD LS:** ○ Transgender girls early: -0.67 to −1.26 ($P < .05$) Transgender girls late: -0.33 to 0.92 ($P < .05$) ○ Transgender boys early: -0.28 to -1.04 ($P < .05$) Transgender boys late: 0.38 to -0.71 ($P < .05$) • **aBMD hip:** ○ Transgender girls early: 0.81 to 0.86 ($P < .05$) Transgender girls late: 0.87 to 0.89 (P = NS) ○ Transgender boys early: 0.79 to 0.83 ($P < .05$) Transgender boys late: 0.93 to 0.89 ($P < .05$) • **Z-score for aBMD hip:** ○ Transgender girls early: -0.49 to -0.93 ($P < .05$) Transgender girls late: -0.43 to -1.01 ($P < .05$) ○ Transgender boys early: 0.09 to-0.50 ($P < .05$) Transgender boys late: 0.46 to -0.56 ($P < .05$) • **Whole body BMD:** ○ Transgender girls early: 0.90 to 0.92 ($P < .05$) Transgender girls late: 0.95 to 0.95 (P = NS) ○ Transgender boys early: 0.88 to 0.92 ($P < .05$) Transgender boys late: 1.03 to 1.01 ($P < .05$) • **Z-score for aBMD WB:** ○ Transgender girls early: -0.56 to -1.51 ($P < .05$) Transgender girls late: -0.51 to -1.62 ($P < .05$)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Transgender boys early: -0.28 to -0.82 (*P* < .05)Transgender boys late: 0.66 to-0.40 (*P* < .05) • **BMAD LS:** ○ Transgender girls early: 0.20 to 0.2 (*P* = NS) Transgender girls late: 0.2 to 0.21 (*P* = NS) ○ Transgender boys early: 0.22 to 0.22 (*P* = NS) Transgender boys late: 0.25 to 0.24 (*P* < .05) • **Z-score for BMAD LS:** ○ Transgender girls early: -0.33 to -1.19 (*P* < .05) Transgender girls late: -0.65 to-1.21 (*P* < .05) ○ Transgender boys early: -0.15 to -0.86 (*P* < .05) Transgender boys late: 0.33 to -0.56 (*P* < .05) • **BMAD hip:** ○ Transgender girls early: 0.28 to 0.27 (*P* = NS) Transgender girls late:0.28 to 0.26 (*P* < .05) ○ Transgender boys early: 0.3 to 0.28 (*P* < .05) Transgender boys late: 0.32 to 0.3 (*P* < .05) • **Z-score for BMAD hip:** ○ Transgender girls early: -0.94 to -1.23 (*P* = NS) Transgender girls late: -1.01 to -1.56 (*P* < .05) ○ Transgender boys early: -0.23 to -0.94 (*P* < .05) Transgender boys late: 0.04 to -0.54 (*P* < .05) **Serum Bone Markers (mg/L),** mean • All four bone markers had **a significant decrease** in early and late transgender girls and early transgender boys. The largest change was seen in the first year of therapy. P3NP and 1CTP significantly decreased in late transgender boys, but osteocalcin and P1NP did not change. • **Osteocalcin:** ○ Early transgender girl: 11.22 (baseline) to 7.58 (plateau); Late Transgender girls: 9.68 (baseline) to 7.19 (plateau) ○ Early Transgender boys: 14 (baseline) to 9.59 (plateau); Late Transgender boys: 3.55 (baseline) to 4.22 (plateau) • **P1NP:** ○ Early transgender girl: 633.3 (baseline) to 400 (plateau); Late Transgender girls: 653 (baseline) to 300 (plateau)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Early Transgender boys: 880 (baseline) to 440 (plateau); Late Transgender boys: 180 (baseline) to 140 (plateau) • **P3NP:** ○ Early transgender girl: 12.88 (baseline) to 5.375 (plateau); Late Transgender girls: 13.5 (baseline) to 5.375 (plateau) ○ Early Transgender boys: 16 (baseline) to 9.125 (plateau); Late Transgender boys: 5.63 (baseline) to 4 (plateau) • **1CTP:** ○ Early transgender girl: 17.01 (baseline) to 9.85 (plateau); Late Transgender girls: 19.07 (baseline) to 9.06 (plateau) ○ Early Transgender boys: 20.34 (baseline) to 9.06 (plateau); Late Transgender boys: 6.20 (baseline) to 4.61 (plateau)
			GnRH analog treatment of Triptorelin to suppress puberty was continued until patients were 16 or older when they started sex hormones. Some patients that were younger when the study was started continued GnRH analogs for up to 4 years. This represents those with prolonged GnRH analog treatment (more than 2 years)	• Data was assessed from baseline before GnRH analog therapy to 3 years after initial GnRH analog therapy and continuing into CSH therapy. Data collected at 12, 24 and 36 months. • aBMD is a measurement obtained from a DXA scan to estimate peak bone mass. It is calculated as bone mineral content divided by scanned area. In this study, they looked at aBMD for lumbar spine (LS), hip, and whole body. • Z-Score: compared patient's bone density to the average values of their same age and gender. In this study, the National Health and Nutrition Examination Surveys values were used for the aBMD. For BMAD, z-scores were calculated from an English reference population using LMS data.	**BMD (g/cm²) scores,** mean • aBMD scores remained stable, while z-scores significantly decreased in transgender girls, and decreased non-significantly for transgender boys. • **aBMD LS:** ○ Transgender girls: 0.73 (T0), 0.74 (12 mo), 0.77 (24 mo), 0.77 (36 mo) *P* = NS ○ Transgender boys: 0.85 (T0), 0.88 (12 mo), 0.9 (24 mo), 0.9 (36 mo) *P* = NS • **Z-score for aBMD LS:** ○ Transgender girls: -0.43 (T0), -0.92 (12 mo), -1.05 (24 mo), -1.15 (36 mo) *P* = NS . ○ Transgender boys: 0.85 (T0), 0.88 (12 mo), 0.9 (24 mo), 0.9 (36 mo) *P* = NS • **aBMD hip:** ○ Transgender girls: 0.8 (T0), 0.82 (12 mo), 0.83 (24 mo), 0.85 (36 mo) *P* = NS ○ Transgender boys: 0.88 (T0), 0.88 (12 mo), 0.87 (24 mo), 0.88 (36 mo) *P* = NS • **Z-score for aBMD hip:** ○ Transgender girls: -0.18 (T0), -0.65 (12 mo), -1.08 (24 mo), -1.08 (36 mo) *P* = .007. ○ Transgender boys: 0.86 (T0), 0.4 (12 mo), -0.18 (24 mo), -0.30 (36 mo) *P* = NS
			Following GnRH analog treatment (Triptorelin injections), CSH were	Data was assessed from baseline before GnRH analog therapy to 3	**BMD (g/cm²) and BMAD(g/cm³),** Mean

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
			given to patients at age 16 years or older. Oral estrogens at increasing dosages were prescribed to transgender girls. Testosterone injections (Sustanon) were given to transgender boys.	years after initial GnRH analog therapy and continuing into CSH therapy. Data collected at 12, 24 and 36 months. • aBMD is a measurement obtained from a DXA scan to estimate peak bone mass. It is calculated as bone mineral content divided by scanned area. In this study, they looked at aBMD for lumbar spine (LS), hip, and whole body. • Z-Score: compared patient's bone density to the average values of their same age and gender. In this study, the National Health and Nutrition Examination Surveys values were used for the aBMD. For BMAD, z-scores were calculated from an English reference population using LMS data. • BMAD: bone mineral apparent density, also referred to as volumetric body density. They used this measure, as bone density may change in youth as they grow. They calculated BMAD for LS and hip. • Serum bone markers- osteocalcin, P1NP, P3NP and 1CTP levels which were taken from blood samples. Osteocalcin was measured by an immunometric assay. 1CTP, P1NP and P3NP was measured using a radioimmunoassay.	• Significant increase in BMAD LS and z- score in all four groups. Increase BMAD hip measurements were significant in transgender girls and early transgender boys. • **aBMD LS:** ○ Early transgender girls: 0.77 (T0) to 0.95 (36 mo) ($P < .05$) Late Transgender girls: 0.83 to 0.95 ($P < .05$) ○ Early Transgender boys: 0.82 to 1.02 ($P < .05$) Late transgender boys: 0.9 to 0.99 ($P < .05$) • **Z-score for aBMD LS:** ○ Early Transgender girls: -1.37 to -0.82 ($P < .05$) Late Transgender girls: -0.99 to -1.05 (P = NS) ○ Early Transgender boys: -1.30 to 0.11 ($P < .05$) Late Transgender boys: -0.68 to -0.26 ($P < .05$) • **aBMD hip:** ○ Early Transgender girls: 0.87 to 1.02 ($P < .05$) Late Transgender girls: 0.88 to 0.96 ($P < .05$) ○ Early Transgender boys: 0.83 to 1.02 ($P < .05$) Late Transgender boys: 0.88 to 0.96 ($P < .05$) • **Z-score for aBMD hip:** ○ Early Transgender girls: -0.99 to -0.09 ($P < .05$) Late Transgender girls: -0.86 to -0.7 (P = NS) ○ Early Transgender boys: -0.82 to 0.59 ($P < .05$) Late Transgender boys: -0.5 to 0.12 ($P < .05$) • **Whole body BMD:** ○ Early Transgender girls: 0.93 to 1.06 ($P < .05$) Late Transgender girls: 0.96 to 0.98 (P = NS) ○ Early Transgender boys: 0.94 to 1.11 (NS) Late Transgender boys: 1.02 to 1.1 ($P < .05$) • **Z-score for aBMD WB:** ○ Early Transgender girls: -1.67 to -1.22 ($P < .05$) Late Transgender girls: -1.42 to -1.48 (P = NS) ○ Early Transgender boys: -1.06 to 0.21($P < .05$) Late Transgender boys: -0.3 to -0.05 ($P < .05$) • **BMAD LS:** ○ Early Transgender girls: 0.2 to 0.24 ($P < .05$) Late Transgender girls: 0.21 to 0.24 ($P < .05$)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Early Transgender boys: 0.22 to 0.26 (*P* < .05) Late Transgender boys: 0.24 to 0.26 *(P* < .05) • **Z-score for BMAD LS:** ○ Early Transgender girls: -1.39 to -0.49 (*P* < .05) Late Transgender girls:-1.29 to -0.5 (*P* < .05) ○ Early Transgender boys: -1.01 to 0.12 (*P* < .05) Late Transgender boys:-0.61 to -0.04 (*P* < .05) • **BMAD hip:** ○ Early Transgender girls: 0.28 to 0.31(*P* < .05) Late Transgender girls: 0.27 to 0.27 (*P* < .05) ○ Early Transgender boys:0.28 to 0.32 (*P* < .05) Late Transgender boys: 0.3 to 0.32 (*P* = NS) • **Z-score for BMAD hip:** ○ Early Transgender girls: -0.88 to -0.35 (*P* < .05) Late Transgender girls: -1.36 to -1.21 (*P* < .05) ○ Early Transgender boys: -0.71 to 0.01 (*P* < .05) Late Transgender boys: -0.41 to -0.1 (*P* = NS) **Serum Bone Markers (mg/L),** mean • Levels of all four bone markers changed slightly in late transgender boys. Bone markers saw a larger change in transgender girls and early transgender boys • Osteocalcin: ○ Early transgender girl: 8.59 (baseline) to 3.83 (36 months) Late transgender girl: 7.11 (baseline) to 3.36 (36 mo) ○ Early transgender boy: 7.52 to 2.08 (36 mo) Late transgender boy:4.43 to 2.15 (36 mo) • **P1NP**: ○ Early transgender girl: 420 to 93.33 (36 mo) Late transgender girl: 260 to 60 (36 mo) ○ Early transgender boy:293.3 to 46.67 (36 mo) Late transgender boy: 123.3 to 20 (36 mo) • **P3NP**: ○ Early transgender girl: 7.25 to 3.58 (36 mo) Late transgender girl:5.1 to 1.52 (36 mo) ○ Early transgender boy: 5.73 to 3.31 (36 mo) Late transgender boy: 3.31 to 2.15 (36 mo) • **1CTP**:

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Early transgender girl: 3.58 to 5.76 (36 mo) Late transgender girl: 1.52 to 2.28 (36 mo) ○ Early transgender boy:3.31 to 1.44 (36 mo) Late transgender boy:2.15 to 0.72 (36 mo)
Stoffers (2019)[149] At a clinic between November 2010 (when the clinic first started) and August 2018 (does not mention the details of this clinic)	**N = 62 TGNB adolescents** • **Eligibility**: diagnosed with gender dysphoria who had started GnRH analog treatment and had subsequently received testosterone treatment for more than 6 months (or had had their 6-month visit, which was sometimes scheduled just before 6 months of treatment) • **Sampling method**: Individuals were assessed by mental health professionals to confirm the diagnosis of gender dysphoria to exclude psychological, medical, or social problems that might interfere with treatment; and to determine if they were able to consent to treatment	• Full cohort (N = 62): All had been treated with a GnRH analog (Decapeptyl-CR; 3.75 mg every 4 weeks s.c.) for a median duration of 8 months (range 3-39) before they began testosterone treatment at a median age of 17.2 years (range 14.9-18.4) (Table I.1). • Median duration of follow-up during testosterone treatment was 12 months (range 5-33). No one discontinued testosterone therapy. • Age, median (range), at start of GnRH analogs was 16.5 (11.8-18.0) years and duration, median (range), of GnRH analog therapy was 8 (3-39) months. Smoker, n (%), accounts for 10 (16%).	Testosterone	Participants were assessed at the start of GnRH analog therapy and then every 6 months during 24 months of testosterone treatment. • BMD at the LS and neck area of the left and right hip was evaluated with DXA using a Hologic Discovery A scanner (Tromp Medical BV; Castricum, the Netherlands) before the start of GnRH analog treatment and before the start of testosterone therapy (unless this was within a year of the previous DXA scan), and then every 1 to 2 years. • BMD z-scores were calculated using female reference data from the Bone Mineral Density in Childhood Study; for those > 16 years of age, reference data from the Third National Health and Nutrition Examination Survey for the neck area of the hip and Hologic adult reference data for the LS were used. • BMAD was calculated and z-scores determined for the lumbar spine and left femoral neck. • Because reference values are provided for up to 17 years of age, reference values for 17-year-olds were used for those aged > 17 years. Around the age of 18 years, adolescents	**BMD (g/cm²)**: • At the start of testosterone treatment, BMD at the LS and hips as well as BMD z-scores were lower than those at the start of GnRH analog treatment (n = 18; all $P < .001$) • After the start of gender-affirming therapy, all parameters increased. BMD measured after 12 to 24 months of testosterone therapy was no longer significantly different from BMD at the start of GnRH analog treatment. However, BMD z-scores after 12 to 24 months of testosterone therapy remained significantly lower than pretreatment values • (LS, -0.77 ± 0.95 vs -0.18 ± 0.76, $P < .001$; left hip, -0.72 ± 0.75 vs -0.16 ± 0.77, $P < .001$; right hip, -0.66 ± 0.74 vs -0.14 ± 0.74, ^$P = .003$; n = 17). **BMAD (g/cm³):** • Similar results were found when BMAD was calculated to take into account the effects of bone size. • BMAD of the LS and left hip after 12 to 24 months of testosterone treatment was not significantly different from that at the start of GnRH analog treatment (LS, 0.24 ± 0.02 vs 0.25 ± 0.02, P = NS ; left hip, 0.32 ± 0.04 vs 0.33 ± 0.03, P = NS ; n = 17). • BMAD z-scores remained lower than pretreatment values although only significantly so at the LS (LS, -0.57 ± 0.76 vs -0.16 ± 0.68, $P = 0.001$; left hip, -0.08 ± 0.79 vs 0.14 ± 0.60, $P = .07$; n = 17). • The use of male reference values resulted in higher BMAD z-scores but similar treatment effects (male z-scores after 12 to 24 months of testosterone compared to before GnRH analogs: LS, -0.34 ± 0.87 vs 0.24 ± 0.91, $P < .001$; left hip, 0.01 ± 1.06 vs 0.24 ± 0.80, P = NS ; n = 17).

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				were referred to an adult clinic elsewhere.	
Vlot (2017)[99] [redacted] the Netherlands between 2001 and 2011.	**N = 70 TGNB adolescents** • **Eligibility**: Adolescents with diagnosed gender dysphoria, a serum BTM measurement of P1NP, osteocalcin or carboxy terminal cross linked telopeptide of type I collagen (ICTP) within 90 days before or after time point D0, C0 and C24, and/or a DXA-scan of the lumbar spine (LS) and/or femoral neck (FN) performed within 90 days before or after time point D0, C0 and C24. • **Sampling method**: Adolescents diagnosed with gender dysphoria who were treated with GnRH analogs and CSHT were recruited at their clinic; data and records were retrospectively reviewed. • **Subset**: ○ 28 trans women and 42 trans men. ○ Participants were categorized into young and old pubertal group, based on their bone age. Young trans men (n = 7), old trans men (n = 15), young trans women (n = 9) and old trans women (n = 6)	• All were treated with GnRH analog triptorelin and CSHT was added in incremental doses from the age of 16 years. • Median ages in years (range) in trans men at start of GnRH analogs, at start of CSHT, and 24 months after initiation of CSHT were 15.1 (11.7-18.6), 16.3 (15.9–19.5) and 18.3 (17.9–21.5), respectively; in trans women, were 13.5 (11.5–18.3), 16.0 (14.0–18.9) and 18.0 (16.0–20.9), respectively. • Median bone ages in years (range) in trans men at start of GnRH analogs, at start of CSHT, and 24 months after initiation of CSHT were 15 (12–17), 16 (12–17) and 17 (14–17), respectively; in trans women, were 13.5 (10–17), 14 (13–17) and 16.75 (14.5–17), respectively.	Patients were initially administered **GnRH analog triptorelin** and then administered **cross-sex hormones** from the age of 16 years (trans men received testosterone and trans women received estrogen)	• Measurements were taken at the start of GnRH analog treatment (D0), at start of CSHT (C0) and then 24 months after starting CSHT (C24) • Median (with range) of all data was presented. All results were then standardized to the measurement performed at D0, which was set at 100%. Subsequent measurements at C0 and C24 were expressed as the percentage of the measurement of D0, with corresponding 95% CI and P values. • Bone turnover markers (BTMs) were measured: ○ The formation markers P1NP and osteocalcin and the resorption marker ICTP were measured in non-fasting state. ○ P1NP was measured using a RIA (Orion Diagnostica, Espoo, Finland) with an intra-assay coefficient of variation (CV) of 4–8% and inter-assay CV of 8%. The lower limit of quantitation (LOQ) was 5 µg/L. ○ Osteocalcin was measured using an immunometric-assay (Biosource, Nivelles, Belgium) with an intra-assay CV of b5%, inter-assay CV of 8–15% and LOQ of 0.4 nmol/L. ICTP was measured using a RIA (Orion	**P1NP (mg/L)** median (range), deltas (95% CI) for comparisons • During puberty suppression, there was a significant decrease in both young trans men and trans women, and a trend or no change in old trans men and trans women. • During CSHT therapy, there was a significant decrease in all groups except young trans men (and it was trending a decrease) ○ young trans men (n = 7) ▪ From D0 to C0, there was a significant decrease of -61.7% (-73.5- -49.9), *P* = .02 ▪ From D0 to C24 there was a significant decrease of -71.8 % (-81.8- -61.7), *P* = .02 ▪ From C0-C24 there was a non-significant decrease of -10.1 (-21.7-1.6), *P* = NS ▪ D0: 783 (516–1090), C0: 324 (194–402), C24: 186 (163–334) ○ old trans men (n = 15): ▪ From D0-C0, there weas a non-significant increase of 32.3% (-0.19-64.8), *P* = NS ▪ From D0-C24, there was a non-significant decrease of -10.9% (-27.5-5.7), *P* = NS ▪ From C0-C24 there was a significant decrease of -43.2% (-71.0- -15.5), *P* = .01 ▪ D0: 110 (38–471), C0: 127 (61–321), C24: 101 (44–181) ○ young trans women (n = 9) ▪ From D0 to C0, there was a significant decrease of -57.9% (-72.6- -43.3), *P* = .008 ▪ From D0 to C24 there was a significant decrease of -76.6 % (-82.7- -70.5), *P* = .008 ▪ From C0-C24 there was a significant decrease of -18.7% (-30.4- -7.0), *P* = .008 ▪ D0: 935 (617–1348), C0: 363 (185–643), C24: 204 (137–314) ○ old trans women (n = 6) ▪ From D0 to C0, there was a non-significant decrease of -23.7% (-57.0- 9.7), *P* = NS ▪ From D0 to C24 there was a significant decrease of -49.0 % (-62.7- -35.3), *P* = .03 ▪ From C0-C24 there was a significant decrease of –25.3 (-55.0-4.3), *P* = .03

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				Diagnostica, Espoo, Finland) with an intra-assay CV of 4–6%, inter-assay CV of 7% and LOQ of 1 µg/L. • BMAD was measured ○ A DXA-scan was used to measure BMD in g/cm² of the LS and FN of the non-dominant hip. ○ To correct for height and height gain the volumetric bone mineral apparent density (BMAD) in g/cm3 for both LS and FN was calculated. BMAD Z-scores were calculated for sex assigned at birth using an UK reference population, due to the lack of consensus with regard to the use of either sex assigned at birth or desired sex reference values in transgender adolescents. The lack of validated reference values of bone age needed to calculate the BMAD and Z-scores limits the use of bone age and therefore the chronological calendar age of the transgender adolescents was used. Furthermore, the reference values of L- M- and S-values of 17-year-old biological males and females were used to calculate the BMAD for patients older than 17 years, due to the lack of reference values of adolescents exceeding the age of 17 years.	▪ D0: 191 (96–792), C0: 140 (111–467), C24: 119 (55–296) **Osteocalcin (mg/L)** median (range), deltas (95% CI) for comparisons • There was a significant increase in old trans men during puberty suppression, and a significant decrease during CSHT therapy, but no other significant changes in any other group. ○ young trans men (n = 7) ▪ From D0 to C0, there was a non-significant increase of 24.2% (-75.1-123.5), *P* = NS ▪ From D0 to C24 there was a non-significant increase of 20.4% (-78.7-119.5), *P* = NS ▪ From C0-C24 there was a non-significant decrease of -3.8% (-54.7-47), *P* = NS ▪ D0: 5 (2.2–11.7), C0: 6.8 (1.8–7.7), C24: 4.9 (4.2–7.8) ○ old trans men (n = 18) ▪ From D0 to C0, there was a significant increase of 59.3% (26.8-91.8), *P* = .004 ▪ From D0 to C24 there was a non-significant increase of 27.0% (3.1-51.0), *P* = NS ▪ From C0-C24 there was a significant decrease of –32.3% (-63.1- -1.5), *P* = .02 ▪ D0: 2.4 (0.4–4.6), C0: 3.9 (0.4–8.6), C24: 2.9 (0.8–5) ○ young trans women (n = 11) ▪ From D0 to C0, there was a non-significant increase of 29.9% (-40.3-100.1), *P* = NS ▪ From D0 to C24 there was a non-significant increase of 30.4% (-48.9-109.8), *P* = NS ▪ From C0-C24 there was a non-significant increase of 0.53% (-48.8-49.8), *P* = NS ▪ D0: 4.8 (2.6–21.9), C0: 6.4 (0.7–12.8), C24: 5.4 (3.9–12.5) ○ old trans women (n = 7) ▪ From D0 to C0, there was a non-significant increase of 5.1% (-78.3-88.6), *P* = NS ▪ From D0 to C24 there was a non-significant increase of 73.0 (-27.8-173.8), *P* = NS ▪ From C0-C24 there was a non-significant increase of 67.8% (-9.8-145.4), *P* = NS ▪ D0: 2.29 (0.8–11), C0: 2.2 (0.5–6.1) C24: 3.3 (1.8–6.8) **1CTP (mg/L)** median (range), deltas (95% CI) for comparisons

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• During suppression of puberty a significant decrease of ICTP concentrations was seen in young trans men and trans women. Young trans men showed an increase after starting CSHT but concentrations were still significantly lower after 24 months on CSHT from baseline. • All groups had a significant decrease from the start of puberty suppression to 24 months after starting CSHT except old trans men. ○ young trans men (n = 7) ▪ From D0 to C0 there was a significant decrease of -53.6% (-66.9- -40.3), *P* = .02 ▪ From D0 to C24 there was a significant decrease of -45.7% (-60.2- -31.1), *P* = .02 ▪ From C0-C24, there was a significant increase of 7.9% (1.5-14.2), *P* < .05 ▪ D0: 24 (17–29.9), C0: 11 (7.8–12). C24: 12 (11–14) ○ old trans men (n = 15) ▪ From D0 to C0, there was a non-significant decrease of -3.8 (-20.3-12.6), *P* = NS ▪ From D0 to C24 there was a non-significant increase of 4.0 (-11.4-19.5), *P* = NS ▪ From C0-C24 there was a non-significant increase of 7.9 (-5.8-21.5, *P* = NS ▪ D0: 7 (5.2–15), C0: 6.9 (4.6–14), C24: 8.2 (4.1–16) ○ young trans women (n = 9) ▪ From D0 to C0 there was a significant decrease of -45.0% (-60.6-29.4), *P* = .008 ▪ From D0 to C24 there was a significant decrease of -52.5% (= 64.2- -40.7), *P* = .008 ▪ From C0-C24, there was a non-significant decrease of -7.44% (1.5-14.2), *P* = NS ▪ D0: 23 (15–34), C0: 13 (8.7–21), C24: 10 (8.5–13) ○ old trans women (n = 5) ▪ From D0 to C0 there was a non-significant decrease of -28.2% (-52.7- -3.7), *P* = NS ▪ From D0 to C24 there was a significant decrease of -39.3 (-51.9- -26.7), *P* = .04 ▪ From C0-C24, there was a non-significant decrease of -11.1 (-34.5-12.3), *P* = NS ▪ D0: 12 (6.9–21), C0: 7.4 (6.9–13). C24: 6.8 (4.8–15)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• **BMAD HIP(g/cm^2)** median (range), deltas (95% CI) for comparisons • During GnRH analog therapy only the old trans men showed a significant decrease of the BMAD. • Young and old trans men showed an increase of BMAD after 24 months of CSHT therapy, but, in general, in both young and old trans women the BMAD did not change after CSHT. ○ young trans men (n = 10) ▪ From D0 to C0 there was a no- significant decrease of -4.8% (-12.1 to 2.6%) , *P* = NS ▪ From D0 to C24 there was a non-significant increase of 3.4% (-3.6 to 10.4%), *P* = NS ▪ From C0 to C24 there was a significant increase of 8.2% (5.4 to 11.0%), *P* = .01 ▪ D0: 0.31 (0.26–0.36), C0: 0.30 (0.22–0.35), C24: 0.33 (0.23–0.37) ○ old trans men (n = 23) ▪ From D0 to C0 there was a significant decrease of -4.3% (-7.2 to -1.4%) with a *P* = .01 ▪ From D0 to C24 there was a non-significant increase of 0.49% (-3.3 to 4.3%) with a *P* = NS ▪ From C0 to C24 there was a significant increase of 4.8% (0.92 to 8.6%) with a *P* = .01 ▪ D0: 0.33 (0.25–0.39), C0: 0.30 (0.23–0.41), C24: 0.32 (0.23–0.41) ○ young trans women (n = 16) ▪ From D0 to C0 there was a non-significant decrease of -3.1% (-11.0 to 4.7%) with a *P* = NS ▪ From D0 to C24 there was a non-significant decrease of -0.7% (-8.6 to 7.2%) with a *P* = NS ▪ From C0 to C24 there was a non-significant increase of 2.4% (-1.6 to 6.4%) with a *P* = NS ▪ D0: 0.29 (0.20–0.33), C0: 0.27 (0.20–0.33), C24: 0.27 (0.20–0.36) ○ old trans women (n = 6) ▪ From D0 to C0 there was a non-significant decrease of -2.9% (-11.8% to 6.0%) *P* = NS ▪ From D0 to C24 there was a non-significant decrease of -2.7% (-15.5% to 10.0%) *P* = NS

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ From C0 to C24 there was a non-significant increase of 0.2% (-8.9% to 9.2%) *P* = NS ▪ D0: 0.30 (0.26–0.36), C0: 0.30 (0.26–0.34), C24: 0.29 (0.24–0.38) **BMAD Z-score** median (range), deltas (95% CI) for comparisons • Both young and old trans women groups showed a BMAD Z-score below zero at D0. In all trans women, the median BMAD Z-score was still below zero after 24 months of CSHT. • Both young and old trans men showed a significant increase in z-scores after CSHT. ○ young trans men (n = 10) ▪ A significant increase was shown during CSHT (95% CI 0.276 to 0.639, *P* = .005) ▪ D0: -0.01 (−1.30–0.91), C0: -0.37 (−2.28–0.47), C24: -0.37 (−2.03–0.85) ○ old trans men (n = 23) ▪ A significant decrease of the BMAD Z-score during GnRH analogs was seen (95% CI −0.548 to −0.147, *P* = .002) ▪ A significant increase was shown during CSHT (95% CI 0.038 to 0.470, *P* = .02) ▪ D0: 0.27 (−1.39–1.32), C0: −0.27 (−1.91–1.29), C24: 0.02 (−2.1–1.35) ○ young trans women (n = 16) ▪ D0: −0.71 (−3.35–0.37), C0: −1.32 (−3.39–0.21), C24: −1.3 (−3.51–0.92) ○ old trans women (n = 6) ▪ D0: −0.44 (1.37–0.93), C0: −0.36 (−1.5–0.46), C24: −0.56 (−2.17–1.29) • **BMAD LS (g/cm3)** median (range), deltas (95% CI) for comparisons • Suppression of puberty resulted in a decrease of BMAD of the old trans men. A substantial increase of BMAD in all groups was seen after 24 months of CSHT. ○ young trans men (n = 11) ▪ From D0 to C0 there was a non-significant decrease of -1.22% (95% CI -4.2 to 1.7%) *P* = NS ▪ From D0 to C24 there was a significant increase of 7.8% (95% CI 2.8 to 12.8%) *P* = .01 ▪ From C0 to C24 there was a significant increase of 9.0% (95% CI 4.9 to 13.2%) *P* = .004 ▪ D0: 0.23 (0.20–0.29), C0: 0.23 (0.19–0.28), C24: 0.25 (0.22–0.28) ○ old trans men (n = 23)

[a]*we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)*

[b]*p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)*

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ From D0 to C0 there was a significant decrease of -5.2% (95% CI -6.5 to -4.0%) *P* = 0.000 ▪ From D0 to C24 there was a significant decrease of -1.4% (95% CI -3.4 to 0.6%) *P* = .04 ▪ From C0 to C24 there was a significant increase of 3.8% (95% CI 2.1 to 5.6%) *P* = .0004 ▪ D0: 0.26 (0.21–0.29), C0: 0.24 (0.20–0.28), C24: 0.25 (0.21–0.30) ○ young trans women (n = 15) ▪ From D0 to C0 there was a non-significant increase of 2.0% (95% CI -0.62 to 4.6%) *P* = NS ▪ From D0 to C24 there was a significant increase of 13.7% (95% CI 8.1 to 19.3%) *P* = .002 ▪ From C0 to C24 there was a significant increase of 11.7% (95% CI 7.4 to 16.0%) *P* = .001 ▪ D0: 0.21 (0.17–0.25), C0: 0.20 (0.18–0.24), C24: 0.22 (0.19–0.27) ○ old trans women (n = 5) ▪ From D0 to C0 there was a non-significant decrease of -2.5% (-6.5% to 1.4%) *P* = NS ▪ From D0 to C24 there was a non-significant increase of 5.3% (-1.3% to 11.9%) *P* = NS ▪ From C0 to C24 there was a significant increase of 7.9% (2.7% to 12.0%) *P* = .04 ▪ D0: 0.22 (0.18–0.25), C0: 0.22 (0.19–0.24), C24: 0.23 (0.21–0.26) • **BMAD LS Z-score** median (range), deltas (95% CI) for comparisons • There was a significant decrease in all scores, except for young trans women, on GnRH analog therapy • There was a significant increase in all scores after CSHT therapy; however, the median z-scores did not reach the zero level ○ young trans men (n = 11) ▪ There was a significant decrease of the BMAD Z-score was seen after suppression of puberty (95% CI −1.304 to −0.582, *P* = .003) ▪ There was a significant increase after 24 months of CSHT (95% CI 0.252 to 0.926, *P* = .008) ▪ D0: −0.05 (−0.78–2.94), C0: −0.84 (−2.2–0.87), C24: −0.15 (−1.38–0.94) ○ old trans men (n = 23)

[a]we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)

[b]p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.5. Longitudinal pre-post studies evaluating bone health outcomes in TGNB patients

First author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ There was a significant decrease of the BMAD Z-score was seen after suppression of puberty (95% CI −0.973 to −0.530, *P* ≤ .0001) ▪ There was a significant increase after 24 months of CSHT (95% CI 0.123 to 0.425, *P* = .001) ▪ D0: 0.27 (−1.6–1.8), C0: −0.29 (−2.28–0.90), C24: −0.06 (−1.76–1.61) ○ young trans women (n = 15) ▪ There was a significant decrease during GnRH analog therapy (95% CI −1.196 to −0.678, *P* = .001). ▪ There was a significant increase in scores after 24 months of CSHT (95% CI = 0.099 to 0.642, *P* = .01) ▪ D0: −0.2 (−1.82–1.18), C0: −1.52 (−2.36–0.42), C24: −1.10 (−2.44–0.69) ○ old trans women (n = 5) ▪ There was a significant increase in scores after 24 months of CSHT (95% CI 0.316 to 0.753, *P* = .04) ▪ D0: −1.18 (−1.78–1.09), C0: −1.15 (−2.21–0.08), C24: −0.66 (−1.66–0.54)

[a]we considered data significant at an alpha of 0.05, but authors deemed it non-significant at their corrected alpha (Carmichael, 2021)

[b]p-scores are implicit from 95% confidence intervals. We considered it significant at an alpha of 0.05 by contrasting 95% CIs, but authors did not do a hypothesis test. (Carmichael, 2021)

Table abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BTMs, bone turnover markers; CI, confidence interval; DXA, dual-energy radiograph absorptiometry; GD, gender dysphoria; ITS, interrupted time series; LS, lumbar spine; LTH, left total hip; N/A, not applicable; N/R, not reported; OC, Osteocalcin; SD, standard deviation; TBLH, total body less head; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Hannema (2017)[59]	**N = 28 TGNB girls** • **Eligibility**: gender dysphoric adolescents seen at clinic. GD was diagnosed using DSM-IV, had been treat with estrogen > 12 months • **Sampling method**: adolescents at the clinic were invited to participant in study.	• Average age was 16 with a range from 13.9 to 18.9. • 28 participants completed one year of treatment. 21 completed 2 years, and 16 completed 3 years. All were trans girls	• Initial treatment was IM triptorelin 3.75 mg every 4 weeks. Oral estradiol was added around the age of 16 years. Two were treated with 200 ug ethinyestradiol and four were treated with 6 mg estradiol.	• Data was collected before treatment as a baseline, then at 1 year of treatment. The whole cohort participated in the one year follow-up, measurements were then taken at years 2 and 3 with dropout occurring. • BP was taken at each time point • Laboratory values were taken including prolactin, hemoglobin, hematocrit, A1c, AST, ALT, γ-glutamyl transferase, ALP, and creatinine.	• **Systolic BP (mmHg):** mean ± SD ○ There was no significant change from baseline to any measurement point ○ T0: 119 ± 16, T1: 121 ±14, T2: 122 ± 15, T3: 125 ± 16 • **Diastolic BP (mmHg)**: mean ± SD ○ There was no significant change from baseline to any measurement point ○ T0: 69 ± 9, T1: 68 ± 9, T2: 69 ± 9, T3:66 ± 9 • **Lab values** ○ There were no significant change in median prolactin levels, hemoglobin, hematocrit, AbA1c, AST, ALT or γ-glutamyl transferase. ○ ALP levels showed a non-significant decrease after first year (195 ± 67 U/L to 178 ± 94 U/L) but then continued to decrease in year 2 (123 ± 48 U/L) and 3 (92 ± 36 U/L) ○ Creatinine showed little change from 70 (46-48) mg/dL at baseline to 72 (56-96) mg/dL at year 1 or 73 (44-86) mg/dL at year 2, but showed a slight decrease in year 3 to 65 (41-90) mg/dL
Jarin (2017)[136] Preexisting databases	**N = 116 TGNB adolescents** • **Eligibility**: Outpatient data from adolescents aged 14 to 25 years diagnosed with GD (International Classification of Diseases, Ninth Revision codes 302.85 and 302.50) and receiving cross-sex hormone therapy from 2008 to 2014 were included • **Sampling method**: Clinic and outpatient records were retrospectively reviewed • **Subset definition**: 72 affirmed male subjects and 44 affirmed female subjects	• The mean age of the affirmed male and female subjects was 16 and 18 years, respectively. Depression was the most common medical comorbidity, with 35 subjects (30%) reportedly undergoing treatment for depression during hormone use. Ten (23%) affirmed female subjects were undergoing medical therapy for HIV; no concurrent HIV was reported among the affirmed male subjects. The longest follow-up time noted was 35 months. Baseline BMI, blood pressure, and metabolic values were within normal limits for all participants. • Seven affirmed male subjects reported undergoing puberty suppression with gonadotropin releasing hormone analogs before treatment, and 2 reported hormone use outside the practice of their medical providers (i.e., street hormones). In affirmed male cohort, mean baseline total cholesterol levels were within normal limits at 151 mg/dL, with a corresponding baseline LDL level of 84 mg/dL. • Previous puberty suppression with gonadotropin-releasing hormone analogs	Affirmed male subjects taking testosterone and affirmed female subjects taking estrogen with or without testosterone blockers (i.e., spironolactone)	Data was collected at baseline (or immediately before initiation of therapy,) at 1-3 months after initiation, at 4-6 months after initiation, and at 6 months and beyond. • Previously recorded measurements of testosterone, estradiol, prolactin, and lipids (total cholesterol, LDL, HDL, TG, and TG/ HDL ratio) were reviewed, as were the levels of electrolytes, liver enzymes, hemoglobin/hematocrit, and hemoglobin A1c (HbA1c).	• **BP**: ○ In affirmed male cohort, mean baseline systolic and diastolic blood pressures were 118 and 71 mm Hg, respectively. A reduction in mean diastolic blood pressure was noted at 6 months (67 mm Hg; *P* = .02); however, values returned to baseline levels at subsequent visits. Otherwise, both systolic and diastolic blood pressures remained within normal limits. ○ In affirmed female cohort, no statistically significant changes in systolic and diastolic blood pressures were noted. • **HbA1c**: ○ In affirmed male cohort, no significant changes in levels of HbA1c were observed (*P* = NS). ○ Not reported in affirmed female cohort. • **Cholesterol**: ○ In affirmed male cohort, there was an overall increase in mean total cholesterol and LDL levels noted after initiation of testosterone; however, these changes were not statistically significant and plateaued after 3 months. ○ In affirmed male cohort, a significant decrease in mean HDL level over time was observed, from a mean baseline of 50.2 to 45.0 mg/dL after 6 months (*P* = NS) ○ In affirmed male cohort, no significant changes in levels of TG and TG/HDL ratio were observed ○ For affirmed female cohort, estrogen was not associated with any changes in total cholesterol, LDL, HDL, TG, or the TG/HDL ratio

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
		was noted in 2 affirmed female subjects, whereas 5 subjects reported exogenous street hormone use.			
Klaver (2020)[139] [redacted] the Netherlands) from 1998 to December 2015	• **N = 192** TGNB subjects • **Eligibility**: subjects were included (1) if they had started treatment with GnRH analogs before the age of 18, (2) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogs or CSH treatment or within 1.5 years before or after the 22nd birthday), and (3) if, on the basis of their age, they were likely to have had at least 1 medical consultation in young adulthood (> 20.5 years • **Sampling method**: Medical records of all adolescents diagnosed with gender dysphoria at this medical center were retrospectively reviewed. • **Subset**: N = 71 trans women and N = 121 trans men	• All transgender subjects started GnRH analog treatment at a mean age of 15 and CSH treatment at a mean age of 17. • White participants accounts for 98% of subjects in trans women group and 94% of subjects in trans men group. • In trans women group, duration of GnRH analogs monotherapy [median (IQR)] = 2.1 (1.0–2.7), duration of GnRH analogs + CSH [median (IQR)] = 3.1 (2.5–3.6) and duration CSH monotherapy [median (IQR)] = 2.2 (1.1–3.1) • In trans men group, duration of GnRH analogs monotherapy [median (IQR)] = 1.0 (0.5–2.9), duration of GnRH analogs + CSH [median (IQR)] = 2.3 (1.8–2.8) and duration CSH monotherapy [median (IQR)] = 2.9 (1.7–3.4	GnRH analog treatment with a subsequent addition of CSHs. The Dutch protocol was followed.	Measurements were taken at the start of GnRH analog treatment, and then followed up at the addition of CSH and again at age 22y (range 20.5-23.5) • BMI: Calculated as weight in kilograms divided by height in meters squared. • BP: Office SBP and DBP were measured with an electronic blood pressure monitor. • Glucose and lipid: Analyses on glucose and lipids were performed by using Roche Cobas chemistry analyzers (Modular P800 or Cobas 8000; Roche Diagnostics, Mannheim, Germany). The intraassay coefficients of variability were as follows: glucose, 1.1%; total cholesterol, 1.4%; HDL cholesterol, 0.9%; and triglycerides, 1.8%. The lower limit of quantification was 0.1 mmol/L for glucose, total cholesterol, and triglycerides and 0.08 mmol/L for HDL cholesterol. • Insulin: To measure insulin, an immunometric assay was used (Luminescence Advia Centaur; Siemens Medical Solutions Diagnostics, Malvern, PA) with an inter-assay CV of 7% and a lower limit of quantification of 10 pmol/L • HOMA-IR: The homeostatic model assessment for HOMA-IR provides a measure for insulin resistance. HOMA-IR is	**BP (mmHg)** DBP levels were increasing during treatment in both sexes. • Trans women ○ There was a non-significant increase in SBP during GnRH analog treatment alone, with the mean change (95% CI) being -3 (-8 - 2), *P* = NS ○ There was a significant increase in DBP during GnRH analog treatment alone. The mean change (95% CI) was +4 (1 to 7), *P* < .005 ○ There was a non-significant decrease in SBP between start of CSH treatment and 22 y, with a mean change (95% CI) of -3 (-8 to 2), *P* > .05 ○ There was a significant increase in DBP between start of CSH treatment and 22 y with a mean change (95% CI) of +6 (3 to 10), *P* < .001 • Trans men ○ There were non significant increases in SBP and DBP during GnRH analog treatment alone, with mean changes (95% CI) of +2 (-1 to 4), *P* > 0.05 and +1 (-1 to 3), *P = NS*, respectively ○ There were significant increases in SBP and DBP between start of CSH treatment and 22 y, with mean changes (95% CI) of +5 (1 to 9), *P* < .05 and +6 (4 to 9), *P* < .001, respectively **Glucose (mmol/L)** Trans women ○ There was a non-significant decrease in glucose during GnRH analog treatment alone, with a mean change (95% CI) of -0.1 (-0.3 to 0.1), *P* = NS ○ There was a non-significant decrease in glucose between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.1 (-0.1 to 0.2), *P* = NS • Trans men ○ There was a non-significant decrease in glucose during GnRH analog treatment alone, with a mean change (95% CI) of +0.1 (-0.1 to 0.2), *P* = NS ○ There was a non-significant decrease in glucose between start of CSH treatment and 22 y, with a mean change (95% CI) of 0.0 (-0.2 to 0.2), *P* = NS **Insulin (mU/L)** Trans women ○ There was a non-significant increase in insulin level during GnRH analog treatment alone, with a mean change (95% CI) of +0.8 (-2.5 to 4.1), *P* = NS;

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
				calculated as (the fasting glucose level in millimoles per liter/the fasting insulin level in milliunits per liter)/22.5.23 • Low-density lipoprotein (LDL) cholesterol was calculated by using the Friedewald formula.	○ There was a non-significant increase in insulin level between start of CSH treatment and 22 y, with a mean change (95% CI) of +2.7 (-1.7 to 7.1), *P* = NS. • Trans men ○ There was a non-significant increase in insulin level during GnRH analog treatment alone, with a mean change (95% CI) of +1.2 (-0.6 to 3.0), *P* = NS; ○ There was a non-significant decrease in insulin level between start of CSH treatment and 22 y, with a mean change (95% CI) of -2.1 (-3.9 to -0.3), *P* = NS. **Lipids (mmol/L)** Trans women ○ HDL cholesterol and LDL cholesterol levels did not change after the addition of estradiol ○ There was a non-significant increase in total cholesterol between start of CSH treatment and 22 y, with a mean change (95% CI) of 0.1 (-0.2 to 0.4), *P* = NS. ○ There was a significant increase in triglycerides levels between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.2 (0.0 to 0.5), *P* < .05 • Trans men ○ There was a significant increase in total cholesterol, between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.4 (0.2 to 0.6), *P* < .001 ○ There was a significant decrease in HDL cholesterol between start of CSH treatment and 22 y, with a mean change (95% CI) of -0.3 (-0.4 to -0.2), *P* < .001 ○ There was a significant increase in LDL cholesterol between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.4 (0.2 to 0.6), *P* < .001 ○ There was a significant increase in triglycerides levels between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.5 (0.3 to 0.7), *P* < .001, **HOMA-IR** Trans women ○ There was no significant change during GnRH analog treatment alone. ○ There was a non-significant increase between start of CSH treatment and 22 y, with a mean change (95% CI) of +0.7 (-0.2 to 1.5), *P* = NS • Trans men ○ There was a non-significant increase during GnRH analog treatment alone, with a mean change (95% CI) of +0.3 (-0.2 to 0.8), *P* = NS ○ There was a significant decrease between start of CSH treatment and 22 yr, with a mean change (95% CI) of -0.5 (-1.0 to -0.1), *P* < .05
Laurenzano (2021)[84] A US gender/endocrine (doesn't specify) clinic	**N = 119 TGNB individuals** • **Eligibility**: Younger than 21 years when starting T and	Average age at presentation to clinic was 16 years. Average age of starting SC-T was 16.5 years. 110 patients were trans male, 3 were nonbinary, 6 patients were classified as	Subcutaneous testosterone injections starting at 50 to 100 mg/month in two injections.	Patients were assessed before starting testosterone as a baseline,	**HDL, LDL, TC and TG (mmol/L),** mean scores • Overall:

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
[redacted] California	received T for a minimum of 6 months, assessed by mental health professional to make sure they were ready to start T and met diagnostic criteria for GD. • **Sampling method**: Patients were selected if they met criteria and were a patient of the clinic.	"other." 99 patients had no menstrual suppression before starting T, 12 used GnRH analogs and 8 used contraceptive. Average BMI was 24.		and then followed up and most recent testosterone lab check • Levels of high density lipoproteins, low density lipoproteins, total cholesterol and triglycerides were collected • Pre and post levels of hematocrit, AST and ALT were collected	○ There was a significant decrease in HDL from 50 at baseline to 43.4 at follow-up ($P < 0.001$) ○ There was no significant change in LDL with slight increase from 91.4 at baseline to 92.9 at follow-up (P = NS) ○ There was no significant change in TC from 158 at baseline to 154.6 at follow-up (P = NS) ○ There was a non-significant increase in TG from 89.6 at baseline to 100.8 at follow-up (P = NS) • Individual dosing groups ○ SC-T < 160 mg: ▪ There was a significant decrease in HDL from 50.4 at baseline to 45.6 at follow-up (P = NS) ▪ There was no significant change from baseline to follow-up of LDL: 90.4 to 93 (P = NS), TC: 161 to 155.6 (P = 0.362), or TG: 96.9 to 96.8 (P = NS) ○ SC-T 160 to 240 mg: ▪ There was a significant decrease in HDL from 50.2 at baseline to 43.5 at follow-up ($P < 0.001$) ▪ There was no significant change from baseline to follow-up of LDL: 90.4 to 91.1 (P = NS), TC: 156.2 to 151.8 (0.182) or TG: 87.6 to 97.5 (P = NS) ○ SC-T > 240 mg: ▪ There was a significant decrease in HDL from 47.6 at baseline to 39.5 at follow-up P = .016) ▪ There was no significant change from baseline to follow-up of LDL: 101.3 to 104.3 (P = NS), TC: 165.2 to 170.7 (P = NS) , or TG: 87.5 to 128.6 (P = NS) **Hematocrit, AST and ALT (U/L),** mean scores • Overall: ○ There was a significant increase in hematocrit from 39.2 at baseline to 44.1at follow-up. ($P < .001$) Mean hematocrit remained in normal range. ○ There was a non-significant increase in AST levels from 21.8 at baseline to 23 at follow-up (P = NS) ○ There was a non-significant increase in ALT levels from 20.8 at baseline to 21.4 at follow-up (P = NS) • Individual dosing groups ○ SC-T < 160 mg- ▪ There was a significant increase in hematocrit from 39.4 at baseline to 43.1 at follow-up, $P < .001$ ▪ There was a significant increase in AST from 24.4 at baseline to 20.8 at follow-up, P = .024

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					▪ There was a non-significant decrease of ALT from 20.1 at baseline to 18.4 at follow-up, *P* = NS ○ SC-T 160-240 mg: ▪ There was a significant increase in hematocrit from 39.1 to 44, *P* < .001 ▪ There was a non-significant increase in AST from 21.1 at baseline to 23.6 at follow-up, *P* = NS ▪ There was non-significant change in ALT from 21 at baseline to 21.3 at follow-up *P* = NS ○ SC-T > 240 mg: ▪ There was a significant increase in hematocrit from 40.1 at baseline to 46.5 at follow-up (*P* < .001) ▪ There was a non-significant increase in AST from 19 at baseline to 23.4 at follow-up, *P* = NS ▪ There was a significant increase in ALT from 20.3 at baseline to 30 at follow-up, *P* = .041 ○ *At all doses was a significant increase in hematocrit. AST and ALT level changes varied among groups*
Millington (2021)[89] [redacted] between July 2016 and September 2018	**N = 269** TGNB adolescents • **Eligibility**: no prior GnRH analog use, starting CSH • **Sampling method**: recruited to participate prior initiating CSH treatment • **Subset:** ○ n = 83 natal male ○ n = 186 natal female		• Estradiol (natal male) • Testosterone (natal female)	• Measurements were collected at the start of CSH therapy and then 6 months after starting therapy. • Laboratory data was collected as part of clinical care. Obesity was defined as baseline BMI more than the 95th percentile of designated sex	**Natal male (all)** • HDL-C, mean difference, 95% CI • Δ between the start of CSH and after 6 months: 11.2 (8.8) mg/dL, 95% CI (8.6 to 13.8), showing a significant increase, *P* < .001 • **Natal male (obese)** • HDL-C, mean difference, 95% CI • Δ between the start of CSH and after 6 months: 36.0 (1.0) mg/dL 95% CI (35.2 to 36.8), to 41.3 (4.0) mg/dL 95% CI (37.6-45.0), showing a non-significant increase, *P* = NS **Natal male (non-obese)** • HDL-C, mean difference, 95% CI • From 46.1 (8.80) mg/dL, 95% CI (43.8-48.4) at baseline, there was a significant increase at 6 months, *P* < .05 **Natal female (all)** • HDL-C, mean difference, 95% CI • Δ between the start of CSH and after 6 months: -7.2 (10.1) mg/dL, 95% CI (-5.3 to -9.1), showing a significant decrease; *P* < .001 **Natal female (obese)** • HDL-C, mean difference, 95% CI;

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					• Δ between the start of CSH and after 6 months: −12.1 (9.9) mg/dL, 95% CI (-16.3 to -7.9), showing a significant decline, $P < 0.05$ **Natal female (non-obese)** • HDL-C, mean difference, 95% CI • Δ between the start of CSH and after 6 months: -5.5 (9.7) mg/dL, 95% CI (-7.7 to -3.4), showing a significant decline; $P = .004$
Millington (2022)[90] Four large hospitals-[redacted], that were taking part in the Trans Youth Care United States Study	**N = 286 patients** • **Eligibility:** clinician diagnosed gender therapy with gender-affirming therapy deemed appropriate, received care at the clinic, age 8-20 and reads and understands English. Those that previously used CSH, were enrolled in the puberty blocker cohort or had severe psychiatric symptoms were excluded • **Sampling method:** patients were selected from clinic if they met inclusion criteria. • **Subset definition**: DMAB (n = 92) and DFAB (n = 194) measured at baseline and 6 mo increments	DMAB: • age- 17.3 years, • Gender ○ 51 identified as trans female ○ 36 as female, ○ 1 as gender fluid ○ 4 as non binary • CSHT ○ 77 were taking oral estrogen and ○ 12 were taking transdermal estrogen, ○ 3 were taking IM estrogen. ○ 58 used spironolactone DFAB: • age- 16.2 years, • Gender ○ 78 identified as male ○ 103 as transgender male ○ 2 as gender fluid ○ 1 as gender queer ○ 10 as non binary • CSHT ○ 189 were taking testosterone SQ, 5 were taking gel. ○ 1 used spironolactone	• **DMAB**- estrogen, average oral dose 4 mg/day, average transdermal dose 0,5 mg/day, average IM dose was 15 mg/week • **DFAB-** testosterone- average SQ dose was 40 mg/week, average transdermal dose was 40.5 mg/day	• Measurements were collected at baseline before starting CSH (B), 6 months (T1), 12 months (T2), 18 months (T3) and 24 months (T4). • Serum Creatinine was measured. • SCr was then adjusted by age and gender to calculate SCr/Q male and SCr/Q female • GFR measured in four different equations- Male CKiDU25, Female CKiCU25, Male CKD-EPI 2021, Female CKD- EPI 2021. They were measured in change from baseline • BMI (kg/m²), Height (cm) and weight (kg)	**Serum Creatinine** Participants saw change in the first six months of therapy. DFAB also saw change from 6 months to 12 months, but no other significant change was observed • DMAB ○ SCr: B-0.83, T1- 0.76 ($P < .05$), T2-0.74, T3- 0.75 T4-0.75 ○ SCr/Q male: B-1.04, T1- 0.93($P < .05$), T2-0.90, T3- 0.90 T4-0.89 ○ SCr/Q female: B-1.24, T1- 1.12 ($P < .05$), T2-1.09, T3- 1.10 T4-1.10 • DFAB ○ SCr: B-0.68, T1- 0.79 ($P < .05$ from baseline), T2-0.82 ($P < 0.05$ from 6 mo), T3-0.81 T4-0.82 ○ SCr/Q male- B-0.88, T1- 1.00 ($P < .05$), T2-1.03, T3- 0.99 T4-1.00 ○ SCr/Q female- B-1.04, T1- 1.20 ($P < .05$), T2-1.24 T3- 1.20 T4-1.21 **GFR** eGFR calculated via the CKiDU25 equation, which accounts for age-related creatinine changes, was inversely associated with changes in creatinine: rising in participants DMAB treated with estradiol by 10.3 (2.2, 22.9) mL/min/1.73 m² using the male equation and by 7.6 (1.8,18.0) mL/min/1.73 m² using the female equation over the first 6 months of treatment. • For participants DMAB, estradiol-induced decreases in serum creatinine led to an increase in eGFR after 6 months calculated via both the CKD-EPI 2021 equation for males (2.7 (−0.4, 6.9) mL/min/1.73 m²) and the equation for females(6.6 (−0.3,12.6) mL/min/1.73 m²). • For participants DFAB treated with testosterone, eGFR calculated via the CKiDU25 equation fell over 6 months using both the female (−13.5 (−22.4,−7.2) mL/min/1.73 m²) and male equations (−12.4 (−19.7,−6.5) mL/min/1.73 m²). • For participants DFAB, testosterone-induced increases in serum creatinine led to a decrease in eGFR after 6 months by both the male equation (−7.1 (−10.3,−3.8) mL/min/1.73 m²) and the female equation (−12.2 (−22.9,−5.4) mL/min/1.73 m²) • DMAB ○ Male CKiDU25: B- 104.3, ΔT1- 10.3, ΔT2- 2.3, ΔT3- 0.7, ΔT4- 3.9 ○ Female CKiCU25: B- 85.5, ΔT1- 7.6, ΔT2- 1.9, ΔT3- 0.3, ΔT4- 1.1

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ Male CKD-EPI 2021: B- 131.2, ΔT1- 2.7, ΔT2- (-0.1), ΔT3- (-0.4) ΔT4- (-0.3) ○ Female CKD-EPI 2021: B- 107.2, ΔT1- 6.6, ΔT2- (-0.1), ΔT3- (-0.4), ΔT4- (-0.3) • DFAB ○ Male CKiDU25: B- 113.5, ΔT1- (-13.5), ΔT2- (-2.2), ΔT3- (-2.9), ΔT4- 0.2 ○ Female CKiCU25: B- 96, ΔT1- (-12.4), ΔT2- (-2.4), ΔT3- 1.9, ΔT4- (-1.4) ○ Male CKD-EPI 2021: B- 139.8, ΔT1- (-7.1), ΔT2- (-2), ΔT3- 0.1, ΔT4-(-1.9) ○ Female CKD-EPI 2021: B- 130.9, ΔT1- (-12.2), ΔT2- (-3.3), ΔT3- 1.2, ΔT4- (-3.5) **BMI (kg/m²), Height (cm) and weight (kg)** For participants DFAB, BMI increased in the first 6 months of testosterone treatment (25.1 ± 6.5 kg/m² to 25.8 ± 6.2 kg/m², *P* < 0.0001), with no further changes from 6 to 12 months • Participants DMAB experienced changes in BMI later in their course of estradiol treatment, with no significant change in BMI from 0 to 6 months (23.9 ± 6.4 kg/m² to 24.0 ± 5.8 kg/m², *P* = NS), then a significant increase in BMI from 6 to 12 months (24.0 ± 5.8 kg/m² to 25.2 ± 7.2 kg/m², *P* = 0.0001). • DMAB ○ Height: B- 173.4, T1- 173.6 (*P* < .05), T2- 173.9, T3- 173.4, T4- 174.2 ○ Weight: B- 72.5, T1- 72.5, T2- 76.4 (*P* < .05 from 6 mo measurement), T3- 78.2, T4- 75.5 ○ BMI: B- 23.9, T1- 24, T2- 25.2, T3- 25.8, T4- 25.0 • DFAB ○ Height: B- 163.1, T1- 163.6 (*P* < .05), T2- 164.2, T3- 163.7, T4- 164 ○ Weight: B- 66.9, T1- 69.4 (*P* < .05), T2- 69.3, T3- 68.9, T4- 69.3 ○ BMI: B- 25.1, T1- 25.8 (*P* < .05), T2- 25.7, T3- 25.7, T4- 25.7
			DMAB: spironolactone		Spironolactone was associated with a different rate of decrease in SCr than patients just taking estradiol, resulting in significant differences in serum creatinine and SCr/Q male at the 6-month mark Baseline- SCr- 0.83, SCr/Q - 1.0 6 months- SCr- 0.78 (*P* = .011), SCr/Q- 0.95 (*P* = .02)
Olson-Kennedy (2018)[143] Center for Trans Youth Health and Development at [redacted]	**N = 101 participants**, data for 59 participants • **Eligibility:** Participants were eligible if they were between the ages of 12 and 24, had gender dysphoria, had a desire to undergo phenotypic gender transitions, were naive to cross	• Mean age 18 years (range 12 years to 23 years) • 22% had started hormones younger than 16 years.	• Transfeminine: testosterone blocking agent (spironolactone or GnRH analog) and feminizing medication (17 B estradiol). Some also have the addition of progesterone. seven youth did not use puberty blockers.	• Measurements were taken at baseline and then at a 24 month follow-up • Mean Blood Pressure, both diastolic and systolic • Mean cholesterol, HDL and Triglycerides	**Blood Pressure (mmHg)** mean (SD) • Transfeminine (n = 25) ○ No significant change in systolic BP from 122.68 mmHg (14.4) at baseline to 124.84 mmHg (12.1) at 24-month follow-up, *P* = NS ○ No significant change in diastolic BP from 71.08 mmHg (10.66), at baseline to 70.8 mmHg (7.68) at 24 month follow-up, *P* = NS

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
[redacted]	sex hormones or less than three months of previous hormone use, ability to read and comprehend English. • **Sampling method:** Patients were selected for the study if they fit the eligibility criteria. Patients from February 2011 to June 2013 were screened for participation. • **Subset:** o n = 25 transfeminine o n = 34 transmasculine		• Transmasculine- testosterone cypionate SQ, with doses ranging from 12.5 to 75 mg weekly. Two patients were on GnRH analogs.	• Mean Liver Enzyme values (AST and ALT) • Mean Potassium, glucose and hemoglobin values were collected	• Transmasculine (n = 34) o There was a mildly clinically significant increase in systolic BP from 115.62 mmHg (15.15) at baseline to 128.03 mmHg at 24 moth follow-up, *P* < .001 o There was a mildly clinically significant increase in diastolic BP from 67.15 mmHg (12.57) at baseline to 72.32 mmHg (12.57) at 24-month follow-up, *P* = .024 **Cholesterol** (mg/dL) mean (SD) • Transfeminine: (n = 23) o Showed a non-significant decrease in total cholesterol from 168.96 (41.68) at baseline to 166.13 (23.97) at 24 months, *P* = NS o Showed a significant increase in HDL from 43.83 (10.42) at baseline to 50.91 (14.34) at 24-month follow-up, *P* < .001. Values still WNL (statistically, but not clinically significant) o Showed a non-significant decrease in TG from 135.52 (83.85), at baseline to 115.96 (66.22) at 24-month follow-up, *P* = NS • Transmasculine: (n = 35) o There was no significant change in TC from 163.57 (33.42) at baseline to 164.49 (41.4) at follow-up, *P* = NS o They experienced a mild clinically significant increase in HDL cholesterol from 51.74 (11.37) at baseline to T1 = 44.49 (12.73) at follow-up, *P* = .001 o There was a significant increase in TG from 109.86 (92.43) at baseline to 144.4 (87.91) at follow-up, *P* = .044 (statistically, but not clinically significant) **Liver Enzymes-AST and ALT (U/L)** mean (SD) • Transfeminine (n = 23) o There was a significant decrease in AST levels from 72.52 (42.19) at baseline to30.83 (17.39) at follow-up, *P* < .001 (statistically, but not clinically significant) o There was a non-significant decrease in ALT levels from 30.09 (12.74) at baseline to T1 = 25.37 (11.59) at follow-up, *P* = NS • Transmasculine (n = 34 for AST, n = 34 for ALT) o There was a significant decrease in AST levels from 55.85 (33.55) at baseline to 40 (27.42) at follow-up ,*P* = .034 (statistically, but not clinically significant) o There was a significant increase in ALT levels from 22.23 (10.64) to 32.86 (16.67) at follow-up, *P* < .001 (statistically, but not clinically significant) **Other lab values-potassium (mEq/L), glucose (mg/dL) and hemoglobin(g/dL), mean (SD)** • Transfeminine (n = 23, except hemoglobin n = 22) o There was a significant increase potassium levels from 4.25 (0.31) at baseline to 4.47 (0.36) at follow-up, *P* = .04 (statistically, but not clinically significant)

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
					○ There was no significant change in glucose levels: T0 = 90.26 (11.14), T1 = 91.96 (14) *P* = NS ○ There was a significant decrease in hemoglobin levels from 15.31 (1.13) at baseline to 14.05 (1.24) at follow-up, *P* < .001 (statistically, but not clinically significant) • Transmasculine (n = 35, except hemoglobin n = 34) ○ There was a significant increase potassium levels from 4.23 (0.36) at baseline to 4.55 (0.41) at follow-up, *P* = .002 (statistically, but not clinically significant) ○ There was no significant change in glucose levels: T0 = 89.2 (17.48), T1 = 84.66 (11.39) *P* = 0.172 ○ There was a significant increase hemoglobin levels from 13.02 (0.97) at baseline to 15.50 at follow-up, *P* < .001 (statistically, but not clinically significant)
Perl (2020)[144] Israeli Pediatric Gender Dysphoria Clinic, [redacted] between 2013 and 2018	**N = 15 TGNB adolescents** • **Eligibility**: All transgender male adolescents who were treated solely with GnRH analogs for ≥ 2 months • **Sampling method**: The medical files of 48 transgender male adolescents who had sought medical attention due to GD at the clinic were reviewed	• Mean age at initiation of pubertal suppression was 14.4 ± 1.0 years. GnRH analogs were administered for a mean period of 3 ± 1 months. • All 15 transgender males had clinical and laboratory evidence of Tanner stage 4/5 puberty. • Their weight status at the initiation of GnRH analog treatment was normal (mean BMI-SDS 0.2 ± 0.9), as were their BP levels and percentiles (mean SBP 115 ±7mmHg [71 ±19 percentile] and mean DBP: 64 ±10mm Hg [56 ±26 percentile]). • Testosterone treatment was initiated in 9 of the 15 transgender male adolescents at a mean age of 15.1 ± 0.9 years. • The mean treatment period of testosterone was 4 ± 2 months	Pubertal suppression therapy consisted of a depot preparation of the GnRH analog D-Trp-6-LHRH (Decapeptyl; Ferring Pharmaceuticals Ltd., Malmö, Sweden) at a dose of 3.75mg administered by intramuscular injection every 4 weeks. Gender-affirming hormone therapy consisted of intramuscular testosterone enanthate 250 mg/mL (Testoviron Depot; Bayer Israel Ltd.) at a starting dose of 50–100 mg administered by intramuscular injection every 4 weeks.	Participants were evaluated withing 1-4 weeks of starting GnRH analogs were as a baseline, and then evaluated within 1-4 weeks of the addition of testosterone injections. • BP was measured during a clinic visit within 1–4 weeks of GnRH analogs and testosterone injections using a Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR), and converted to BP percentiles according to assigned sex at birth (females) based on reference ranges in the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. • Normal BP was defined when BP values were < 90th percentile, prehypertension was defined by either SBP and/or DBP levels ≥ 90th percentile to < 95th percentile, and hypertension was defined by either SBP and/or diastolic BP levels ≥ 95th percentile.	**Blood pressure:** (Mean percentiles) • DBP percentiles increased significantly after GnRH analog treatment (from the 56.0 ± 26.0 percentile to 74.0 ± 9.0 percentile, *P* = .019), and that increase remained significant after adjusting for the change in BMI-SDS (*P* = .047). • SBP percentiles did not change significantly, and the BP levels were within the normal range and did not meet the criteria for pediatric hypertension. • DBP percentiles decreased significantly after adding testosterone therapy (from 74.0 ± 9.0 to 56.0 ± 17), only after adjusting for the change in BMI-SDS (*P* = .033). • DBP percentiles did not differ significantly compared with baseline, after testosterone treatment. • SBP percentiles did not change significantly.
Perl (2021)[145]			Pubertal suppression: an intramuscular injection of depot-	Patients were assessed before pubertal suppression (GnRH analog	**Blood Pressure:** Mean ± SD

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Israeli Pediatric Gender Dysphoria Clinic [redacted] between 2013 and 2018	**Population: N = 19 TGNB female adolescents (AMAB)** • **Eligibility Criteria:** Files were reviewed retrospectively among TGNB female adolescent that sought medical attention due to GD at site who had been treated solely with GnRH analogs for ≥ 2 months and had BP data in file • **Sampling Method:** 86 files were reviewed at facility and then files were excluded that did not meet the study criteria • **Subset Definition:** Of the N = 19 TGNB female adolescents, n = 15 received estradiol therapy after GnRH analogs alone	• The mean age at initiation of pubertal suppression was 15.7 ± 1.6 years. • All 19 transgender females had clinical and laboratory evidence of Tanner stage 4/5 puberty. • Weight status at the initiation of GnRH analog treatment was as follows: mean BMI-SDS −0.21 ± 1.42. Three participants were underweight with BMI-SDS < −2. • Mean SBP was 116 ± 8 mm Hg (55 ± 29 percentile) with three participants having systolic pre- hypertension. • Mean DBP was 70 ± 9 mm Hg (64 ± 27 percentile), with three participants having diastolic prehypertension (one participant had both systolic and diastolic prehypertension). • Four (21%) adolescents re- ported smoking, with one having prehypertension, none reported alcohol consumption or drug abuse. • Four (21%) reported a diagnosis of anxiety, all with normal BP.	preparation GnRH analogs D-Trp-6-LHRH (Decapeptyl, Ferring Pharmaceuticals Ltd., Malmo, Sweden) at a dose of 3.75 mg was administered every 4 weeks.	treatment) and then at a Follow-up appointment after GnRH analog administration (mean period of 9 ± 6 months) • Data was reviewed for anthropometric measurements. BP was measured by a Welch Allyn Vital Signs Monitor VSM 300. Measurements were converted to BP percentiles for the assigned sex at birth (male) published by the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents	DBP percentiles did not change significantly during GnRH analog therapy (from 64 ± 27 at baseline to 62 ± 23 at follow-up, *P* = NS) • SBP percentiles did not change significantly during GnRH analog therapy (from 55 ± 29 at baseline to 52 ± 23 at follow-up, *P* = NS)
			Gender-affirming hormone therapy: consisted of oral tab beta estradiol 1 or 2 mg (Estrofem, Novo Nordisk LTD, Israel) at a starting dose of 1 mg daily for 6 months. Dose was increased to 2 mg after 6 months, and continued to be increased every 4–6 months for serum estradiol to not exceed the peak physiologic range of 367– 734 pmol/L	Patients were assessed before the addition of CSH and then at a follow-up appointment after the addition of CSH. Median treatment period 18.5 months (range 3-36 months) • Data was reviewed for anthropometric measurements. BP was measured by a Welch Allyn Vital Signs Monitor VSM 300. Measurements were converted to BP percentiles for the assigned sex at birth (male) published by the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents	**Blood Pressure:** Mean ± SD DBP percentiles showed a non-significant decrease with the addition of CSH therapy (from 59 ± 25 at baseline to 44 ± 24 at follow-up, *P* = NS) • SBP percentiles did not change significantly with the addition of CSH (from 52 ± 23 at baseline to 46 ± 26 at follow-up, *P* = NS)
Roy (2023)[146] [redacted] Colorado	**N = 15 TGNB boys** • **Eligibility**: not described • **Sampling method:** not described • **Subset definition:** of N = 15 TGNB boys, n = 7 received GnRH analog treatment	Age: average age 15.0 ± 1.0 years, range (13-16)	Testosterone treatment (subcutaneous testosterone cypionate with dose escalation over 12 months)	Metabolic analysis was performed-testosterone levels, hematocrit levels, hemoglobin A1C, total cholesterol and LDL levels were analyzed at baseline, one month and 12 months.	**Cardiometabolic parameters:** • There was a significant increase in free testosterone • There was a minor, albeit significant increase in hematocrit levels over time • There was a nonsignificant decrease in total cholesterol levels over time • There were no significant changes in Hemoglobin A1C or LDL levels

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Schagen (2016)[148] [redacted] the Netherlands) from 1998 through 2009	**N:116 TGNB adolescents** • **Eligibility**: being treated by the VU University Medical Centre's treatment protocol with sufficient background data • **Sampling method:** All eligible patients with data were included in study • **Subset:** of total group (N = 116) o n = 49 MTF o n = 67 FTM	• Median (range) age of transgender females was 13.6 (11.6-17.9) • Median (range) age of transgender males was 14.2 (11.1-18.6)	Triptorelin (GnRH analog)	• Patients were compared from baseline, at the start of GnRH analog therapy, to 1 year after starting treatment. • After 0, 3, and 6 months of treatment, and every 6 months thereafter, blood was drawn for measurements of AP, AST, ALT and Creatinine.	<u>Transgender females</u> • AP (n = 19), mean (SD) o There was a significant decrease in AP from 303 U/L (109), T1: 216 U/L (79) after the first year of treatment, *P* < .001 o Individuals with high AP levels at baseline showed the largest decrease • l-Glutamyl transferase, AST and ALT levels did not significantly change from baseline to 12 months of treatment • Creatinine (n = 28), mean (SD) o There was no significant change in levels after the first year of treatment, with a slight decrease from 70 micromol/L (12) to 66 micromol/L (13) o No creatinine levels above the upper limit of normal were detected during the first year of treatment. <u>Transgender males</u> • AP (n = 21), mean (SD) o There was a significant decrease in AP from 215 U/L (101) to 168 U/L (58) after the first year of treatment, *P* < .001 o Individuals with high AP levels at baseline showed the largest decrease • l-Glutamyl transferase, AST and ALT levels did not significantly change from baseline to 12 months of treatment • Creatinine (n = 29), mean (SD) o There was a significant decrease from 73 micromol/L (8) to 68 micromol/L (13) after the first year of treatment, *P* = .01
Stoffers (2019)[149] At a clinic between November 2010 (when the clinic first started) and August 2018 (does not mention the details of this clinic)	**N = 62 TGNB adolescents** • **Eligibility**: diagnosed with gender dysphoria who had started GnRH analog treatment and had subsequently received testosterone treatment for more than 6 months (or had had their 6-month visit, which was sometimes scheduled just before 6 months of treatment) • **Sampling method**: Individuals were assessed by mental health professionals to confirm the diagnosis of gender dysphoria to exclude psychological, medical,	• Full cohort (N = 62): All had been treated with a GnRH analog (Decapeptyl-CR; 3.75 mg every 4 weeks s.c.) for a median duration of 8 months (range 3-39) before they began testosterone treatment at a median age of 17.2 years (range 14.9-18.4) (Table I.1). • Median duration of follow-up during testosterone treatment was 12 months (range 5-33). No one discontinued testosterone therapy. • Age, median (range), at start of GnRH analogs was 16.5 (11.8-18.0) years and duration, median (range), of GnRH analog	Testosterone	• Cardiovascular outcomes (blood pressure, cholesterol, HbA1c) was examined at the start of GnRH analog therapy (G0) and during 24 months of testosterone treatment (T0, T6, T12 and T24) in TGNB youths	**Blood pressure:** • Systolic blood pressure significantly increased from 118 mmHg (114-125) to 124 mmHg (118-132) during the first 6 months of testosterone treatment (n = 47; *P* = .003), after which it did not change. • Systolic blood pressure after 6 months of testosterone was not significantly different from that before the start of GnRH analog treatment. • The diastolic blood pressure did not show any significant changes during 2 years of follow-up. **Cholesterol**: • Total cholesterol significantly decreased during the first 6 months, from 4.59 ± 0.92 mmol/L to 4.24 ± 0.92 nmol/L (n = 39; *P* = .001) but then slightly increased again and did not differ significantly from baseline after 12 and 24 months of testosterone therapy.

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
	or social problems that might interfere with treatment; and to determine if they were able to consent to treatment	therapy was 8 (3-39) months. Smoker, n (%), accounts for 10 (16%).			• HDL cholesterol significantly decreased during the first 6 months, from 1.58 ± 0.28 mmol/L to 1.33 ± 0.24 mmol/L (n = 39; *P* < .001) and remained unchanged thereafter. • LDL cholesterol and triglycerides did not change during follow-up. One individual who already had elevated LDL cholesterol levels at the start of GnRH analog therapy was diagnosed with familial hypercholesterolemia; after initiation of treatment with simvastatin, cholesterol levels normalized. **HbA1c**: • Showed no significant changes
Tack (2017)[150] The multidisciplinary child-gender team [redacted] from 2008 through October 2016	N = 27 TGNB adolescent girls (AMAB) • **Eligibility**: All trans-girls who received CA for at least 6 months from 2008 through October 2016 • **Sampling method:** Intake visits were aimed at excluding a disorder of sexual development underlying GD and at determining the pubertal (Tanner) stage by a physical examination performed by a pediatric endocrinologist. Follow-up visits were scheduled every 6 months. • Subset definition: All of participants (N = 27) had received CA and incremental doses of estrogen in a subset (n = 21) were added for at least 6 months after initiation of CA.	• Mean age at start of CA and CA + E was 16 years 6 months and 17 years 7 months, respectively. • Mean treatment duration for CA was 12 months and that for CA + E was 16 months. • For side effects at "baseline", 12/21 (57.1%) participants had breast tenderness, 6/21 (28.6%) had emotionality, 5/21 (23.8%) had changes in hunger, 3/21 (14.3%) had fatigue, 3/21 (14.3%) had flushes and 15/21 (71.4%) had decreased shaving need. B • Breast development for Tanner stages B3 was in 14/21 (66.7%) and for Tanner stages B4 was in 2/21 (9.5%) participants.	• Cyproterone acetate (CA) (50 mg/d) was started in trans-girls. • After at least 6 months, 17b-estradiol (E) was added if the adolescent was at least 16 years old and had a persistent desire to proceed with the gender change process. E doses were increased at every visit until a maximum of 2 mg was reached (0.5 mg/d at start, 0.75 mg/d after 6 months, 1 mg/d after 1 year, 1.5 mg/d after 18 months, 2 mg/d after 2 years).	• Measurements was taken at baseline-at the start of adding E to those who had already received CA • Measurements were then taken at 6- and 12-month follow-ups after taking the combination therapy. • Cardiovascular-related biochemical levels were collected (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol) • Insulin sensitivity • Hemoglobin and hematocrit	**Cholesterol** There were no significant changes in TC, HDL, LDL or HDL from baseline of adding E to CA at 6 or 12 month follow ups. ○ After 6 months of CA + E vs start of CA + E, ▪ There was a nonsignificant increase in mean triglycerides in mmol/L (SD) from 0.633 (0.117) to 0.929 (0.427), *P* = NS ▪ There was a non-significant increase in mean total cholesterol in mmol/L (SD) from 3.716 (0.682) to 3.781 (0.632), *P* = NS ▪ There was a non-significant increase in mean HDL cholesterol in mmol/L (SD) from 1.205 (0.306) to 1.225 (0.296), *P* = NS ▪ There was a non-significant decrease in mean LDL cholesterol in mmol/L (SD) from 1.851 (0.431) to 1.741 (0.505), *P* = NS ○ After 12 months of CA + E vs start of CA + E, ▪ There was a non-significant increase in mean triglycerides in mmol/L (SD) from 0.633 (0.117) to 0.821 (0.329), *P* = NS ▪ There was a non-significant mean in total cholesterol in mmol/L (SD) from 3.716 (0.682) to 3.515 (0.889), *P* = NS ▪ There was a non-significant increase in mean HDL cholesterol in mmol/L (SD) from 1.205 (0.306) to 1.269 (0.240), *P* = NS ▪ There was a non-significant increase in mean LDL cholesterol in mmol/L (SD) from 1.851 (0.431) to 2.272 (0.495), *P* = NS **Insulin** There were no significant changes were noticed in any of the parameters assessing insulin sensitivity (HbA1c, glucose levels, insulin levels, or homeostasis model assessment index) from baseline of CA +E at either the 6- or 12-month follow-up **Hemoglobin and Hematocrit** • There were no significant changes in Hemoglobin and Hematocrit levels from baseline of CA +E at either the 6- or 12-month follow-up

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

Table I.L.6. Longitudinal pre-post studies evaluating cardiovascular outcomes in TGNB patients

Study first author (publication year) and study setting	Population	Select baseline characteristics	Exposure/intervention	Outcome measures and timing	Results
Valentine (2021)[97] At a large Midwestern pediatric academic center with a multidisciplinary program serving transgender and gender-diverse youth	**N = 124 Participants** • **Eligibility** of transgender cohort: 14-21 years old and taking testosterone 2014–2018 were eligible • **Sampling method:** of transgender cohort: Transgender males (14–21 years) taking testosterone from 2014–2018 were identified (no other description about the sampling method). • **Subset definition:** ○ Out of total participants (N = 124), there was a subset of TGNB males patients receiving testosterone therapy (n = 42) and BMI-matched cisgender female adolescents (n = 82) ○ Of the TGNB male patients, n = 28 had lipid panels drawn and n = 18 had laboratories both pre- and post-treatment testosterone	Transgender males: • Mean age (range) in years = 16.6 years (14–19 years); • Majority white, with bi-/multiracial subjects being the second most common race represented; • Total cholesterol, LDL, HDL, and triglycerides, in mg/dL, at baseline were 156 ± 30, 87 ± 29, 45 (39, 59) and 90 (69, 111), respectively. • Time (range) between visits was an average of 4.9 months (0.5–17.7). • The average total follow-up time (range) was 10.8 months (2.6–25.7).	**Testosterone** cypionate dosing started at 50mg intramuscularly (IM) monthly and subsequently increased to 50–150 mg IM every other week.	**Lipid parameters:** Twenty-eight transgender males had lipid panels drawn, and 18 had laboratories both pre- and post-treatment testosterone, with an average of 15.6 months between laboratory draws.	• Total cholesterol: ○ In TGNB males who had lipid panel drawn (n = 28), mean total cholesterol ± standard deviation in mg/dL was 156 ± 30 before testosterone. The change of total cholesterol in n = 18 TGNB males between pre- and post-treatment testosterone was not statistically significant (*P* = NS). • LDL-C: ○ In TGNB males who had lipid panel drawn (n = 28), mean LDL-C ± standard deviation in mg/dL was 87 ± 29 before testosterone. The change of LDL-C in n = 18 TGNB males between pre- and post-treatment testosterone was not statistically significant (*P* = NS). • HDL: ○ In TGNB males who had lipid panel drawn (n = 28), median HDL (25, 75%ile) in mg/dL was 45 (39, 59) before testosterone. Transgender males had a significant decrease in HDL (*P* < 0.01) after testosterone exposure. • Triglycerides: ○ In TGNB males who had lipid panel drawn (n = 28), median triglycerides (25, 75%ile) in mg/dL was 90 (69, 111) before testosterone. The change of triglycerides in n = 18 TGNB males between pre- and post-treatment testosterone was not statistically significant (*P* = NS).

Table abbreviations: AP, alkaline phosphatase; CI, confidence interval; DBP, diastolic blood pressure ;DFAB, defined female at birth; DMAB, defined male at birth; GD, gender dysphoria; HDL high-density lipoproteins; ITS, interrupted time series; LDL, low-density lipoproteins; N/A, not applicable; N/R, not reported; SCr, serum creatinine; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TGNB, transgender, non-binary, or gender-diverse.

Return to TOC

PART II
LONG-TERM OUTCOMES

Return to TOC

II.1.0 INTRODUCTION

II.1.1 Objective

The University of Utah's Drug Regimen Review Center (DRRC) conducted a systematic review of the medical evidence related to the use of hormone and hormone analogs in the treatment of pediatric gender dysphoria in 2023 and 2024. The 900-page report emerging from this work was titled "Gender Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria."

Upon completion of the report, the DRRC prepared a summary of the work and a synthesis of mental health and psychosocial outcomes in pediatric patients treated with these agents; these findings were presented to a special task force charged with making recommendations to the Utah Legislature about gender-affirming care in Utah. After the presentation, many members of the task force noted that most of the primary studies reported only short-term findings, including many studies that only followed patients for 1-2 years. We suggested that this limitation may have been due to the study eligibility criteria in the primary report; we had only included studies reporting findings separately in pediatric patients. Many of these pediatric studies may have stopped following patients when they reached adulthood. We suggested that we might find more studies with longer-term outcomes if we were willing to look at studies that included mixed populations (ie, a mix of patients who started treatment as adolescents and as adults). These studies had previously been excluded.

The task force then charged the DRRC to conduct a systematic search for evidence with the expanded eligibility criteria, specifically focused on finding long-term outcomes. We defined "long-term" as studies that measured outcomes after patients had received at least 5 years of hormone and/or hormone analog treatment.

II.2.0 EVIDENCE SYNTHESIS METHODS

II.2.1 Search Strategy

Our original searches from the primary report (see Section I.3.2.2) were comprehensive enough to identify all the relevant studies despite the changed eligibility criteria. We were still looking for studies with pediatric patients; what was changed was that we were not excluding studies that also included adults. Consequently, we did not have to conduct new searches; we only had to re-screen some studies that had previously been excluded.

II.2.2 Study Eligibility Assessment

We rescreened studies that had previously been excluded because they included adult patients, a mix or pediatric and adult patients, or that had been noted as having a 'wrong population.' We also rescreened studies that had been included in the primary report's bibliography only (due to a lack of high-priority outcomes) and studies that had undergone data extraction for the primary report to ensure complete capture of all long-term outcomes.

II.2.2.1 Title/Abstract screening

All studies that met eligibility for rescreening were uploaded into Covidence, an online tool designed to support systematic review work (Covidence.org, Veritas Health Innovation, Melbourne, Australia). Studies that had been excluded at title/abstract screening were re-screened starting at title/abstract screening, and those that were excluded at full-text screening were re-screened starting at full-text screening. Title and abstract (TIAB) screening was conducted in duplicate in Covidence using the eligibility criteria given in Table I.1 of the primary report, with modifications to the population and treatment length requirement. Reviewers were instructed to assess eligibility and resolve disagreements as directed in the original screening described in Section I.3.3.1 of the primary report with the following modifications:

II.2.2.1.1 Population

The original requirement for the population was as follows:

The population of interest was pediatric patients (ie, ages < 18 years) described as having gender dysphoria/transition/diversity or being non-binary and/or transgender (ie, pediatric TGNB patients). We included studies that mixed TGNB children and adults if the studies met at least one of the following conditions:

- Findings were reported separately for minors (ie, ages < 18 years).
- The mean ages of the cohorts (or any sub-cohorts for which findings were reported separately) are < 18 years.
- The study was a long-term follow-up of patients who started treatment as minors.

For our new criteria, we included studies that included adult populations if TGNB pediatric patients were also included.

II.2.2.1.2 Length of Treatment

For this set of studies, we required study participants to have a diagnosis of gender dysphoria that was treated with hormones or hormone analogs of interest, and that had a mean or median duration of follow-up of ≥ 5 years. If the direction of inquiry was retrospective (eg, a case-control study) or cross-sectional in nature, we required study participants to have received ≥5 years of treatment before the outcomes were measured.

II.2.2.2 Full-text Screening and Tagging

All citations that were previously excluded, but deemed potentially relevant for long-term outcomes were rescreened in Covidence as previously described in Section I.3.3. of the primary report. Studies excluded at TIAB screening underwent re-screening at that stage. Those deemed potentially relevant were retrieved for full-text screening. Studies that were initially excluded at full-text screening were retrieved in full text and underwent duplicate full-text screening in Covidence. Studies that did not meet the eligibility criteria from Table I.1 of the primary report with population and length of treatment modifications were excluded at this stage and a reason for exclusion was selected.

A single study design category was assigned to each primary study using a simple taxonomy (Gehlbach's)[1] as defined in Section I.3.3.2 in the primary report. Guidelines and systematic reviews were not included in this addendum. Case reports and case series were included in the bibliography only.

II.2.2.3 Re-screening of Included Studies

Studies included in the primary report were re-screened for long-term outcomes (>5 years) and included in the data collection. Studies that were included in the bibliography only of the primary report were re-screened to be included in the bibliography of the long-term outcomes report.

II.2.3 Deliverable-specific Methods

Deliverable-specific methods, data-collection methods, and risk-of-bias assessment methods for each study design are summarized in the sections dedicated to each study type, below.

II.2.3.1 Observational Study-specific Methods

II.2.3.1.1 Final Full-text Eligibility Assessment and Tagging

Observational studies that met the new eligibility requirements were included in this review. Observational studies that did not examine high-priority outcomes of interest (listed below) were tagged for inclusion in the bibliography only. The high-priority outcomes are the same as the primary report except for the addition of mortality outcomes.

- Mental health
- Psychosocial functioning
- Body changes
- Body image
- Bone health
- Cardiovascular/metabolic risk factors
- Cancer
- Mortality

Included studies were further examined to determine the study design (ie, cohort study, case-control study, or cross-sectional study), and were categorized further according to the types of between-group comparisons made, as in the primary report, including the following:

A. Between-TGNB-group comparisons: These studies made inferential comparisons between 2 or more TGNB groups. For example, a study that compared treated TGNB participants with untreated TGNB participants (eg, comparisons between treated and untreated TGNB participants).
B. TGNB vs cisgender peer group comparisons: These studies made inferential comparisons between 1 or more TGNB groups and one or more cisgender control groups from the general population.

Some observational studies had comparisons that met more than 1 of the group comparison types listed above. If these had high-priority outcomes, these were assigned to data collection in multiple stages.

II.2.3.1.2 Data Extraction and Record Annotation

Data extraction was conducted by a team of authors as described in the primary report in Section I.3.4.5.2. Data collection included confirmation of data, extraction of details for included comparisons, risk of bias assessment and identification of any other comparisons in other categories.

II.2.3.1.3 Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was used for ROB assessment. Descriptions of this assessment are found in Section I.3.2.5.3 of the primary report.

II.2.3.2 Descriptive Study-specific Methods

II.2.3.2.1 Final Full-text Eligibility Assessment and Tagging

Descriptive studies that met the new eligibility requirements were included in this review. Descriptive studies that did not examine high-priority outcomes of interest (listed below) were tagged for inclusion in the bibliography only. The high-priority outcomes are the same as the primary report except for the addition of mortality outcomes.

- Mental health
- Psychosocial functioning
- Body changes
- Body image
- Bone health
- Cardiovascular/metabolic risk factors
- Cancer
- Mortality

Data extraction was restricted to only 2 types of descriptive studies (ie, single-arm clinical trials and longitudinal, pre-post descriptive studies). All case series, case reports, and other descriptive studies not assessing high-priority outcomes at 2 or more time points did not undergo data extraction; these were included in the bibliography only. Potentially relevant, non-English, descriptive studies were also assigned to the bibliography only.

II.2.3.2.2 Data Extraction and Record Annotation

Data extraction was conducted by a team of authors as described in the primary report in Section I.3.4.6.2. Data collection included confirmation of data, extraction of details for included comparisons, risk of bias assessment and identification of any other comparisons in other categories.

II.2.3.2.3 Risk of Bias Assessment

The National Institutes of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group was used for ROB assessment of longitudinal, pre-post descriptive studies. Descriptions of this assessment are found in Section I.3.2.6.3 of the primary report.

II.3.0 RESULTS OF EVIDENCE SYNTHESIS

II.3.1 Search and Rescreening Results

II.3.1.1 PRISMA

As shown Figure II.1, a total of 196 studies initially excluded from the primary report were rescreened during TIAB or full-text screening. Of these, 54 irrelevant citations were excluded at the TIAB screening stage. The remaining 142 previously excluded studies were examined in full text, of which 126 were excluded. Another 11 studies that had undergone data extraction in the primary report were also determined to be eligible, totaling 27 studies that met eligibility criteria for the long-term outcomes report. Of these 17 underwent data extraction for this report, and 10 citations that lacked high-priority comparisons or outcomes were included in the bibliography only.

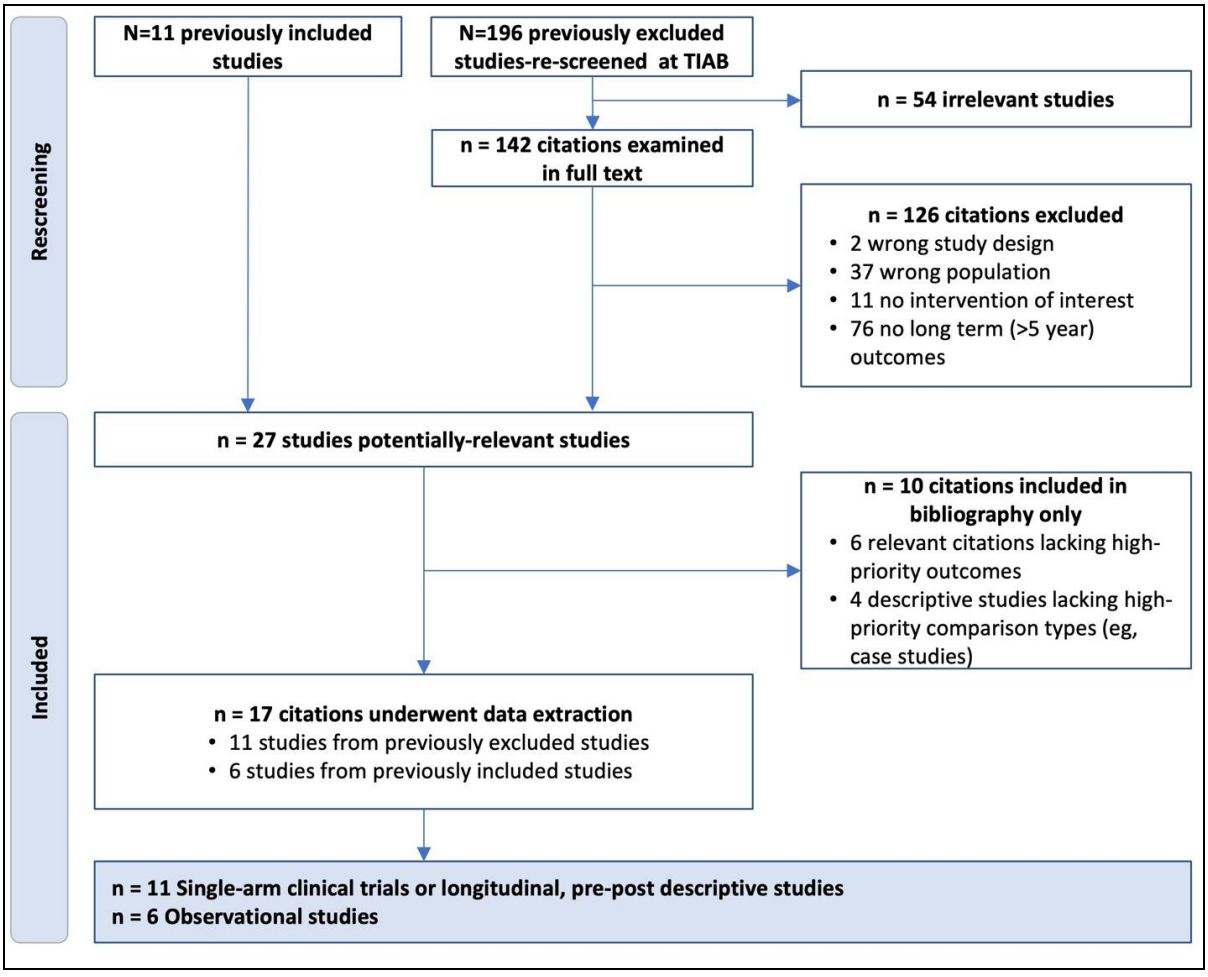


Figure II.1. PRISMA diagram

Studies that were excluded from eligibility, along with reasons for exclusion, are listed in Appendix II.A.

Return to TOC

II.3.2 Included Relevant Clinical Studies

II.3.2.1 Characteristics of Relevant Clinical Studies

The largest number of long-term studies came from the Amsterdam cohort from VU University Medical Center in Amsterdam, the Netherlands. The Amsterdam cohort is more fully described in the initial report in Section I.4.5.3. Table II.1 of this report includes a summary of the numbers of studies in each geographic location. These include a total of N=27 studies, with n=21 outside of the United States, and n=13 coming from the Netherlands. There were n=6 long-term studies conducted in the United States. Collectively, these studies included more than 10,147 subjects from Europe and the United States.

Table II.1. Summary of N=27 Relevant, Long-term Clinical Studies Conducted in Mixed Pediatric and Adult TGNB Populations

Geographic Location	Number of Studies/Publications	All Subjects	Pediatric TGNB Subjects
The Netherlands (Amsterdam, Leiden)	15	≥8263	≥812
Belgium (Ghent)	3	50	≥1
Spain (Barcelona, Las Palmas)	2	489	80
New York, US (Albany, New York City)	2	≥421	≥15
Austria (Vienna)	1	251	≥1
Massachusetts, US (Boston)	1	14	≥1
Minnesota, US (Rochester)	1	214	214
Pennsylvania, US (Philadelphia)	1	377	34
Washington DC, US	1	68	68

II.3.2.2 Risk of Bias Analyses

Tables II.2 and II.3 summarize the risk of bias (ROB) for all studies with any observational comparison that underwent data extraction using the Newcastle-Ottawa Scales for cohort studies, and an adapted version for cross-sectional studies. The ROB details are in Appendix II.B.

Table II.4 summarizes the risk of bias for all studies with a descriptive, longitudinal, pre-post comparison. The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group was used. Limitations of the tool are summarized in Section I.4.5.6 of the initial report. The ROB details are in Appendix II.C.

Table II.2. Newcastle-Ottawa Quality Assessment Scale Data for TGNB vs TGNB Cohort Observational Studies

Cohort Studies First Author (year)	Selection ☆☆☆☆ max	Comparability ☆☆ max	Outcomes ☆☆☆ max	Total Stars
Arnoldussen (2022)[2]	☆☆☆☆	☆	☆☆	7/9
Asscheman (2011)[3]	☆☆☆☆	☆	☆☆☆	8/9
de Vries (2014)[4]	☆☆☆☆	☆	☆	6/9
Martinez-Martin (2023)[5]	☆☆☆☆	☆☆	☆☆	8/9
Wiepjes (2020)[6]	☆☆☆☆	none	☆☆☆	7/9

Low risk of bias (higher quality): 7-9 stars, Fair risk of bias: 5-6 stars, High risk of bias 1-4

Selection criteria composed of questions about: Adequacy of the case definition, representativeness of the cases, selection of controls, and definition of controls; Comparability criteria composed of question about: Comparability of cohorts on the basis of design or analysis; Outcome criteria composed of questions about: Assessment of exposure, same method of ascertainment for cases and controls, and non-response rates.

Table II.3. Newcastle-Ottawa Quality Assessment Scale Data for TGNB vs TGNB or TGNB vs Peer Cross-sectional Observational Studies

Cross-sectional Studies First Author (year)	Selection ☆☆☆ max	Comparability ☆☆ max	Outcome ☆ max	Total Stars
Gomez-Gil (2012)[7]	☆☆☆	☆☆	none	5/6
Ott (2010)[8]	☆☆☆	none	☆	4/6
Wierckx (2011)[9]	☆☆	none	none	2/6
Wierckx (2012)[10]	☆☆☆	☆	none	4/6

Low risk of bias (higher quality): 5-6 stars, Fair risk of bias: 3-4 stars, High risk of bias: 1-2 stars

Selection criteria composed of questions about: Adequacy of the case definition, representativeness of the cases, selection of controls, and definition of controls; Comparability criteria composed of question about: Comparability of cohorts on the basis of design or analysis; Outcome criteria composed of questions about: Assessment of exposure, same method of ascertainment for cases and controls, and non-response rates.

Return to TOC

Table II.4. Quality Assessment of Included Pre-post Studies Using the NIH Quality Assessment Tool for Before-after Studies with No Control Group

First Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Quality (total Yes answers)
Arnoldussen (2022)[11]	Y	Y	N	Y	U	N	Y	N	Y	Y	N	N/A	6/11
Asscheman (2011)[3]	Y	Y	Y	Y	U	Y	Y	U	Y	Y	U	N/A	8/11
De Blok (2021)[12]	Y	Y	Y	Y	U	Y	Y	U	Y	Y	U	N/A	8/11
De Nie (2020)[13]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
De Vries (2014)[4]	Y	Y	U	N	U	U	Y	N	Y	Y	N	N/A	5/11
Gooren (2013)[14]	Y	Y	Y	Y	U	Y	Y	U	Y	Y	U	N/A	8/11
Gooren (2014)[15]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	U	N/A	8/11
Klink (2015)[16]	Y	Y	Y	Y	U	Y	Y	N	N	Y	N	N/A	7/11
Nota (2018)[17]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
Ott (2010)[8]	Y	Y	Y	U	U	Y	Y	N	Y	Y	N	N/A	7/11
Van der Loos (2021)[18]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N/A	8/11
Wiepjes (2020)[6]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	U	N/A	8/11

Good: Met 8+ criteria, Fair: Met 5-7 criteria, Poor: met <4 criteria.

Y=Yes, N=No, U=Unclear, N/A=not applicable, NIH= National Institutes of Health

Q1: Was the study question or objective clearly stated? Q2: Were eligibility/selection criteria for the study population prespecified and clearly described? Q3: Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest? Q4: Were all eligible participants that met the prespecified entry criteria enrolled? Q5: Was the sample size sufficiently large to provide confidence in the findings? Q6: Was the test/service/intervention clearly described and delivered consistently across the study population? Q7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants? Q8: Were the people assessing the outcomes blinded to the participants' exposures/interventions? Q9: Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis? Q10: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? Q11: Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)? Q12: If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

II.3.3 Observational Studies

A total of 7 studies were primarily observational (although some had descriptive components) and met the eligibility criteria. Of these, 6 had at least one high-priority outcome of interest, included high-priority comparisons, and reported long-term outcomes.

Return to TOC

II.3.3.1 TGNB Patients Compared to Other TGNB Subgroups

Overall, we identified 8 studies with observational comparisons (4 observational studies and 4 descriptive studies with observational comparisons) between TGNB groups containing pediatrics and other TGNB subgroups with at least one outcomes of interest (Table II.5; see Appendix II.E). Of the 4 observational studies, 2 also had longitudinal, pre-post descriptive comparisons of interest.

The outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 2
- Psychosocial functioning: 4
- Body changes: 0
- Body image: 1
- Bone health: 0
- Cardiovascular risk factors: 2
- Cancer: 0
- Mortality: 2

II.3.3.2 TGNB Patients Compared to Cisgender Peers

We identified 1 observational study with comparisons between TGNB cohorts containing youth and cisgender peer groups with at least one outcome of interest (see Table II.4 and Appendix II.F) Only the following outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 1
- Psychosocial functioning: 1

II.3.3.3 Summary of Outcomes of Observational Studies

Table II.5 contains all observational studies that underwent data extraction and Table II.6 contains all descriptive studies that had observational comparisons. Evidence tables for TGNB vs TGNB comparisons are found in Appendix II.E and TGNB vs Peer comparisons are found in Appendix II.F. Some observational studies also have pre-post comparisons and have data included in Appendix II.G.

There were only a few studies in each outcome, so it is difficult for generalizations to be made. The following is a summary of the outcomes found within the studies divided by comparison type. More details are found in the evidence tables (Appendix II.E and F).

Table II.5. Comparison Types Reported in Observational Studies that Underwent Full Data Extraction

Author (year)	Description	TGNB/TGNB Appendix II.E	TGNB/Peer Appendix II.F	Pre-post Appendix II.G
Arnoldussen (2022)[2]	A Dutch cohort study that examines changes in IQ and educational achievement after puberty suppression with GnRH agonists and GAHT in TGNB adolescents from a gender specialty clinic.	X		
de Vries (2014)[4]	A Dutch cohort study examining psychosocial functioning after GnRH analogs, cross-sex hormones, and surgery among TGNB adolescents. Also reports within-group comparisons vs baseline of psychosocial functioning.	X		X
Gomez-Gil (2012)[7]	Observational study comparing symptoms of current social distress, anxiety, and depression between a mixed population of adolescent and adult hormone treated TGNB vs untreated TGNB.	X		
Martinez-Martin (2023)[5]	A Spanish cohort study comparing blood pressure outcomes in N=302 young transgender patients receiving different hormone therapies, including treatment groups with mean ages <18 years.	X		
Van der Loos (2021)[18]	A Dutch observational study comparing bone outcomes in N=322 TGNB adolescents compared to cisgender controls and a pre-post descriptive study reporting on bone changes over time			X
Wierckx (2011)[9]	Observational cohort study examining quality of life, sexual health, and satisfaction of surgical results among transgender men after GAS who had started CSHT as an adolescent or adult with QOL scores compared to a Dutch sample population. Also, a longitudinal, descriptive pre-post study comparing sexual functioning before and after hormone therapy and GAS.		X	

Abbreviations: CSHT, cross-sex hormone therapy; GAHT, gender-affirming hormone therapy; GAS, gender-affirming surgery; GnRH, gonadotropin-releasing hormone; IQ, intelligence quotient; QOL, quality of life; TGNB, transgender, non-binary, or other gender-diverse person

Return to TOC

Table II.6. Comparison Types Reported in Descriptive Studies that Underwent Full Data Extraction

Author (year)	Description	TGNB/TGNB Appendix II.E	TGNB/Peer Appendix II.F	Pre-post Appendix II.G
Arnoldussen (2022)[11]	A longitudinal, pre-post descriptive study that examines changes in psychosocial outcomes in TGNB adolescents before (while on hormonal treatments only) vs after gender-affirming surgery.			X
Asscheman (2011)[3]	Longitudinal, retrospective, descriptive study examining long-term mortality rates in a mixed population of TGNB adolescents and adults; comparisons were made to a reference population. This was also a cohort study comparing mortality risks in MTF patients receiving different estrogen compounds.	X		X
De Blok (2021)[12]	Longitudinal, retrospective, pre-post descriptive study examining long-term mortality rates over time in a mixed population of hormone treated TGNB adolescents and adults; comparisons were made to a reference population of both natal and chosen gender.			X
De Nie (2020)[13]	Longitudinal, retrospective, pre-post descriptive study examining long-term mortality rates over time in a mixed population of hormone treated TGNB adolescents and adults; comparisons were made to a reference population of both natal and chosen gender.			X
Gooren (2013)[14]	Longitudinal, retrospective, pre-post descriptive study examining the incidence of breast cancer in a TGNB population who received CSHT as an adolescent and/or an adult as part of their treatment; incidence rate was compared to the expected incidence for the Dutch population.			X
Gooren (2014)[15]	Longitudinal, retrospective, pre-post descriptive study examining the incidence of prostate cancer in transgender women who received antiandrogens and estrogens followed by a bilateral orchiectomy as an adolescent and/or an adult as part of their treatment.			X
Klink (2015)[16]	A Dutch pre-post descriptive study examining patient characteristics and bone outcomes over time in N=34 GnRH analogs and CSHT-treated adolescents with GD			X

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GAS, gender-affirming surgery; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; QOL, quality of life; TGNB, transgender, non-binary, or other gender-diverse person; VTE, venous thromboembolism

Return to TOC

Table II.6. Comparison Types Reported in Descriptive Studies that Underwent Full Data Extraction

Author (year)	Description	TGNB/TGNB Appendix II.E	TGNB/Peer Appendix II.F	Pre-post Appendix II.G
Nota (2018)[17]	Longitudinal, retrospective pre-post study examining the occurrence of benign brain tumors in a mixed population of adolescent and adult TGNB patients who received CSHT. A standardized incidence ratio was calculated using incidence data of general Dutch or European reference populations.			X
Ott (2010)[8]	Longitudinal, retrospective, pre-post study examining the incidence of thrombophilia and VTE in a mixed pediatric and adult TGNB population using CSHT, as well as a cohort study comparing MTF and FTM TGNB participants, and a comparison of incidence of VTE to reference population.	X		X
Wiepjes (2020)[6]	Longitudinal, retrospective, pre-post study examining trends in suicide death risk in a mixed pediatric and adult TGNB population. Incidence compared to a reference Dutch population.	X		X
Wierckx (2012)[10]	Descriptive study examining the reproductive wishes of transgender men following CHST and GAS as an adolescent and/or adult, as well as a cohort study comparing transgender men with and without children and their quality of life.	X		

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GAS, gender-affirming surgery; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; QOL, quality of life; TGNB, transgender, non-binary, or other gender-diverse person; VTE, venous thromboembolism

Return to TOC

II.3.3.3.1 Transgender Men versus Transgender Women

- Over time, treated transgender men showed reduced anger and anxiety, whereas treated transgender women were more stable. There was not a significant effect between sex on depression scores
- Over time, there was no significant difference in psychological functioning between treated transgender men and women
- Treated transgender women reported more satisfaction over time with primary sex characteristics than treated transgender men and a continuous improvement in satisfaction with secondary and neutral sex characteristics.
- A mixed group of treated and untreated transgender women had a higher overall suicide death risk than transgender men
- In transgender women, suicide death rates decreased slightly over time, while there was no significant change in suicide death rates of transgender men over time.
- There was no significant difference in IQ levels or educational achievement after gender affirming treatment.

II.3.3.3.2 TGNB versus Cisgender Peers

- In mental and physical health measures, compared to cisgender men, transgender men had significantly lower vitality and mental health scores and comparable physical functioning, physical role, bodily pain, general health, social functioning, and emotional role scores.
- In mental and physical health measures, compared to cisgender women, transgender men had significantly higher physical functioning scores and comparable physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health scores.

II.3.3.3.3 Hormonally Treated versus Untreated TGNB Cohorts

- Treated TGNB participants had significantly lower anxiety, depression, and social distress scores than untreated TGNB participants

II.3.3.3.4 Differences in Treatments

- Spironolactone use in transgender women was shown to have marginally protective effect on HTN risk compared to LHRH analogs, which did not. Compared to LHRH analog, spironolactone caused more weight change, and less SBP change, but similar effects on glucose, LDL, and triglyceride changes.
- Significantly more aPC-resistant than non aPC-resistant transgender women reported former self-administration of cyproterone acetate compared to those who had not.
- Current and continuous use of ethinyl estradiol was not significantly associated with an increase in the risk of all-cause mortality but was significantly associated with cardiovascular mortality.

II.3.3.3.5 Other TGNB versus TGNB Comparisons

- In mental and physical health measures, compared to transgender men without children, transgender men with children had had significantly higher mental health and vitality scores and

Return to TOC

comparable bodily pain, general health, social role, emotional role, physical functioning, and physical role scores.

- Compared to TGNB individuals referred to a gender identity clinic as an adult, TGNB individuals referred before the age of 18 had a lower suicide risk.

II.3.4 Descriptive Studies

A total of 20 studies were primarily descriptive (although some had observational components) and met the eligibility criteria, including 4 studies with lacking high priority-comparison types and 5 studies that lacked any high-priority outcomes of interest (these studies are in the bibliography only, Appendix II.D) There were 11 descriptive studies that had at least one high-priority outcome of interest, made high-priority group comparisons and contained study data for long-term outcomes (followed the subjects for ≥ 5 years, or made comparisons of subjects who had been on hormone or hormone blocking therapy for ≥ 5 years.)

With the descriptive studies described in below sections, 3 studies had an observational comparison.

II.3.4.1 Descriptive Study Outcomes

Overall, we identified 12 studies (11 descriptive studies, and 1 observational study with a pre-post comparison) with descriptive long-term (≥ 5 years) comparisons between TGNB groups containing pediatrics with at least one outcomes of interest. (see Table II.6 and Appendix II.G). Of the 10 descriptive studies, 4 had observational comparisons of interest. Their findings are in Appendix II.E.

The outcomes of interest were reported in the following number of studies (note that more than 1 outcome of interest may have been reported in a single study):

- Mental health: 1
- Psychosocial functioning: 2
- Body changes: 1
- Body image: 1
- Bone health: 1
- Cardiovascular risk factors: 1
- Cancer: 4
- Mortality: 3

II.3.4.2 Summary of Outcomes for Descriptive Studies

Table II.6 contains all descriptive studies that underwent data extraction, and Table II.5 contains all observational studies that had descriptive comparisons. Evidence tables for Pre-post comparisons are found in Appendix II.G. Some descriptive studies also have observational comparisons and have data included in Appendix II.E.

There were only a few studies in each outcome, so no generalizations can be made. The following is a summary of the outcomes found within the studies divided by outcome type. More details are found in the evidence tables (Appendix II.G)

II.3.4.2.1 Mental Health and Psychosocial Functioning

- With treatment, over time, there were non-significant decreases in depression, anger, and anxiety score
- With treatment, over time, there were significant increases in psychological functioning scores
- With treatment, over time, there were significant decreases in behavior and emotional problem scores, and significant increases in global self worth.

II.3.4.2.2 Cardiovascular, Bone Health and Body Change Outcomes

- There were 0 incidences of venous thrombosis, even in patients with thrombophilic defects
- In transgender women, there was a significant increase in LS aBMD from start of GnRH analogs to age 22, but the corresponding z-score had significantly declined from the start of treatment. LS and FN BMAD and FN a BMD showed no significant change
- In transgender men, there was no significant change in LS BMAD and their corresponding z-score or absolute aBMD. There was also no significant change in FN BMAD and its corresponding z-score or aBMD and its corresponding z-score. The only significant change was a decrease in the LS aBMD z-score
- There were significant changes in subperiosteal width and endocortical diameter in all adolescent groups with hormone blocking and then cross-sex hormone treatment.

II.3.4.2.3 Body Image Outcomes

- With treatment, over time, there was a significant improvement in gender dysphoria and physical appearance scores
- There was a significant decrease in body dissatisfaction of primary and secondary sex characteristics, but no significant change of neutral body characteristics.

II.3.4.2.4 Cancer

II.3.4.2.4.1 Transgender Women

- Transgender women's incidence of breast cancer was close to the expected incidence for cisgender men, and much lower than the expected incidence in cisgender women
- There was a 5-fold decrease in prostate cancer risk in transgender women using hormone treatment compared to Dutch cisgender men. The incidence of prostate cancer in transgender women was lower than the incidence rate found in US men.
- Transgender women showed significantly more cases of meningiomas than could be expected based on the incidence rate of European (French) cisgender female and male populations. Also, more prolactinomas were identified in transwomen than in Dutch cisgender female and male populations. Expected incidence of benign brain tumors occurred in all other tumor types.

II.3.4.2.4.2 Transgender Men

- Transgender men showed significantly more somatotropinomas, as they occur very rarely, so the 2 cases were significantly higher than expected. Expected incidence of benign brain tumors occurred in all other tumor types.

- Transgender men had a lower incidence of breast cancer compared to cisgender women, in the same range as the incidence expected for cisgender men

II.3.4.2.5 Mortality

- When compared with the adjusted expected mortality in the general population, transgender women had a significantly increased mortality.
- When compared with the adjusted expected mortality in the general population, transgender men had increased mortality-with one study showing a significant increase, and one a nonsignificant increase.
- The mean number of suicides was higher in the transgender population (mixed treated and untreated) compared with the Dutch population in the same time frame. Transgender women had a higher rate of suicide compared to transgender men.

II.4.0 CONCLUSIONS

We found N=25 primary clinical studies reporting on the patient-level experience of at least N=10,147 GD patients Europe and the United States. These studies report data for TGNB patients who have at least 5 years of hormonal and/or hormone blocking exposure when outcomes were measured. Studies included TGNB populations that had started hormonal therapy as an adolescent, and included adult populations as long as TGNB pediatric patients were included. We included studies where it couldn't be ruled out that some of the population started hormonal or hormone blocking therapy as a pediatric patient. There may be other studies that report on long-term outcomes where the length and start age of treatment was ambiguous or not reported. In continuing with our previous extraction, we prioritized studies using high-priority comparisons and outcomes. Reasoning for this choice is described in the primary report in Section I.6.0. Due to this, we extracted data from N=15 studies for the following comparison and outcome types:

- High-priority comparison types: Between TGNB-group; TGNB versus cisgender peer group; and TGNB within-group, before-after (pre-post) comparisons
- High-priority outcomes: Mental health and psychosocial changes; body changes; body image; bone health; cardiovascular risk factors and metabolic changes; cancer; and mortality.

ROB analysis is provided for each study based on study and comparison type. Evidence tables provide summarizing safety and efficacy findings. Because of the long-term nature of these studies, we were able to add data for cancer and mortality outcomes for the TGNB population. Findings were varied, with many using the Amsterdam cohort to collect retrospective data. Overall, there were positive mental health and psychosocial functioning outcomes. While gender affirming treatment showed a possibly protective effect in prostate cancer in transgender men and breast cancer in transgender women, there was an increase in some specific types of benign brain tumors. There were increased mortality risks in both transgender men and women treated with hormonal therapy, but more so in transgender women. Increase risk of mortality was consistently due to increase in suicide, non-natural causes, and HIV/AIDS. Patients that were seen at the gender clinic before the age of 18 had a lower risk of suicide compared to those referred as an adult. The studies that addressed mortality included thousands of transgender individuals.

II.5.0 LIMITATIONS

- We performed no formal synthesis. Conclusions are those of DRRC authors who reviewed the individual studies.
- Our search consisted of re-screening studies that were initially excluded for adult population, mixed/peds adult populations and wrong population. It is possible there were some studies that could have been missed or not tagged correctly.
- Because we did not do an additional search in studies primarily for adult populations, it is possible that there are more adult studies that included patients that started hormone therapy as an adolescent where the start timeframe of treatment was not sufficiently described.
- Data extraction was not performed in duplicate; but a pharmacist author double-checked all extracted data performed by other authors.
- We would have liked to extract data from clinical case studies and other descriptive studies. However, due to time constraints, the best we can do is provide those studies in the bibliography.

PART II REFERENCES CITED

1. Gehlbach SH. *Interpreting the Medical Literature*. 5th ed., McGraw-Hill, Medical Pub. Division; 2006:293.

2. Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry*. 2022;27(4):1069-1076. doi:10.1177/13591045221091652 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35638479

3. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;164(4):635-642. doi:10.1530/EJE-10-1038 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21266549

4. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25201798

5. Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. *Hypertens Res*. 2023;46(1):219-225. doi:10.1038/s41440-022-01067-z Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36229533

6. Wiepjes CM, den Heijer M, Bremmer MA, et al. Trends in suicide death risk in transgender people: results from the Amsterdam Cohort of Gender Dysphoria study (1972-2017). *Acta Psychiatr Scand*. 2020;141(6):486-491. doi:10.1111/acps.13164 https://www.ncbi.nlm.nih.gov/pubmed/32072611

7. Gomez-Gil E, Zubiaurre-Elorza L, Esteva I, et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;37(5):662-670. doi:10.1016/j.psyneuen.2011.08.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21937168

8. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267-1272. doi:10.1016/j.fertnstert.2008.12.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19200981

9. Wierckx K, Van Caenegem E, Elaut E, et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;8(12):3379-3388. doi:10.1111/j.1743-6109.2011.02348.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21699661

10. Wierckx K, Van Caenegem E, Pennings G, et al. Reproductive wish in transsexual men. *Hum Reprod*. 2012;27(2):483-487. doi:10.1093/humrep/der406 Accessed September 15, 2023. Available at https://watermark.silverchair.com/der406.pdf

Return to TOC

11. Arnoldussen M, van der Miesen AIR, Elzinga WS, et al. Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT health*. 2022;9(4):238-246. doi:10.1089/lgbt.2020.0494 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/pdf/10.1089/lgbt.2020.0494?download=true

12. de Blok CJ, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol*. 2021;9(10):663-670. doi:10.1016/S2213-8587(21)00185-6 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34481559

13. de Nie I, de Blok CJM, van der Sluis TM, et al. Prostate Cancer Incidence under Androgen Deprivation: Nationwide Cohort Study in Trans Women Receiving Hormone Treatment. *J Clin Endocrinol Metab*. 2020;105(9):e3293-3299. doi:10.1210/clinem/dgaa412 https://www.ncbi.nlm.nih.gov/pubmed/32594155

14. Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *J Sex Med*. 2013;10(12):3129-3134. doi:10.1111/jsm.12319 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24010586

15. Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014;46(10):1156-1160. doi:10.1111/and.12208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24329588

16. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;100(2):E270-275. doi:10.1210/jc.2014-2439 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25427144

17. Nota NM, Wiepjes CM, de Blok CJM, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. *Brain*. 2018;141(7):2047-2054. doi:10.1093/brain/awy108 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29688280

18. van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *J Bone Miner Res*. 2021;36(5):931-941. doi:10.1002/jbmr.4262 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33507568

19. de Nie I, Meisner A, Kostelijk EH, et al. Impaired semen quality in trans women: prevalence and determinants. *Human reproduction (Oxford, England)*. 2020;35(7):1529-1536. doi:10.1093/humrep/deaa133 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32613241

20. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *J Sex Med*. 2018;15(4):582-590.

doi:10.1016/j.jsxm.2018.01.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463477

21. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055-1068. doi:10.1016/s0895-4356(98)00097-3 https://www.ncbi.nlm.nih.gov/pubmed/9817123

22. Langlois NJ, Wells PS. Risk of venous thromboembolism in relatives of symptomatic probands with thrombophilia: a systematic review. *Thromb Haemost*. 2003;90(1):17-26. https://www.ncbi.nlm.nih.gov/pubmed/12876621

APPENDIX II.A: STUDIES EXCLUDED AT FULL-TEXT SCREENING, BY CRITERION

Studies Included in Part I but without Long-term Outcomes

Abu-Ghname A, Grome L, Raj S, Axelrad ME, Chapman SG. Health Care Services Utilization by Transgender Patients in a Medicaid Managed Program. *J Health Care Poor Underserved*. 2021;32(1):435-448. doi:10.1353/hpu.2021.0033 Accessed September 15, 2023. Available at https://muse.jhu.edu/article/783119

Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol*. 2020;2020(1):8. doi:10.1186/s13633-020-00078-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32368216

Adeleye AJ, Stark BA, Jalalian L, Mok-Lin E, Smith JF. Evidence of Spermatogenesis in the Presence of Hypothalamic Suppression and Low Testosterone in an Adolescent Transgender Female: A Case Report. *Transgender Health*. 2023;8(1):104-107. doi:10.1089/trgh.2021.0034 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0034

Akgül S, Bonny AE, Ford N, Holland-Hall C, Chelvakumar G. Experiences of Gender Minority Youth With the Intrauterine System. *J Adolesc Health*. 2019;65(1):32-38. doi:10.1016/j.jadohealth.2018.11.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691940

Akgül S, Tuzun Z, Pehlivanturk Kizilkan M, Ozon ZA. Menstrual Suppression in Gender Minority Youth. *J Clin Res Pediatr Endocrinol*. 2022;14(4):463-468. doi:10.4274/jcrpe.galenos.2021.2020.0283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34044500

Alaniz VI, Sheeder JL, Whitmore GT, et al. Menstrual Suppression in Adolescent and Young Adult Transgender Males. *J Pediatr Adolesc Gynecol*. 2023;36(2):116-121. doi:10.1016/j.jpag.2022.10.007 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2021591277&from=export

Alegria CA. Gender nonconforming and transgender children/youth: Family, community, and implications for practice. *J Am Assoc Nurse Pract*. 2016;28(10):521-527. doi:10.1002/2327-6924.12363 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27031444

Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. *Clinical Practice in Pediatric Psychology*. 2019;7(3):302-311. doi:10.1037/cpp0000288 Accessed September 15, 2023. Available at https://psycnet.apa.org/record/2019-52280-009

Alvares LAM, Santos MR, Souza FR, et al. Cardiopulmonary capacity and muscle strength in transgender women on long-term gender-affirming hormone therapy: a cross-sectional study. *Br J Sports*

Med. 2022;56(22):1292-1298. doi:10.1136/bjsports-2021-105400 Accessed September 15, 2023. Available at https://bjsm.bmj.com/content/bjsports/56/22/1292.full.pdf

American College of Obstetricians, Gynecologists' Committee on Clinical Consensus-Gynecology. General Approaches to Medical Management of Menstrual Suppression: ACOG Clinical Consensus No. 3. *Obstet Gynecol*. 2022;140(3):528-541. doi:10.1097/AOG.0000000000004899 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36356248

Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? *Eur Child Adolesc Psychiatry*. 2020;29(6):803-811. doi:10.1007/s00787-019-01394-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305255/pdf/787_2019_Article_1394.pdf

Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. *J Adolesc Health*. 2019;65(6):815-817. doi:10.1016/j.jadohealth.2019.06.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31500946

Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. *J Endocr Soc*. 2021;5(4):bvab011. doi:10.1210/jendso/bvab011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644622

Baram S, Myers SA, Yee S, Librach CL. Fertility preservation for transgender adolescents and young adults: a systematic review. *Hum Reprod Update*. 2019;25(6):694-716. doi:10.1093/humupd/dmz026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31633751

Barnard EP, Dhar CP, Rothenberg SS, et al. Fertility Preservation Outcomes in Adolescent and Young Adult Feminizing Transgender Patients. *Pediatrics*. 2019;144(3)doi:10.1542/peds.2018-3943 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31383814

Barthel EM, Werny DM, Hayden LL, Salehi P. Gender Affirming Hormone Replacement for the Adolescent and Young Adult Cancer Survivor with Hypogonadism. *J Adolesc Young Adult Oncol*. 2020;9(1):128-131. doi:10.1089/jayao.2019.0070 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31580768

Bauer GR, Pacaud D, Couch R, et al. Transgender Youth Referred to Clinics for Gender-Affirming Medical Care in Canada. *Pediatrics*. 2021;148(5)doi:10.1542/peds.2020-047266 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34620727

Becker I, Auer M, Barkmann C, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. *Arch Sex Behav*. 2018;47(8):2335-2347. doi:10.1007/s10508-018-1278-4 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30088234

Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity

Service. *Eur Child Adolesc Psychiatry*. 2021;30(11):1755-1767. doi:10.1007/s00787-020-01640-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32990772

Beking T, Burke SM, Geuze RH, et al. Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. *Psychoneuroendocrinology*. 2020;111:104461. doi:10.1016/j.psyneuen.2019.104461 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31630051

Bentsianov S, Gordon L, Goldman A, Jacobs A, Steever J. Use of Copper Intrauterine Device in Transgender Male Adolescents. *Contraception*. 2018;98(1):74-75. doi:10.1016/j.contraception.2018.02.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29490287

Biggs M. Gender Dysphoria and Psychological Functioning in Adolescents Treated with GnRHa: Comparing Dutch and English Prospective Studies. *Arch Sex Behav*. 2020;49(7):2231-2236. doi:10.1007/s10508-020-01764-1 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32594279

Bonifacio JH, Maser C, Stadelman K, Palmert M. Management of gender dysphoria in adolescents in primary care. *CMAJ*. 2019;191(3):E69-E75. doi:10.1503/cmaj.180672 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30665976

Boogers LS, Wiepjes CM, Klink DT, et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. *J Clin Endocrinol Metab*. 2022;107(9):e3805-e3815. doi:10.1210/clinem/dgac349 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35666195

Boris JR, McClain ZBR, Bernadzikowski T. Clinical Course of Transgender Adolescents with Complicated Postural Orthostatic Tachycardia Syndrome Undergoing Hormonal Therapy in Gender Transition: A Case Series. *Transgend Health*. 2019;4(1):331-334. doi:10.1089/trgh.2019.0041 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31754630

Brik T, Vrouenraets L, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of Fertility Preservation Among a Cohort of Transgirls in the Netherlands. *J Adolesc Health*. 2019;64(5):589-593. doi:10.1016/j.jadohealth.2018.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30691936

Burke SM, Bakker J. The Role of Pubertal Hormones in the Development of Gender Identity: fMRI Studies. In: Bourguignon J-P, Carel J-C, Christen Y, eds. *Research and Perspectives in Endocrine Interactions*. Springer Cham; 2015:29-43:chap 3. Accessed May 17, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L601349832&from=export

Burke SM, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Klink DT, Bakker J. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. *J Psychiatry Neurosci*. 2016;41(6):395-404. doi:10.1503/jpn.150147 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27070350

Burke SM, van Heesewijk JO, Menks WM, et al. Postnatal Effects of Sex Hormones on Click-Evoked Otoacoustic Emissions: A Study of Adolescents with Gender Dysphoria. *Arch Sex Behav*.

2020;49(2):455-465. doi:10.1007/s10508-020-01652-8 Accessed September 15, 2023. Available at https://orbi.uliege.be/bitstream/2268/259356/1/BurkeArchSexBehav%202020.pdf

Butler G, Adu-Gyamfi K, Clarkson K, et al. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child*. 2022;107(11):1018-1022. doi:10.1136/archdischild-2022-324302 Accessed September 15, 2023. Available at https://adc.bmj.com/content/107/11/1018

Byne W, Bradley SJ, Coleman E, et al. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav*. 2012;41(4):759-796. doi:10.1007/s10508-012-9975-x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22736225

Campos-Munoz L, Lopez-De Lara D, Rodriguez-Rojo ML, Conde-Taboada A, Lopez-Bran E. Transgender adolescents and acne: A cases series. *Pediatr Dermatol*. 2018;35(3):e155-e158. doi:10.1111/pde.13448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29575091

Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. *Transgend Health*. 2020;5(3):196-200. doi:10.1089/trgh.2019.0077 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644311

Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS One*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33529227

Cesur E, Yuksel S, Basar K, Kaptan S. Clinical Follow-up of Two Adolescents Diagnosed with Gender Dysphoria. *Turk Psikiyatri Derg*. 2022;33(3):214-219. doi:10.5080/u26795 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36148573

Chen D, Abrams M, Clark L, et al. Psychosocial Characteristics of Transgender Youth Seeking Gender-Affirming Medical Treatment: Baseline Findings From the Trans Youth Care Study. *J Adolesc Health*. 2021;68(6):1104-1111. doi:10.1016/j.jadohealth.2020.07.033 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32839079

Chen D, Bernardi LA, Pavone ME, Feinberg EC, Moravek MB. Oocyte cryopreservation among transmasculine youth: a case series. *J Assist Reprod Genet*. 2018;35(11):2057-2061. doi:10.1007/s10815-018-1292-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30136015

Chen D, Berona J, Chan YM, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *N Engl J Med*. 2023;388(3):240-250. doi:10.1056/NEJMoa2206297 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36652355

Chen D, Matson M, Macapagal K, et al. Attitudes Toward Fertility and Reproductive Health Among Transgender and Gender-Nonconforming Adolescents. *J Adolesc Health*. 2018;63(1):62-68. doi:10.1016/j.jadohealth.2017.11.306 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29503031

Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. *J Adolesc Health*. 2017;61(1):120-123. doi:10.1016/j.jadohealth.2017.01.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28363716

Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. *Pediatrics*. 2018;141(4)doi:10.1542/peds.2017-3742 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29514975

Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of Adolescents Referred to a Gender Clinic: Are Youth Seen Now Different from Those in Initial Reports? *Horm Res Paediatr*. 2018;89(6):434-441. doi:10.1159/000489608 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29920505

Chiniara LN, Viner C, Palmert M, Bonifacio H. Perspectives on fertility preservation and parenthood among transgender youth and their parents. *Arch Dis Child*. 2019;104(8):739-744. doi:10.1136/archdischild-2018-316080 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30894340

Chou K, Johnson B. Working with Transgender Adolescents: Essential Guidelines and Applications. *Adolesc Psychiatry*. 2022;12(3):159-173. doi:10.2174/2210676611666210831161929 Accessed September 15, 2023. Available at https://www.eurekaselect.com/article/117582

Chu L, Gold S, Harris C, et al. Incidence and Factors Associated With Acne in Transgender Adolescents on Testosterone: A Retrospective Cohort Study. *Endocr Pract*. 2023;29(5):353-355. doi:10.1016/j.eprac.2023.02.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36889581

Churcher Clarke A, Spiliadis A. 'Taking the lid off the box': The value of extended clinical assessment for adolescents presenting with gender identity difficulties. *Clin Child Psychol Psychiatry*. 2019;24(2):338-352. doi:10.1177/1359104518825288 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L627311211&from=export

Clark BA, Marshall SK, Saewyc EM. Hormone therapy decision-making processes: Transgender youth and parents. *J Adolesc*. 2020;79:136-147. doi:10.1016/j.adolescence.2019.12.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31972534

Clark BA, Virani A, Marshall SK, Saewyc EM. Conditions for shared decision making in the care of transgender youth in Canada. *Health Promot Int*. 2021;36(2):570-580. doi:10.1093/heapro/daaa043 Accessed September 15, 2023. Available at https://academic.oup.com/heapro/article-abstract/36/2/570/5864519?redirectedFrom=fulltext

Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health*. 2022;23(Suppl 1):S1-S259. doi:10.1080/26895269.2022.2100644 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36238954

Conard LE. Supporting and caring for transgender and gender nonconforming youth in the urology practice. *J Pediatr Urol*. 2017;13(3):300-304. doi:10.1016/j.jpurol.2017.02.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28645619

Condat A, Bekhaled F, Mendes N, Lagrange C, Mathivon L, Cohen D. Gender dysphoria in children and adolescents: French history and clinical observations. *Neuropsychiatr Enfance Adolesc*. 2016;64(1):7-15. doi:10.1016/j.neurenf.2015.06.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L605213392&from=export

Conn BM, Chen D, Olson-Kennedy J, et al. High Internalized Transphobia and Low Gender Identity Pride Are Associated With Depression Symptoms Among Transgender and Gender-Diverse Youth. *J Adolesc Health*. 2023;72(6):877-884. doi:10.1016/j.jadohealth.2023.02.036 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00146-5/pdf

Connolly MD, Zervos MJ, Barone CJ, 2nd, Johnson CC, Joseph CL. The Mental Health of Transgender Youth: Advances in Understanding. *J Adolesc Health*. 2016;59(5):489-495. doi:10.1016/j.jadohealth.2016.06.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27544457

Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *J Sex Med*. 2015;12(11):2206-2214. doi:10.1111/jsm.13034 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26556015

D'hoore L, T'Sjoen G. Gender-affirming hormone therapy: An updated literature review with an eye on the future. *J Intern Med*. 2022;291(5):574-592. doi:10.1111/joim.13441 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34982475

Daley T, Grossoehme D, McGuire JK, Corathers S, Conard LA, Lipstein EA. "I Couldn't See a Downside": Decision-Making About Gender-Affirming Hormone Therapy. *J Adolesc Health*. 2019;65(2):274-279. doi:10.1016/j.jadohealth.2019.02.018 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31196783

Daniolos PT, Telingator CJ. Engendering identity. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1245-1247. doi:10.1016/j.jaac.2013.09.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24290454

Davidge-Pitts C, Clarke BL. Transgender bone health. *Maturitas*. 2019;127:35-42. doi:10.1016/j.maturitas.2019.05.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31351518

Day DS, Saunders JJ, Matorin A. Gender Dysphoria and Suicidal Ideation: Clinical Observations from a Psychiatric Emergency Service. *Cureus*. 2019;11(11):e6132. doi:10.7759/cureus.6132 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6903884/pdf/cureus-0011-00000006132.pdf

de Graaf NM, Steensma TD, Carmichael P, et al. Suicidality in clinic-referred transgender adolescents. *Eur Child Adolesc Psychiatry*. 2022;31(1):67-83. doi:10.1007/s00787-020-01663-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33165650

de Nie I, Mulder CL, Meissner A, et al. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. *Hum Reprod*. 2022;37(2):297-308. doi:10.1093/humrep/deab240 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34791270

de Vries AL, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011;52(11):1195-1202. doi:10.1111/j.1469-7610.2011.02426.x Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21671938

de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010;40(8):930-936. doi:10.1007/s10803-010-0935-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20094764

de Vries AL, Steensma TD, Cohen-Kettenis PT, VanderLaan DP, Zucker KJ. Poor peer relations predict parent- and self-reported behavioral and emotional problems of adolescents with gender dysphoria: a cross-national, cross-clinic comparative analysis. *Eur Child Adolesc Psychiatry*. 2016;25(6):579-588. doi:10.1007/s00787-015-0764-7 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26373289

de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;8(8):2276-2283. doi:10.1111/j.1743-6109.2010.01943.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20646177

de Vries ALC. Autism Spectrum Disorders in Gender Dysphoric Children and Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:51-62:chap 4. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. *Gender Dysphoria in Adolescents*. PhD Thesis. Vrije Universiteit Amsterdam; 2010. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Psychiatric Comorbidity in Gender Dysphoric Adolescents. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:63-76:chap 5. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Puberty Suppression Followed by Cross-sex Hormones and Gender Reassignment Surgery: A Prospective Follow-up of Gender Dysphoric Adolescents into Adulthood. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:91-106:chap 7. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

de Vries ALC. Puberty Suppression in Adolescents with Gender Identity Disorder: A Prospective Follow-up Study. *Gender Dysphoria in Adolescents.* PhD Thesis. Vrije Universiteit Amsterdam; 2010:77-90:chap 6. Accessed June 12, 2023. Available at https://research.vu.nl/en/publications/gender-dysphoria-in-adolescents-mental-health-and-treatment-evalu

Dilday EA, Bukulmez O, Saner K, Lopez X, Jarin J. Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy. *Transgend Health*. 2022;7(6):528-532. doi:10.1089/trgh.2021.0037 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644123

Donaldson AA, Hall A, Neukirch J, et al. Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series. *Int J Eat Disord*. 2018;51(5):475-479. doi:10.1002/eat.22868 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29740834

Durwood L, McLaughlin KA, Olson KR. Mental Health and Self-Worth in Socially Transitioned Transgender Youth. *J Am Acad Child Adolesc Psychiatry*. 2017;56(2):116-123 e112. doi:10.1016/j.jaac.2016.10.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28117057

Eisenberg L. Minor Patient, Major Decisions: Caring for a Rural Child With Gender Dysphoria. *Am J Bioeth*. 2019;19(7):64-65. doi:10.1080/15265161.2019.1619346 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31237514

Eitel KB, Hodax JK, DiVall S, Kidd KM, Salehi P, Sequeira GM. Leuprolide Acetate for Puberty Suppression in Transgender and Gender Diverse Youth: A Comparison of Subcutaneous Eligard Versus Intramuscular Lupron. *J Adolesc Health*. 2023;72(2):307-311. doi:10.1016/j.jadohealth.2022.09.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36404242

Expösito-Campos P, Gomez-Balaguer M, Hurtado-Murillo F, Garcia-Moreno RM, Morillas-Arino C. Medical detransition following transgender identity reaffirmation: two case reports. *Sex Health*. 2022;18(6):498-501. doi:10.1071/SH21089 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34883041

Fan EM, Gordner C, Luty J. Venous Thromboembolism in a Transgender Adolescent on Testosterone Therapy: A Case Report and Literature Review. *J Pediatr Hematol Oncol*. 2020;42(5):e352-e354. doi:10.1097/MPH.0000000000001755 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32079984

Fernandez M, Guerra P, Martin E, Martinez N, Alvarez-Diz JA, Grupo G. [Health care for adolescents with gender dysphoria]. *Rev Esp Salud Publica*. 2018;92Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29493565

Fernandez Rodriguez M, Guerra Mora P, Martin Sanchez E, Grupo G. [Characteristics of Adolescents with Gender Dysphoria Referred to the Gender Identity Treatment Unit]. *Rev Esp Salud Publica*. 2017;91Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28141788

Fung R, Greenaway MK, McEvenue G. Gynecomastia in a Transgender Boy: A Case Report. *AACE clinical case reports*. 2021;7(6):350-352. doi:10.1016/j.aace.2021.05.003 Accessed September 15, 2023. Available at https://www.aaceclinicalcasereports.com/article/S2376-0605(21)00065-1/pdf

Fuss J, Auer MK, Briken P. Gender dysphoria in children and adolescents: a review of recent research. *Curr Opin Psychiatry*. 2015;28(6):430-434. doi:10.1097/YCO.0000000000000203 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26382161

Garborcauskas G, Boskey ER, Guss CE, Grimstad FW. Retrospective Review of Sexual and Reproductive Health Conversations During Initial Visits of Adolescents Seeking Gender-Affirming Testosterone. *J Pediatr Adolesc Gynecol*. 2023;36(1):25-32. doi:10.1016/j.jpag.2022.09.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36162722

Garborcauskas G, McCabe E, Boskey ER, Grimstad FW. Family Building Perspectives of Assigned Female at Birth Transgender and Gender Diverse Adolescents Seeking Testosterone Gender-Affirming Hormone Therapy. *LGBT Health*. 2022;9(7):463-470. doi:10.1089/lgbt.2022.0004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35802494

Gawlik A, Antosz A, Kasparek K, Nowak Z, Grabski B. Gender confirmation hormonal treatment use in young Polish transgender binary and non-binary persons. *Endokrynol Pol*. 2022;73(6):922-927. doi:10.5603/EP.a2022.0088 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36519648

Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. *J Pediatr Endocrinol Metab*. 2020;33(1):107-112. doi:10.1515/jpem-2019-0045 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31834861

Gilani M, Wallach P, Kyriakou A. Levels of physical activity and barriers to sport participation in young people with gender dysphoria. *J Pediatr Endocrinol Metab*. 2021;34(6):747-753. doi:10.1515/jpem-2021-0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33818040

Grannis C, Leibowitz SF, Gahn S, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology*. 2021;132:105358. doi:10.1016/j.psyneuen.2021.105358 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34333318

Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolesc Health*. 2022;70(4):643-649. doi:10.1016/j.jadohealth.2021.10.036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34920935

Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. *J Pediatr Adolesc Gynecol*. 2021;34(5):706-716. doi:10.1016/j.jpag.2021.04.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33910088

Grimstad F, Moyer Q, Williams CR, Kremen J. A Body-Neutral and Gender-Neutral Modified Ferriman-Gallwey Diagram. *J Pediatr Adolesc Gynecol*. 2022;35(3):375-378. doi:10.1016/j.jpag.2021.10.015 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34748917

Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in Referrals to a Pediatric Transgender Clinic. *Pediatrics*. 2019;144(5)doi:10.1542/peds.2019-1368 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31619510

Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. *J Clin Endocrinol Metab*. 2017;102(7):2356-2363. doi:10.1210/jc.2017-00373 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28419243

Harris RM, Kolaitis IN, Frader JE. Ethical issues involving fertility preservation for transgender youth. *J Assist Reprod Genet*. 2020;37(10):2453-2462. doi:10.1007/s10815-020-01873-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550448/pdf/10815_2020_Article_1873.pdf

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *Endocr Pract*. 2017;23(12):1437. doi:10.4158/1934-2403-23.12.1437 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29320642

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658 Accessed May 18, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945902

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. CORRIGENDUM FOR "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline". *J Clin Endocrinol Metab*. 2018;103(7):2758-2759. doi:10.1210/jc.2018-01268 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29905821

Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust*. 2012;196(9):578-581. doi:10.5694/mja12.10222 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22621149

Hewitt JK, Paul C, Newman LK. Author Reply to Conway, et al. regarding “Hormone treatment of gender identity disorder in a cohort of children and adolescents”. *Med J Aust*. 2012;197(5):274. doi:10.5694/mja12.10911 Accessed June 16, 2023. Available at https://pubmed.ncbi.nlm.nih.gov/22938117/

Hobson BJ, Lett E, Hawkins LA, Swendiman RA, Nance ML, Dowshen NL. Transgender Youth Experiences with Implantable GnRH Agonists for Puberty Suppression. *Transgend Health*. 2022;7(4):364-368. doi:10.1089/trgh.2021.0006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36033209

Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. *Headache*. 2023;63(4):517-522. doi:10.1111/head.14493 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36988085

Insogna IG, Ginsburg E, Srouji S. Fertility Preservation for Adolescent Transgender Male Patients: A Case Series. *J Adolesc Health*. 2020;66(6):750-753. doi:10.1016/j.jadohealth.2019.12.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32001141

James HA, Chang AY, Imhof RL, et al. A community-based study of demographics, medical and psychiatric conditions, and gender dysphoria/incongruence treatment in transgender/gender diverse individuals. *Biol Sex Differ*. 2020;11(1):55. doi:10.1186/s13293-020-00332-5 Accessed September 15, 2023. Available at https://bsd.biomedcentral.com/counter/pdf/10.1186/s13293-020-00332-5.pdf

Jarin J, Pine-Twaddell E, Trotman G, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. *Pediatrics*. 2017;139(5)doi:10.1542/peds.2016-3173 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28557738

Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. *Transgend Health*. 2019;4(1):300-303. doi:10.1089/trgh.2018.0061 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31663037

Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab*. 2019;32(10):1077-1081. doi:10.1515/jpem-2019-0046 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31472062

Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nord J Psychiatry*. 2020;74(3):213-219. doi:10.1080/08039488.2019.1691260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31762394

Kameg BN, Nativio DG. Gender dysphoria in youth: An overview for primary care providers. *J Am Assoc Nurse Pract*. 2018;30(9):493-498. doi:10.1097/JXX.0000000000000068 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30095668

Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. *Int J Transgend*. 2019;20(4):413-420. doi:10.1080/15532739.2019.1631929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999626

Karakilic Ozturan E, Ozturk AP, Bas F, et al. Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey. *J Clin Res Pediatr Endocrinol*. 2023, 10.4274/jcrpe.galenos.2023.2023-1-13doi:10.4274/jcrpe.galenos.2023.2023-1-13 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36987788

Karalexi MA, Georgakis MK, Dimitriou NG, et al. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2020;119:104721. doi:10.1016/j.psyneuen.2020.104721 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32512250

Kerman HM, Pham A, Crouch JM, et al. Gender Diverse Youth on Fertility and Future Family: A Qualitative Analysis. *J Adolesc Health*. 2021;68(6):1112-1120. doi:10.1016/j.jadohealth.2021.01.002 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(21)00004-5/fulltext

Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Pediatr*. 2014;164(4):906-911. doi:10.1016/j.jpeds.2013.10.068 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24315505

Khazal S, Abdel-Azim H, Kapoor N, Mahadeo KM. Overcoming psychosocial and developmental barriers to blood and marrow transplantation (BMT) in an adolescent/young adult (AYA) transgender patient with chronic myelogenous leukemia. *Pediatr Hematol Oncol*. 2014;31(8):765-767. doi:10.3109/08880018.2014.909914 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24854505

Klaver M, de Mutsert R, van der Loos M, et al. Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. *Pediatrics*. 2020;145(3)doi:10.1542/peds.2019-0741 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32102929

Klaver M, de Mutsert R, Wiepjes CM, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. *J Sex Med*. 2018;15(2):251-260. doi:10.1016/j.jsxm.2017.12.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29425666

Komorowski AS, Fisher AR, Jungheim ES, Lewis CS, Omurtag KR. Fertility preservation discussions, referral and follow-up in male-to-female and female-to-male adolescent transgender patients. *Hum Fertil (Camb)*. 2021, 10.1080/14647273.2021.2015804:1-5. doi:10.1080/14647273.2021.2015804 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34915792

Korte A, Beier KM, Wermuth I, Bosinski HAG. The treatment of gender dysphoria (gender identity disorders) in childhood and adolescence open-outcome psychotherapeutic support or early setting of therapy course with the introduction of hormonal therapy? *Padiatrische Praxis*. 2017;88(1):67-87. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L617597046&from=export

Korte A, Beier KM, Wermuth I, Bosinski HAG. The treatment of gender dysphoria (gender identity disorders) in childhood and adolescence open-outcome psychotherapeutic support or early setting of therapy course with the introduction of hormonal therapy? *Gynakologische Praxis*. 2018;43(2):303-323. Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L617597046&from=export

Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. *Nat Rev Endocrinol*. 2011;7(8):466-472. doi:10.1038/nrendo.2011.78 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21587245

Krishna V, Lee SL, DeUgarte DA. Optimizing pediatric histrelin implantation to improve success rates in clinic without sedation. *J Pediatr Endocrinol Metab*. 2021;34(11):1443-1448. doi:10.1515/jpem-2021-0432 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34407329

Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*. 2020;145(4)doi:10.1542/peds.2019-3006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32220906

Kyweluk MA, Sajwani A, Chen D. Freezing for the future: Transgender youth respond to medical fertility preservation. *International Journal of Transgenderism*. 2018;19(4):401-416. doi:10.1080/15532739.2018.1505575 Accessed September 15, 2023. Available at https://doi.org/10.1080/15532739.2018.1505575

Lambert A, Pratt A, Conard LAE, et al. Supporting Gender-Related Medical Decision Making for Transgender and Gender-Diverse Individuals: A Scoping Review. *Transgend Health*. 2023;8(2):113-123. doi:10.1089/trgh.2021.0030 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37013094

Laurenzano SE, Newfield RS, Lee E, Marinkovic M. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents and Young Adults: A Single Center's 8-Year Experience. *Transgend Health*. 2021;6(6):343-352. doi:10.1089/trgh.2020.0103 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34988290

Lavender R, Shaw S, Maninger JK, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. *LGBT Health*. 2023, 10.1089/lgbt.2022.0201doi:10.1089/lgbt.2022.0201 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36989498

Lawlis SM, Donkin HR, Bates JR, Britto MT, Conard LAE. Health Concerns of Transgender and Gender Nonconforming Youth and Their Parents Upon Presentation to a Transgender Clinic. *J Adolesc Health*. 2017;61(5):642-648. doi:10.1016/j.jadohealth.2017.05.025 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(17)30254-9/fulltext

Lee G, Ferri-Huerta R, Greenberg KB, Somers KE. Acne fulminans in a transgender boy after an increase in testosterone dosage. *JAAD Case Rep*. 2022;21:32-34. doi:10.1016/j.jdcr.2021.11.029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35141385

Lee JY, Finlayson C, Olson-Kennedy J, et al. Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study. *J Endocr Soc*. 2020;4(9):bvaa065. doi:10.1210/jendso/bvaa065 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32832823

Lee WG, Butler G, Carmichael P, et al. Urological and Gynaecological Considerations for the Use of Gonadotropin-releasing Hormone Analogues in Transgender and Nonbinary Adolescents: A Narrative Review. *Eur Urol Focus*. 2023;9(1):35-41. doi:10.1016/j.euf.2022.11.002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36396559

Leibowitz S, de Vries ALC. Gender dysphoria in adolescence. *International review of psychiatry (Abingdon, England)*. 2016;28(1):21-35. doi:10.3109/09540261.2015.1124844 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26828376

Lin AJ, Baranski T, Chaterjee D, Chapman W, Foltz G, Kim H. Androgen-receptor-positive hepatocellular carcinoma in a transgender teenager taking exogenous testosterone. *Lancet*. 2020;396(10245):198. doi:10.1016/S0140-6736(20)31538-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32682485

Lopez CM, Solomon D, Boulware SD, Christison-Lagay E. Trends in the "Off-Label" Use of GnRH Agonists Among Pediatric Patients in the United States. *Clin Pediatr (Phila)*. 2018;57(12):1432-1435. doi:10.1177/0009922818787260 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30003804

Lopez CM, Solomon D, Boulware SD, Christison-Lagay ER. Trends in the use of puberty blockers among transgender children in the United States. *J Pediatr Endocrinol Metab*. 2018;31(6):665-670. doi:10.1515/jpem-2018-0048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29715194

Lopez de Lara D, Perez Rodriguez O, Cuellar Flores I, et al. [Psychosocial assessment in transgender adolescents]. *An Pediatr (Engl Ed)*. 2020;93(1):41-48. doi:10.1016/j.anpedi.2020.01.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32144041

Lopez X, Stewart S, Jacobson-Dickman E. Approach to Children and Adolescents with Gender Dysphoria. *Pediatr Rev*. 2016;37(3):89-96; quiz 97-88. doi:10.1542/pir.2015-0032 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26933223

Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*. 2023, 10.1111/apa.16791:ePub ahead of print. doi:10.1111/apa.16791 Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/apa.16791?download=true

Mahfouda S, Moore JK, Siafarikas A, et al. Gender-affirming hormones and surgery in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2019;7(6):484-498. doi:10.1016/S2213-8587(18)30305-X Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30528161

Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2017;5(10):816-826. doi:10.1016/S2213-8587(17)30099-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28546095

Margolin EA, Mason RH. Female-to-male transgender patient with idiopathic intracranial hypertention. *J Neurol Sci*. 2020;415:116970. doi:10.1016/j.jns.2020.116970 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32521344

Martin CE, Lewis C, Omurtag K. Successful oocyte cryopreservation using letrozole as an adjunct to stimulation in a transgender adolescent after GnRH agonist suppression. *Fertil Steril*. 2021;116(2):522-527. doi:10.1016/j.fertnstert.2021.02.025 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33795140

Martinez S, Mazoyer AV. Impacts of the sexual reassignment on the parenthood. *Ann Med Psychol (Paris)*. 2017;175(9):797-802. doi:10.1016/j.amp.2017.09.001 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618996605&from=export

Maru J, Millington K, Carswell J. Greater Than Expected Prevalence of Type 1 Diabetes Mellitus Found in an Urban Gender Program. *Transgend Health*. 2021;6(1):57-60. doi:10.1089/trgh.2020.0027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644323

Marwa A, Misra M, Lopez X. Determinants of Bone Mineral Density in Transgender Youth. *Transgend Health*. 2022;7(3):213-218. doi:10.1089/trgh.2020.0111 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36643057

Maschião LF, Bastos FI, Wilson E, et al. Nonprescribed Sex Hormone Use Among Trans Women: The Complex Interplay of Public Policies, Social Context, and Discrimination. *Transgend Health*. 2020;5(4):205-215. doi:10.1089/trgh.2020.0012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644312

Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child*. 2022;107(11):1012-1017. doi:10.1136/archdischild-2022-324283 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35902230

Mason KA, Schoelwer MJ, Rogol AD. Androgens During Infancy, Childhood, and Adolescence: Physiology and Use in Clinical Practice. *Endocr Rev*. 2020;41(3):421-456. doi:10.1210/endrev/bnaa003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32115641

McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr*. 2021;180(9):2969-2976. doi:10.1007/s00431-021-04075-2 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33855617

Mejia-Otero JD, White P, Lopez X. Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth. *Transgend Health*. 2021;6(1):31-35. doi:10.1089/trgh.2020.0007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33614957

Mendes N, Lagrange C, Condat A. Gender dysphoria in children and adolescents: Literature review. *Neuropsychiatr Enfance Adolesc*. 2016;64(4):240-254. doi:10.1016/j.neurenf.2016.04.003 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L610761157&from=export

Meyenburg B. [Gender dysphoria in adolescents: difficulties in treatment]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):510-522. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296511

Meyenburg B, Korte A, Moller B, Romer G, Deutsche Gesellschaft fur Kinder- und Jugendpsychiatrie PuP. [Gender identity disorders in childhood and adolescence (F64)]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):542-552. Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296513

Meyenburg B, Kroger A, Neugebauer R. [Gender dysphoria in children and adolescents - treatment guidelines and follow-up study]. *Z Kinder Jugendpsychiatr Psychother*. 2015;43(1):47-55. doi:10.1024/1422-4917/a000332 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25536896

Millington K, Barrera E, Daga A, et al. The effect of gender-affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: implications for estimating GFR. *Pediatr Nephrol*. 2022;37(9):2141-2150. doi:10.1007/s00467-022-05445-0 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35083530

Millington K, Finlayson C, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Association of High-Density Lipoprotein Cholesterol With Sex Steroid Treatment in Transgender and Gender-Diverse

Youth. *JAMA Pediatr*. 2021;175(5):520-521. doi:10.1001/jamapediatrics.2020.5620 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33587098

Millington K, Hayes K, Pilcher S, et al. A serous borderline ovarian tumour in a transgender male adolescent. *Br J Cancer*. 2021;124(3):567-569. doi:10.1038/s41416-020-01129-4 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106582

Millington K, Liu E, Chan YM. The Utility of Potassium Monitoring in Gender-Diverse Adolescents Taking Spironolactone. *J Endocr Soc*. 2019;3(5):1031-1038. doi:10.1210/js.2019-00030 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31065620

Mirabella M, Piras I, Fortunato A, et al. Gender Identity and Non-Binary Presentations in Adolescents Attending Two Specialized Services in Italy. *J Sex Med*. 2022;19(6):1035-1048. doi:10.1016/j.jsxm.2022.03.215 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/19/6/1035/6961405?redirectedFrom=fulltext

Morningstar M, Thomas P, Anderson AM, et al. Exogenous testosterone administration is associated with differential neural response to unfamiliar peer's and own caregiver's voice in transgender adolescents. *Dev Cogn Neurosci*. 2023;59:101194. doi:10.1016/j.dcn.2022.101194 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36634500

Morrison A, Olezeski C, Cron J, Kallen AN. A Pilot Study to Assess Attitudes Toward Future Fertility and Parenthood in Transgender and Gender Expansive Adolescents. *Transgender Health*. 2020;5(2):129-137. doi:10.1089/trgh.2019.0075 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L632152015&from=export

Mullins ES, Geer R, Metcalf M, et al. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. *Pediatrics*. 2021;147(4)doi:10.1542/peds.2020-023549 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33753543

Nahata L, Chen D, Quinn GP, et al. Reproductive Attitudes and Behaviors Among Transgender/Nonbinary Adolescents. *J Adolesc Health*. 2020;66(3):372-374. doi:10.1016/j.jadohealth.2019.09.008 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(19)30451-3/fulltext

Nahata L, Quinn GP, Caltabellotta NM, Tishelman AC. Mental Health Concerns and Insurance Denials Among Transgender Adolescents. *LGBT health*. 2017;4(3):188-193. doi:10.1089/lgbt.2016.0151 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L621194440&from=export

Nasomyont N, Meisman AR, Ecklund K, et al. Changes in Bone Marrow Adipose Tissue in Transgender and Gender Non-Conforming Youth Undergoing Pubertal Suppression: A Pilot Study. *J Clin Densitom*. 2022;25(4):485-489. doi:10.1016/j.jocd.2022.06.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36064698

Navabi B, Tang K, Khatchadourian K, Lawson ML. Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2020-039339 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34497118

Nayman T, Hebert M, Ospina LH. Idiopathic intracranial hypertension in a pediatric transgender patient. *Am J Ophthalmol Case Rep*. 2021;24:101208. doi:10.1016/j.ajoc.2021.101208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34622090

Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an Androgen Blocker With Secondary Effect of Promoting Feminization in Male-to-Female Transgender Adolescents. *J Adolesc Health*. 2019;64(4):544-546. doi:10.1016/j.jadohealth.2018.10.296 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30612811

Ni J, Chi C, Aye T. Review of implant gonadotrophin-releasing hormone agonist use: experience in a single academic center. *Horm Res Paediatr*. 2023, 10.1159/000529733doi:10.1159/000529733 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36791687

Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. *J Sex Med*. 2021;18(3):632-645. doi:10.1016/j.jsxm.2020.12.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33642235

Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. *J Clin Endocrinol Metab*. 2020;105(3):e704-714. doi:10.1210/clinem/dgz029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31544944

Nokoff NJ, Scarbro SL, Moreau KL, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists. *Transgend Health*. 2021;6(2):111-119. doi:10.1089/trgh.2020.0029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33937527

Nos AL, Klein DA, Adirim TA, et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. *JAMA Netw Open*. 2022;5(11):e2239758. doi:10.1001/jamanetworkopen.2022.39758 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36318207

O'Bryan J, Leon K, Wolf-Gould C, Scribani M, Tallman N, Gadomski A. Building a Pediatric Patient Registry to Study Health Outcomes Among Transgender and Gender Expansive Youth at a Rural Gender Clinic. *Transgend Health*. 2018;3(1):179-189. doi:10.1089/trgh.2018.0023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30581991

O'Connell MA, Nguyen TP, Ahler A, Skinner SR, Pang KC. Approach to the Patient: Pharmacological Management of Trans and Gender-Diverse Adolescents. *J Clin Endocrinol Metab*. 2022;107(1):241-257. doi:10.1210/clinem/dgab634 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34476487

Olsavsky AL, Grannis C, Bricker J, et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. *J Adolesc Health*. 2023;72(6):860-868. doi:10.1016/j.jadohealth.2023.01.031 Accessed September 15, 2023. Available at https://www.jahonline.org/article/S1054-139X(23)00097-6/pdf

Olson KR, Durwood L, Horton R, Gallagher NM, Devor A. Gender Identity 5 Years After Social Transition. *Pediatrics*. 2022;150(2)doi:10.1542/peds.2021-056082 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35505568

Olson-Kennedy J, Chan Y-M, Garofalo R, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. *JMIR research protocols*. 2019;8(7):e14434. doi:10.2196/14434 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31290407

Olson-Kennedy J, Streeter LH, Garofalo R, Chan YM, Rosenthal SM. Histrelin Implants for Suppression of Puberty in Youth with Gender Dysphoria: A Comparison of 50 mcg/Day (Vantas) and 65 mcg/Day (SupprelinLA). *Transgend Health*. 2021;6(1):36-42. doi:10.1089/trgh.2020.0055 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644320

Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr*. 2018;172(5):431-436. doi:10.1001/jamapediatrics.2017.5440 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29507933

Pamfile D, Soldati L, Brovelli S, et al. [Role of the psychiatrist-psychotherapist in the assessment and treatment of gender dysphoria]. *Rev Med Suisse*. 2020;16(709):1877-1880. Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33026731

Pang KC, Nguyen TP, Upreti R. Case Report: Successful Use of Minoxidil to Promote Facial Hair Growth in an Adolescent Transgender Male. *Front Endocrinol (Lausanne)*. 2021;12:725269. doi:10.3389/fendo.2021.725269 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34659117

Pang KC, Notini L, McDougall R, et al. Long-term Puberty Suppression for a Nonbinary Teenager. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1606 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974217

Parikh N, Chattha A, Gargollo P, Granberg C. Fertility Preservation: A Tale of Two Testicles. *Urology*. 2021;153:298-300. doi:10.1016/j.urology.2020.11.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33221414

Parks MA, Zwayne N, Temkit M. Bleeding Patterns among Adolescents Using the Levonorgestrel Intrauterine Device: A Single Institution Review. *J Pediatr Adolesc Gynecol*. 2020;33(5):555-558. doi:10.1016/j.jpag.2020.04.006 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(20)30223-0/fulltext

Pauli D, Günthard M, Schenker T, et al. The Zurich Specialist Clinic for Adolescent with Gender Dysphoria - Preliminary Follow-up Results. *Prax Kinderpsychol Kinderpsychiatr*. 2020;69(6):570-589. doi:10.13109/prkk.2020.69.6.570 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L633037474&from=export

Penney SW, Jung JH, Ballantyne AJ, Parekh DS, Klein DA, Viola SA. Affirming Hormone Treatment for a Transgender Adolescent After a Venous Thromboembolic Event. *J Pediatr Hematol Oncol*. 2022;44(5):E892-E895. doi:10.1097/MPH.0000000000002442 Accessed September 15, 2023.

Available at https://www.ingentaconnect.com/content/wk/jpho/2022/00000044/00000005/art00019

Perl L, Elkon-Tamir E, Segev-Becker A, Israeli G, Brener A, Oren A. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab*. 2021;34(6):741-745. doi:10.1515/jpem-2021-0172 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33823098

Perl L, Segev-Becker A, Israeli G, Elkon-Tamir E, Oren A. Blood Pressure Dynamics After Pubertal Suppression with Gonadotropin-Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents: A Pilot Study. *LGBT Health*. 2020;7(6):340-344. doi:10.1089/lgbt.2020.0026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32735503

Persky RW, Gruschow SM, Sinaii N, Carlson C, Ginsberg JP, Dowshen NL. Attitudes Toward Fertility Preservation Among Transgender Youth and Their Parents. *J Adolesc Health*. 2020;67(4):583-589. doi:10.1016/j.jadohealth.2020.02.027 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32359942

Pham A, Kasenic A, Hayden L, et al. A Case Series on Disordered Eating Among Transgender Youth With Autism Spectrum Disorder. *J Adolesc Health*. 2021;68(6):1215-1219. doi:10.1016/j.jadohealth.2020.12.143 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33707147

Pierce S, Mazziotta A, Möller-Kallista B. Experiences of Children with Gender Dysphoria/Gender Incongruence and their Parents with the Health Care System in Germany. *Prax Kinderpsychol Kinderpsychiatr*. 2022;71(7):597-619. doi:10.13109/prkk.2022.71.7.597 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L639549895&from=export

Poirier F, Condat A, Laufer L, Rosenblum O, Cohen D. Non-binary gender and transgender youth: A literature review. *Neuropsychiatr Enfance Adolesc*. 2019;67(5-6):268-285. doi:10.1016/j.neurenf.2018.08.004 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2001164253&from=export

Pullen Sansfaçon A, Temple Newhook J, Douglas L, et al. Experiences and Stressors of Parents of Trans and Gender-Diverse Youth in Clinical Care from Trans Youth CAN! *Health Soc Work*. 2022;47(2):92-101. doi:10.1093/hsw/hlac003 Accessed September 15, 2023. Available at https://academic.oup.com/hsw/article-abstract/47/2/92/6544691?redirectedFrom=fulltext

Pullen Sansfaçon A, Temple-Newhook J, Suerich-Gulick F, et al. The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. *Int J Transgend*. 2019;20(4):371-387. doi:10.1080/15532739.2019.1652129 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32999623

Quain KM, Kyweluk MA, Sajwani A, et al. Timing and Delivery of Fertility Preservation Information to Transgender Adolescents, Young Adults, and Their Parents. *J Adolesc Health*. 2021;68(3):619-

622. doi:10.1016/j.jadohealth.2020.06.044 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32826153

Ramos GGF, Mengai ACS, Daltro CAT, Cutrim PT, Zlotnik E, Beck APA. Systematic Review: Puberty suppression with GnRH analogues in adolescents with gender incongruity. *J Endocrinol Invest*. 2021;44(6):1151-1158. doi:10.1007/s40618-020-01449-5 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33111215

Razzak M. Pediatrics: evaluation and management of gender identity disorder--an American tale. *Nat Rev Urol*. 2012;9(4):175. doi:10.1038/nrurol.2012.36 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22410681

Rebetez N. [I want an accepting society]. *Krankenpfl Soins Infirm*. 2014;107(11):56-57. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25438414

Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child Adolesc Ment Health*. 2021;26(1):3-14. doi:10.1111/camh.12437 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33320999

Riggs DW, Bartholomaeus C, Sansfacon AP. 'If they didn't support me, I most likely wouldn't be here': Transgender young people and their parents negotiating medical treatment in Australia. *International journal of transgender health*. 2020;21(1):3-15. doi:10.1080/15532739.2019.1692751 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430428/pdf/WIJT_21_1692751.pdf

Ristori J, Fisher AD, Castellini G, et al. Gender Dysphoria and Anorexia Nervosa Symptoms in Two Adolescents. *Arch Sex Behav*. 2019;48(5):1625-1631. doi:10.1007/s10508-019-1396-7 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s10508-019-1396-7

Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. *J Clin Endocrinol Metab*. 2022;107(9):e3937-e3943. doi:10.1210/clinem/dgac251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35452119

Roden RC. Reversible interventions for menstrual management in adolescents and young adults with gender incongruence. *Ther Adv Reprod Health*. 2023;17:26334941231158251. doi:10.1177/26334941231158251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36938373

Rodriguez-Wallberg K, Obedin-Maliver J, Taylor B, Van Mello N, Tilleman K, Nahata L. Reproductive health in transgender and gender diverse individuals: A narrative review to guide clinical care and international guidelines. *Int J Transgend Health*. 2023;24(1):7-25. doi:10.1080/26895269.2022.2035883 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36713139

Rogers C, Webberley M, Mateescu R, El Rakhawy Y, Daly-Gourdialsing A, Webberley H. A retrospective study of positive and negative determinants of gamete storage in transgender and gender-diverse patients. *International journal of transgender health*. 2021;22(1-2):167-178.

doi:10.1080/26895269.2020.1848693 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040686/pdf/WIJT_22_1848693.pdf

Roy MK, Wilkerson RB, Alexander K, Nokoff NJ, Cree-Green M, D'Alessandro A. Longitudinal metabolic study of red blood cells from patients undergoing gender-affirming testosterone therapy. *Blood Adv*. 2023;7(16):4269-4277. doi:10.1182/bloodadvances.2022008061 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36001490

Rozga M, Linsenmeyer W, Cantwell Wood J, Darst V, Gradwell EK. Hormone therapy, health outcomes and the role of nutrition in transgender individuals: A scoping review. *Clin Nutr ESPEN*. 2020;40:42-56. doi:10.1016/j.clnesp.2020.08.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33183572

Russell I, Pearson B, Masic U. A Longitudinal Study of Features Associated with Autism Spectrum in Clinic Referred, Gender Diverse Adolescents Accessing Puberty Suppression Treatment. *J Autism Dev Disord*. 2021;51(6):2068-2076. doi:10.1007/s10803-020-04698-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32936414

Rutzen KM, Nieder TO, Schreier H, Moller B. [Clinical treatment of children and adolescents with gender dysphoria from international experts' point of view]. *Prax Kinderpsychol Kinderpsychiatr*. 2014;63(6):449-464. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25296508

Salvatore L, Dancyger I, Shadianloo S, Fornari V. Caring for Transgender Youth with Eating Disorders in a Day Treatment Program. *Adolesc Psychiatry*. 2022;12(3):196-206. doi:10.2174/2210676613666221027124554 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2018683391&from=export

Sanchez Lorenzo I, Mora Mesa JJ, Oviedo de Lucas O. Psychomedical care in gender identity dysphoria during adolescence. *Revista de psiquiatria y salud mental*. 2017;10(2):96-103. doi:10.1016/j.rpsm.2015.04.002 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26055932

Sayeem M, Carter B, Phulwani P, Zempsky WT. Gender Dysphoria and Chronic Pain in Youth. *Pediatrics*. 2021;148(4)doi:10.1542/peds.2021-050128 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34561268

Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. *J Sex Med*. 2016;13(7):1125-1132. doi:10.1016/j.jsxm.2016.05.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27318023

Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. *J Sex Med*. 2018;15(9):1357-1363. doi:10.1016/j.jsxm.2018.07.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30224022

Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *J Clin Endocrinol Metab*. 2020;105(12):e4252-4263. doi:10.1210/clinem/dgaa604 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32909025

Schneider MA, Spritzer PM, Soll BMB, et al. Brain Maturation, Cognition and Voice Pattern in a Gender Dysphoria Case under Pubertal Suppression. *Front Hum Neurosci*. 2017;11:528. doi:10.3389/fnhum.2017.00528 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29184488

Schulmeister C, Millington K, Kaufman M, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. *J Adolesc Health*. 2022;70(1):108-113. doi:10.1016/j.jadohealth.2021.06.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34315674

Schwartz BI, Bear B, Kazak AE. Menstrual Management Choices in Transgender and Gender Diverse Adolescents. *J Adolesc Health*. 2023;72(2):207-213. doi:10.1016/j.jadohealth.2022.09.023 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36443161

Schwartz BI, Bear B, Short VL, Kazak AE. Outcomes of Menstrual Management Use in Transgender and Gender-Diverse Adolescents. *Obstet Gynecol*. 2023;141(4):748-755. doi:10.1097/AOG.0000000000005123 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36897186

Schwartz BI, Effron A, Bear B, et al. Experiences with Menses in Transgender and Gender Nonbinary Adolescents. *J Pediatr Adolesc Gynecol*. 2022;35(4):450-456. doi:10.1016/j.jpag.2022.01.015 Accessed September 15, 2023. Available at https://www.jpagonline.org/article/S1083-3188(22)00037-7/fulltext

Segev-Becker A, Israeli G, Elkon-Tamir E, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. *Endocr Pract*. 2020;26(4):423-428. doi:10.4158/EP-2019-0418 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32045294

Shaffer LR, McCormack E, Sawicki GS, Keller A, Jain R. Understanding the Intersection between Gender Transition and Health Outcomes in Cystic Fibrosis. *Ann Am Thorac Soc*. 2022;19(3):504-506. doi:10.1513/AnnalsATS.202105-535RL Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34469707

Shim JY, Laufer MR, Grimstad FW. Dysmenorrhea and Endometriosis in Transgender Adolescents. *J Pediatr Adolesc Gynecol*. 2020;33(5):524-528. doi:10.1016/j.jpag.2020.06.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32535219

Shumer DE, Tishelman AC. The Role of Assent in the Treatment of Transgender Adolescents. *Int J Transgend*. 2015;16(2):97-102. doi:10.1080/15532739.2015.1075929 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27175107

Silverstein L, Zander E, Middleman AB. Adolescent identity: The importance of the social history. *SAGE Open Med Case Rep*. 2020;8:2050313X20952980. doi:10.1177/2050313X20952980 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32922796

Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. *Front Psychiatry*. 2021;12:632784. doi:10.3389/fpsyt.2021.632784 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33854450

Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental Health and Timing of Gender-Affirming Care. *Pediatrics*. 2020;146(4)doi:10.1542/peds.2019-3600 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_20193600.pdf

Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3):418-425. doi:10.1542/peds.2011-0907 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22351896

Stanley K, Cooper J. Hormone Therapy and Venous Thromboembolism in a Transgender Adolescent. *J Pediatr Hematol Oncol*. 2018;40(1):e38-e40. doi:10.1097/MPH.0000000000000984 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28945660

Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;56:190-199. doi:10.1016/j.psyneuen.2015.03.007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25837854

Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. doi:10.1177/1359104510378303 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21216800

Stevens J, Gomez-Lobo V, Pine-Twaddell E. Insurance Coverage of Puberty Blocker Therapies for Transgender Youth. *Pediatrics*. 2015;136(6):1029-1031. doi:10.1542/peds.2015-2849 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26527547

Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J Sex Med*. 2019;16(9):1459-1468. doi:10.1016/j.jsxm.2019.06.014 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31405768

Strang JF, Jarin J, Call D, et al. Transgender Youth Fertility Attitudes Questionnaire: Measure Development in Nonautistic and Autistic Transgender Youth and Their Parents. *J Adolesc Health*. 2018;62(2):128-135. doi:10.1016/j.jadohealth.2017.07.022 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29033160

Strang JF, Powers MD, Knauss M, et al. "They Thought It Was an Obsession": Trajectories and Perspectives of Autistic Transgender and Gender-Diverse Adolescents. *J Autism Dev Disord*. 2018;48(12):4039-4055. doi:10.1007/s10803-018-3723-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30140984

Strittmatter E, Holtmann M. [Gender identities in transition]. *Z Kinder Jugendpsychiatr Psychother*. 2020;48(2):93-102. doi:10.1024/1422-4917/a000724 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32162593

T'Sjoen G, Arcelus J, De Vries ALC, et al. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention

for Sexual Function and Satisfaction". *J Sex Med*. 2020;17(4):570-584. doi:10.1016/j.jsxm.2020.01.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32111534

Tack LJW, Heyse R, Craen M, et al. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. *J Sex Med*. 2017;14(5):747-757. doi:10.1016/j.jsxm.2017.03.251 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28499525

Tankersley AP, Grafsky EL, Dike J, Jones RT. Risk and Resilience Factors for Mental Health among Transgender and Gender Nonconforming (TGNC) Youth: A Systematic Review. *Clin Child Fam Psychol Rev*. 2021;24(2):183-206. doi:10.1007/s10567-021-00344-6 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33594611

Tollit MA, May T, Maloof T, et al. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. *International journal of transgender health*. 2023;24(1):59-69. doi:10.1080/26895269.2021.1939221 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9879187/pdf/WIJT_24_1939221.pdf

Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. *JAMA Netw Open*. 2022;5(2):e220978. doi:10.1001/jamanetworkopen.2022.0978 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35212746

Turban JL, Carswell J, Keuroghlian AS. Understanding Pediatric Patients Who Discontinue Gender-Affirming Hormonal Interventions. *JAMA Pediatr*. 2018;172(10):903-904. doi:10.1001/jamapediatrics.2018.1817 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30178056

Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2)doi:10.1542/peds.2019-1725 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31974216

Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLoS One*. 2022;17(1):e0261039. doi:10.1371/journal.pone.0261039 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35020719

Valentine A, Davis S, Furniss A, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. *J Clin Endocrinol Metab*. 2022;107(10):e4004-e4014. doi:10.1210/clinem/dgac469 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35945152

Valentine A, Nokoff N, Bonny A, et al. Cardiometabolic Parameters Among Transgender Adolescent Males on Testosterone Therapy and Body Mass Index-Matched Cisgender Females. *Transgend Health*. 2021;6(6):369-373. doi:10.1089/trgh.2020.0052 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993308

van de Grift TC, van Gelder ZJ, Mullender MG, Steensma TD, de Vries ALC, Bouman MB. Timing of Puberty Suppression and Surgical Options for Transgender Youth. *Pediatrics*.

2020;146(5)doi:10.1542/peds.2019-3653 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33106340

van der Loos M, Hannema SE, Klink DT, den Heijer M, Wiepjes CM. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health*. 2022;6(12):869-875. doi:10.1016/S2352-4642(22)00254-1 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36273487

van der Loos M, Klink DT, Hannema SE, et al. Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol. *J Sex Med*. 2023;20(3):398-409. doi:10.1093/jsxmed/qdac029 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36763938

Van Der Miesen AI, Hurley H, De Vries AL. Gender dysphoria and autism spectrum disorder: A narrative review. *Int Rev Psychiatry*. 2016;28(1):70-80. doi:10.3109/09540261.2015.1111199 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26753812

Van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *J Adolesc Health*. 2020;66(6):699-704. doi:10.1016/j.jadohealth.2019.12.018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32273193

Van Donge N, Schvey NA, Roberts TA, Klein DA. Transgender Dependent Adolescents in the U.S. Military Health Care System: Demographics, Treatments Sought, and Health Care Service Utilization. *Mil Med*. 2019;184(5-6):e447-e454. doi:10.1093/milmed/usy264 Accessed September 15, 2023. Available at https://watermark.silverchair.com/usy264.pdf

Vehmas N, Holopainen E, Suomalainen L, Savolainen-Peltonen H. Somatic Health and Psychosocial Background Among Finnish Adolescents with Gender Dysphoria Seeking Hormonal Interventions. *Transgend Health*. 2022;7(6):505-513. doi:10.1089/trgh.2021.0084 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36644116

Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*. 2017;95:11-19. doi:10.1016/j.bone.2016.11.008 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27845262

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. *Arch Sex Behav*. 2016;45(7):1697-1703. doi:10.1007/s10508-016-0764-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27251640

Vrouenraets LJJJ, de Vries ALC, Arnoldussen M, et al. Medical decision-making competence regarding puberty suppression: perceptions of transgender adolescents, their parents and clinicians. *Eur Child Adolesc Psychiatry*. 2022;32(11):2343-2361. doi:10.1007/s00787-022-02076-6 Accessed September 15, 2023. Available at https://link.springer.com/content/pdf/10.1007/s00787-022-02076-6.pdf

Vrouenraets LJJJ, de Vries ALC, de Vries MC, van der Miesen AIR, Hein IM. Assessing Medical Decision-Making Competence in Transgender Youth. *Pediatrics*. 2021;148(6)doi:10.1542/peds.2020-049643 Accessed September 15, 2023. Available at https://watermark.silverchair.com/peds_2020049643.pdf

Vrouenraets LJJJ, de Vries MC, Hein IM, Arnoldussen M, Hannema SE, de Vries ALC. Perceptions on the function of puberty suppression of transgender adolescents who continued or discontinued treatment, their parents, and clinicians. *International journal of transgender health*. 2022;23(4):428-441. doi:10.1080/26895269.2021.1974324 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9621271/pdf/WIJT_23_1974324.pdf

Wagner S, Panagiotakopoulos L, Nash R, et al. Progression of Gender Dysphoria in Children and Adolescents: A Longitudinal Study. *Pediatrics*. 2021;148(1)doi:10.1542/peds.2020-027722 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34099504

Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. *Transgender Health*. 2023;8(1):84-88. doi:10.1089/trgh.2021.0102 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/trgh.2021.0102

Warwick RM, Araya AC, Shumer DE, Selkie EM. Transgender Youths' Sexual Health and Education: A Qualitative Analysis. *J Pediatr Adolesc Gynecol*. 2022;35(2):138-146. doi:10.1016/j.jpag.2021.09.011 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34619356

Wilhelm S, Kelsberg G, Safranek S. How does gender-affirming hormone therapy affect QOL in transgender patients? *The Journal of family practice*. 2022;71(10):442-444. doi:10.12788/jfp.0521 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L640249400&from=export

Willemsen LA, Boogers LS, Wiepjes CM, et al. Just as Tall on Testosterone; a Neutral to Positive Effect on Adult Height of GnRHa and Testosterone in Trans Boys. *The Journal of clinical endocrinology and metabolism*. 2023;108(2):414-421. doi:10.1210/clinem/dgac571 Accessed September 15, 2023. Available at https://watermark.silverchair.com/dgac571.pdf

Wolf-Gould CS, Riley MR, Carswell JM. A Trans-Feminine Youth with a BRCA1 Mutation: Case Study. *LGBT health*. 2018;5(4):270-272. doi:10.1089/lgbt.2017.0148 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626215648&from=export

Wright T, Candy B, King M. Conversion therapies and access to transition-related healthcare in transgender people: a narrative systematic review. *BMJ Open*. 2018;8(12):e022425. doi:10.1136/bmjopen-2018-022425 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30580262

Zucker KJ, Bradley SJ, Owen-Anderson A, Singh D, Blanchard R, Bain J. Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study. *Journal of Gay & Lesbian Mental Health*. 2010;15(1):58-82. doi:10.1080/19359705.2011.530574 Accessed June 12, 2023. Available at https://www.tandfonline.com/doi/abs/10.1080/19359705.2011.530574

Zupanič S, Kruljac I, Sostaric Zvonar M, Drobnic Radobuljac M. Case Report: Adolescent With Autism and Gender Dysphoria. *Front Psychiatry*. 2021;12:671448. doi:10.3389/fpsyt.2021.671448 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34122187

No Long-term (>5 year) Outcomes

Alpern S, Yaish I, Wagner-Kolasko G, et al. Why fertility preservation rates of transgender men are much lower than those of transgender women. *Reprod Biomed Online*. 2022;44(5):943-950. doi:10.1016/j.rbmo.2022.01.003 Accessed September 15, 2023. Available at https://www.rbmojournal.com/article/S1472-6483(22)00029-3/fulltext

Amir H, Yaish I, Oren A, Groutz A, Greenman Y, Azem F. Fertility preservation rates among transgender women compared with transgender men receiving comprehensive fertility counselling. *Reprod Biomed Online*. 2020;41(3):546-554. doi:10.1016/j.rbmo.2020.05.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32651108

Andrzejewski J, Dunville R, Johns MM, Michaels S, Reisner SL. Medical Gender Affirmation and HIV and Sexually Transmitted Disease Prevention in Transgender Youth: Results from the Survey of Today's Adolescent Relationships and Transitions, 2018. *LGBT Health*. 2021;8(3):181-189. doi:10.1089/lgbt.2020.0367 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33566718

Aranda G, Fernandez-Rebollo E, Pradas-Juni M, et al. Effects of sex steroids on the pattern of methylation and expression of the promoter region of estrogen and androgen receptors in people with gender dysphoria under cross-sex hormone treatment. *J Steroid Biochem Mol Biol*. 2017;172:20-28. doi:10.1016/j.jsbmb.2017.05.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28539237

Aranda G, Mora M, Hanzu FA, Vera J, Ortega E, Halperin I. Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. *Endocrinol Diabetes Nutr (Engl Ed)*. 2019;66(6):385-392. doi:10.1016/j.endinu.2018.11.004 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30704917

Araya AC, Warwick R, Shumer D, Selkie E. Romantic relationships in transgender adolescents: A qualitative study. *Pediatrics*. 2021;147(2)doi:10.1542/peds.2020-007906 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2011108095&from=export

Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk Factors for Non-Suicidal Self-Injury Among Trans Youth. *J Sex Med*. 2016;13(3):402-412. doi:10.1016/j.jsxm.2016.01.003 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26944465

Borba Soll BM, Robles-Garcia R, Brandelli-Costa A, et al. Gender incongruence: a comparative study using ICD-10 and DSM-5 diagnostic criteria. *Braz J Psychiatry*. 2018;40(2):174-180. doi:10.1590/1516-4446-2016-2224 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28977069

Bui HN, Schagen SE, Klink DT, Delemarre-van de Waal HA, Blankenstein MA, Heijboer AC. Salivary testosterone in female-to-male transgender adolescents during treatment with intra-muscular

injectable testosterone esters. *Steroids*. 2013;78(1):91-95. doi:10.1016/j.steroids.2012.10.006 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23123742

Caanen MR, Soleman RS, Kuijper EA, et al. Antimullerian hormone levels decrease in female-to-male transsexuals using testosterone as cross-sex therapy. *Fertil Steril*. 2015;103(5):1340-1345. doi:10.1016/j.fertnstert.2015.02.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25772768

Carlson KJ, Irwin JA, Dowdall JR, Figy SC, Amoura NJ. Integrated Comprehensive Care for Transcare and Gender Diverse Clinic Patients: An Assessment of Physical, Mental, and Social Needs. *Cureus*. 2021;13(12):e20544. doi:10.7759/cureus.20544 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35070571

Chan KL, Mok CC. Development of systemic lupus erythematosus in a male-to-female transsexual: The role of sex hormones revisited. *Lupus*. 2013;22(13):1399-1402. doi:10.1177/0961203313500550 Accessed September 15, 2023. Available at https://journals.sagepub.com/doi/10.1177/0961203313500550?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Chen D, Kyweluk MA, Sajwani A, et al. Factors Affecting Fertility Decision-Making Among Transgender Adolescents and Young Adults. *LGBT Health*. 2019;6(3):107-115. doi:10.1089/lgbt.2018.0250 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30985275

Clark BA, Virani A. “This Wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy. *J Bioeth Inq*. 2021;18(1):151-164. doi:10.1007/s11673-020-10086-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33502682

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013;10(12):3049-3058. doi:10.1111/jsm.12155 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23574768

de Nie I, Meisner A, Kostelijk EH, et al. Impaired semen quality in trans women: prevalence and determinants. *Human reproduction (Oxford, England)*. 2020;35(7):1529-1536. doi:10.1093/humrep/deaa133 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32613241

Defreyne J, Van Schuylenbergh J, Motmans J, Tilleman KL, T'Sjoen GGR. Parental desire and fertility preservation in assigned female at birth transgender people living in Belgium. *Fertil Steril*. 2020;113(1):149-157 e142. doi:10.1016/j.fertnstert.2019.09.002 https://www.ncbi.nlm.nih.gov/pubmed/31727413

Dowshen N, Lee S, Franklin J, Castillo M, Barg F. Access to Medical and Mental Health Services Across the HIV Care Continuum Among Young Transgender Women: A Qualitative Study. *Transgend Health*. 2017;2(1):81-90. doi:10.1089/trgh.2016.0046 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28861551

Durcan E, Turan S, Bircan BE, et al. Fertility Desire and Motivation Among Individuals with Gender Dysphoria: A Comparative Study. *J Sex Marital Ther*. 2022;48(8):789-803.

doi:10.1080/0092623X.2022.2053617 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L637611845&from=export

Fernandez JD, Tannock LR. Metabolic Effects of Hormone Therapy in Transgender Patients. *Endocr Pract*. 2016;22(4):383-388. doi:10.4158/EP15950.OR Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26574790

Frederick MJ, Berhanu AE, Bartlett R. Chest Surgery in Female to Male Transgender Individuals. *Ann Plast Surg*. 2017;78(3):249-253. doi:10.1097/SAP.0000000000000882 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618622007&from=export

Fuss J, Hellweg R, Van Caenegem E, et al. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). *Eur Neuropsychopharmacol*. 2015;25(1):95-99. doi:10.1016/j.euroneuro.2014.11.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25498415

Gavidia R, Whitney DG, Hershner S, Selkie EM, Tauman R, Dunietz GL. Gender identity and transition: relationships with sleep disorders in US youth. *J Clin Sleep Med*. 2022;18(11):2553-2559. doi:10.5664/jcsm.10158 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35912700

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio IE, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2014;23(2):669-676. doi:10.1007/s11136-013-0497-3 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s11136-013-0497-3

Gridley SJ, Crouch JM, Evans Y, et al. Youth and Caregiver Perspectives on Barriers to Gender-Affirming Health Care for Transgender Youth. *J Adolesc Health*. 2016;59(3):254-261. doi:10.1016/j.jadohealth.2016.03.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27235374

Grimstad FW, Fowler KG, New EP, et al. Uterine pathology in transmasculine persons on testosterone: a retrospective multicenter case series. *Am J Obstet Gynecol*. 2019;220(3):257 e251-257 e257. doi:10.1016/j.ajog.2018.12.021 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30579875

Hisle-Gorman E, Schvey NA, Adirim TA, et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. *J Sex Med*. 2021;18(8):1444-1454. doi:10.1016/j.jsxm.2021.05.014 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/18/8/1444/6956103?redirectedFrom=fulltext

Humble RM, Imborek KL, Nisly N, Greene DN, Krasowski MD. Common Hormone Therapies Used to Care for Transgender Patients Influence Laboratory Results. *J Appl Lab Med*. 2019;3(5):799-814. doi:10.1373/jalm.2018.027078 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31639755

Jain J, Kwan D, Forcier M. Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results From a Retrospective Study. *J Clin Endocrinol Metab*. 2019;104(11):5148-5156. doi:10.1210/jc.2018-02253 https://www.ncbi.nlm.nih.gov/pubmed/31127826

Jalowiecka I, Gómez Balaguer M, Cañete San Pastor P, et al. Reproductive desire and gamete preservation in transgender people: Survey on real interest in a cohort from a Spanish tertiary hospital. *Progresos de Obstetricia y Ginecologia*. 2023;66(1):8-13. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2023301187&from=export

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co-morbidities in an irish adult population. *Front Endocrinol (Lausanne)*. 2014;5(JUN):87. doi:10.3389/fendo.2014.00087 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24982651

Keo-Meier CL, Herman LI, Reisner SL, Pardo ST, Sharp C, Babcock JC. Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. *J Consult Clin Psychol*. 2015;83(1):143-156. doi:10.1037/a0037599 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25111431

Ker A, Shaw RM, Byrne J, Veale J. Access to fertility preservation for trans and non-binary people in Aotearoa New Zealand. *Culture, health & sexuality*. 2022;24(9):1273-1288. doi:10.1080/13691058.2021.1944670 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L635611012&from=export

Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol*. 2018;178(2):163-171. doi:10.1530/EJE-17-0496 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29183889

Klein A, Golub SA. Enhancing Gender-Affirming Provider Communication to Increase Health Care Access and Utilization Among Transgender Men and Trans-Masculine Non-Binary Individuals. *LGBT health*. 2020;7(6):292-304. doi:10.1089/lgbt.2019.0294 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7475086/pdf/lgbt.2019.0294.pdf

Krüger A, Sperandei S, Bermudez XPCD, Merchán-Hamann E. Characteristics of hormone use by travestis and transgender women of the Brazilian Federal District. *Revista brasileira de epidemiologia = Brazilian journal of epidemiology*. 2019;22Suppl 1((Krüger A.; Bermudez X.P.C.D.; Merchán-Hamann E.) Post-Graduate Program in Collective Health, School of Health Sciences, University of Brasília, Brasília (DF), Brazil(Sperandei S.) Institute of Communication and Scientific Information and Technology in He):e190004. doi:10.1590/1980-549720190004.supl.1 Accessed September 15, 2023. Available at https://www.scielo.br/j/rbepid/a/9Cshmsw95pNmdmGtxMZcqYc/?lang=en&format=pdf

Lehmann K, Rosato M, McKenna H, Leavey G. Dramaturgical Accounts of Transgender Individuals: Impression Management in the Presentation of Self to Specialist Gender Services. *Arch Sex Behav*. 2021;50(8):3539-3549. doi:10.1007/s10508-021-02028-2 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8604840/pdf/10508_2021_Article_2028.pdf

Leung A, Sakkas D, Pang S, Thornton K, Resetkova N. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. *Fertil Steril*. 2019;112(5):858-865. doi:10.1016/j.fertnstert.2019.07.014 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31594633

Makino T, Fujita T, Nakano T. Fatty degeneration of mammary glands in female-to-male transsexuals. *Eur J Plast Surg*. 2017;40(4):309-314. doi:10.1007/s00238-016-1269-4 Accessed June 28, 2023. Available at https://link.springer.com/article/10.1007/s00238-016-1269-4

Mattelin E, Strandell A, Bryman I. Fertility preservation and fertility treatment in transgender adolescents and adults in a Swedish region, 2013-2018. *Human reproduction open*. 2022;2022(2):hoac008. doi:10.1093/hropen/hoac008 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35309678

Mehra G, Boskey ER, Peters CJ, Njubigbo C, Charlton BM, Ganor O. Assessing Fertility Intentions in Patients Presenting for Gender-Affirming Surgery. *LGBT health*. 2022;9(5):325-332. doi:10.1089/lgbt.2021.0148 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/10.1089/lgbt.2021.0148?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Meier SC, Pardo ST, Labuski C, Babcock J. Measures of clinical health among female-to-male transgender persons as a function of sexual orientation. *Arch Sex Behav*. 2013;42(3):463-474. doi:10.1007/s10508-012-0052-2 Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s10508-012-0052-2

Menino DD, Katz-Wise SL, Vetters R, Reisner SL. Associations Between the Length of Time from Transgender Identity Recognition to Hormone Initiation and Smoking Among Transgender Youth and Young Adults. *Transgend Health*. 2018;3(1):82-87. doi:10.1089/trgh.2018.0002 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29795789

Meyer G, Mayer M, Mondorf A, Flugel AK, Herrmann E, Bojunga J. Safety and rapid efficacy of guideline-based gender-affirming hormone therapy: an analysis of 388 individuals diagnosed with gender dysphoria. *Eur J Endocrinol*. 2020;182(2):149-156. doi:10.1530/EJE-19-0463 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31751300

Meyer G, Mayer M, Mondorf A, Herrmann E, Bojunga J. Increasing normality-persisting barriers: Current socio-demographic characteristics of 350 individuals diagnosed with gender dysphoria. *Clin Endocrinol (Oxf)*. 2020;92(3):241-246. doi:10.1111/cen.14140 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31821578

Millington K, Chan YM. Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. *J Clin Lipidol*. 2021;15(6):840-844. doi:10.1016/j.jacl.2021.09.051 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34657833

Nguyen HB, Loughead J, Lipner E, Hantsoo L, Kornfield SL, Epperson CN. What has sex got to do with it? The role of hormones in the transgender brain. *Neuropsychopharmacology*. 2019;44(1):22-37. doi:10.1038/s41386-018-0140-7 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30082887

Nikkelen SWC, Kreukels BPC. Sexual Experiences in Transgender People: The Role of Desire for Gender-Confirming Interventions, Psychological Well-Being, and Body Satisfaction. *J Sex Marital Ther*. 2018;44(4):370-381. doi:10.1080/0092623X.2017.1405303 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/pdf/10.1080/0092623X.2017.1405303

Oda H, Kinoshita T. Efficacy of hormonal and mental treatments with MMPI in FtM individuals: cross-sectional and longitudinal studies. *BMC Psychiatry*. 2017;17(1):256. doi:10.1186/s12888-017-1423-y Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28716082

Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men. *LGBT Health*. 2014;1(3):165-167. doi:10.1089/lgbt.2014.0018 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26789709

Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. *J Adolesc Health*. 2018;62(4):397-401. doi:10.1016/j.jadohealth.2017.08.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29056436

Owen-Smith AA, Gerth J, Sineath RC, et al. Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals. *The journal of sexual medicine*. 2018;15(4):591-600. doi:10.1016/j.jsxm.2018.01.017 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463478

Pang KC, Peri AJS, Chung HE, et al. Rates of Fertility Preservation Use Among Transgender Adolescents. *JAMA Pediatr*. 2020;174(9):890-891. doi:10.1001/jamapediatrics.2020.0264 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32282014

Papalini C, Lagi F, Schiaroli E, Sterrantino G, Francisci D. Transgender people living with HIV: characteristics and comparison to homosexual and heterosexual cisgender patients in two Italian teaching hospitals. *Int J STD AIDS*. 2021;32(2):194-198. doi:10.1177/0956462420950573 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33327898

Pena ÉD, Westin MR, Duarte MJ, et al. When prevention is the best remedy: HIV pre-exposure prophylaxis (PrEP) among adolescents gays and transgender women in Belo Horizonte, Minas Gerais State, Brazil. *Cad Saude Publica*. 2023;39((Pena É.D., ericadumont@gmail.com) Escola de Enfermagem, Universidade Federal de Minas Gerais, Av. Prof. Alfredo Balena 190, MG, Belo Horizonte, Brazil(Pena É.D., ericadumont@gmail.com) Escola de Enfermagem, Universidade Federal de Minas Gerais, Belo Hori):e00097921. doi:10.1590/0102-311XEN097921 Accessed September 15, 2023. Available at https://www.scielo.br/j/csp/a/jfPMB6tYHHMnJjgsV3ZBgnG/?lang=en&format=pdf

Pivo S, Montes J, Schwartz S, et al. Breast Cancer Risk Assessment and Screening in Transgender Patients. *Clin Breast Cancer*. 2017;17(5):e225-e227. doi:10.1016/j.clbc.2016.08.003 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28428098

Puckett JA, Cleary P, Rossman K, Newcomb ME, Mustanski B. Barriers to Gender-Affirming Care for Transgender and Gender Nonconforming Individuals. *Sexuality research & social policy : journal*

of NSRC : SR & SP. 2018;15(1):48-59. doi:10.1007/s13178-017-0295-8 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29527241

Quinn VP, Nash R, Hunkeler E, et al. Cohort profile: Study of Transition, Outcomes and Gender (STRONG) to assess health status of transgender people. *BMJ Open*. 2017;7(12):e018121. doi:10.1136/bmjopen-2017-018121 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29284718

Quirós C, Patrascioiu I, Mora M, et al. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015;62(5):210-216. doi:10.1016/j.endonu.2015.02.001 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25790747

Rametti G, Carrillo B, Gomez-Gil E, et al. Effects of androgenization on the white matter microstructure of female-to-male transsexuals. A diffusion tensor imaging study. *Psychoneuroendocrinology*. 2012;37(8):1261-1269. doi:10.1016/j.psyneuen.2011.12.019 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/22260939

Reisner SL, Vetters R, White JM, et al. Laboratory-confirmed HIV and sexually transmitted infection seropositivity and risk behavior among sexually active transgender patients at an adolescent and young adult urban community health center. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*. 2015;27(8):1031-1036. doi:10.1080/09540121.2015.1020750 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624263/pdf/nihms731729.pdf

Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A. Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. *Am J Public Health*. 2013;103(10):1830-1836. doi:10.2105/AJPH.2013.301348 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23948009

Roznovjak D, Petroll AE, Lakatos AEB, Narayan R, Cortina CS. Perceptions of Transgender and Nonbinary Persons Toward Breast and Cervical Cancer Development, Screening, and Potential Impact on Gender-Affirming Hormone Therapy. *JCO oncology practice*. 2023;19(5):e794-e800. doi:10.1200/OP.22.00681 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36800556

Schultz JJ, Naides AI, Bai D, Shulzhenko NO, Keith JD. Pathological Evaluation of Breast Specimens in Transgender Chest Masculinization: Incidental Findings and Effect of Prior Chest Binding and Androgen Therapy in 74 Consecutive Patients. *Transgend Health*. 2021;6(6):353-357. doi:10.1089/trgh.2020.0108 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34993306

Sequeira GM, Kidd K, El Nokali NE, et al. Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. *J Adolesc Health*. 2019;65(6):818-820. doi:10.1016/j.jadohealth.2019.06.009 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31543405

Simonsen R, Hald GM, Giraldi A, Kristensen E. Sociodemographic Study of Danish Individuals Diagnosed with Transsexualism. *Sexual Medicine*. 2015;3(2):109-117. doi:10.1002/sm2.48 Accessed

September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L604885291&from=export

Singh K, Sung CJ, Lawrence WD, Quddus MR. Testosterone-induced "Virilization" of Mesonephric Duct Remnants and Cervical Squamous Epithelium in Female-to-Male Transgenders: A Report of 3 Cases. *Int J Gynecol Pathol*. 2017;36(4):328-333. doi:10.1097/PGP.0000000000000333 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27571240

Soleman RS, Staphorsius AS, Cohen-Kettenis PT, et al. Oestrogens are Not Related to Emotional Processing: a Study of Regional Brain Activity in Female-to-Male Transsexuals Under Gonadal Suppression. *Cereb Cortex*. 2016;26(2):510-516. doi:10.1093/cercor/bhu201 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25246514

Strauss P, Cook A, Watson V, et al. Mental health difficulties among trans and gender diverse young people with an autism spectrum disorder (ASD): Findings from Trans Pathways. *J Psychiatr Res*. 2021;137:360-367. doi:10.1016/j.jpsychires.2021.03.005 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33761424

Tack LJ, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ*. 2016;7:14. doi:10.1186/s13293-016-0067-9 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26885361

Tan KKH, Byrne JL, Treharne GJ, Veale JF. Unmet need for gender-affirming care as a social determinant of mental health inequities for transgender youth in Aotearoa/New Zealand. *Journal of public health (Oxford, England)*. 2022;45((Tan K.K.H.; Byrne J.L.; Veale J.F.) Trans Health Research Lab, School of Psychology, University of Waikato, Hamilton, New Zealand(Tan K.K.H.) Faculty of Māori and Indigenous Studies, University of Waikato, Hamilton, New Zealand(Treharne G.J.) Department):e225-e233. doi:10.1093/pubmed/fdac131 Accessed September 15, 2023. Available at https://watermark.silverchair.com/fdac131.pdf

Vita R, Settineri S, Liotta M, Benvenga S, Trimarchi F. Changes in hormonal and metabolic parameters in transgender subjects on cross-sex hormone therapy: A cohort study. *Maturitas*. 2018;107:92-96. doi:10.1016/j.maturitas.2017.10.012 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29169588

Vyas N, Douglas CR, Mann C, Weimer AK, Quinn MM. Access, barriers, and decisional regret in pursuit of fertility preservation among transgender and gender-diverse individuals. *Fertil Steril*. 2021;115(4):1029-1034. doi:10.1016/j.fertnstert.2020.09.007 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33276964

Walton E, Abhari S, Tangpricha V, Futral C, Mehta A. Family Planning and Fertility Counseling Perspectives of Gender Diverse Adults and Youth Pursuing or Receiving Gender Affirming Hormone Therapy. *Urology*. 2023;171:244-250. doi:10.1016/j.urology.2022.10.007 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36404476

Witcomb GL, Bouman WP, Claes L, Brewin N, Crawford JR, Arcelus J. Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. *J Affect Disord*. 2018;235:308-315. doi:10.1016/j.jad.2018.02.051 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29665513

Zhou Y, Furutani M, Athurupana R, Nakatsuka M. Relation Between Identity Disclosure to Family Members and Mental Health in Japanese Transgender People. *Acta medica Okayama*. 2021;75(5):611-623. doi:10.18926/AMO/62774 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L636627235&from=export

Adult Population Only

Anderson WJ, Kolin DL, Neville G, et al. Prostatic Metaplasia of the Vagina and Uterine Cervix: An Androgen-associated Glandular Lesion of Surface Squamous Epithelium. *Am J Surg Pathol*. 2020;44(8):1040-1049. doi:10.1097/PAS.0000000000001486 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32282346

Auer MK, Fuss J, Nieder TO, et al. Desire to Have Children Among Transgender People in Germany: A Cross-Sectional Multi-Center Study. *J Sex Med*. 2018;15(5):757-767. doi:10.1016/j.jsxm.2018.03.083 Accessed September 15, 2023. Available at https://academic.oup.com/jsm/article-abstract/15/5/757/6980540?redirectedFrom=fulltext

Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018;141(5)doi:10.1542/peds.2017-3845 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29661941

Bouman WP, Claes L, Marshall E, et al. Sociodemographic Variables, Clinical Features, and the Role of Preassessment Cross-Sex Hormones in Older Trans People. *J Sex Med*. 2016;13(4):711-719. doi:10.1016/j.jsxm.2016.01.009 https://www.ncbi.nlm.nih.gov/pubmed/26897462

Castelo-Branco C, RiberaTorres L, Gomez-Gil E, Uribe C, Canizares S. Psychopathological symptoms in Spanish subjects with gender dysphoria. A cross-sectional study. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*. 2021;37(6):534-540. doi:10.1080/09513590.2021.1913113 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33904350

Chan KJ, Jolly D, Liang JJ, Weinand JD, Safer JD. Estrogen Levels Do Not Rise with Testosterone Treatment for Transgender Men. *Endocr Pract*. 2018;24(4):329-333. doi:10.4158/EP-2017-0203 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29561193

Cupisti S, Giltay EJ, Gooren LJ, et al. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010;94(7):2647-2653. doi:10.1016/j.fertnstert.2010.03.048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/20451188

Gooren LJ, Sungkaew T, Giltay EJ. Exploration of functional health, mental well-being and cross-sex hormone use in a sample of Thai male-to-female transgendered persons (kathoeys). *Asian J Androl*. 2013;15(2):280-285. doi:10.1038/aja.2012.139 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/23353716

Haselbacher G. [Escape from the wrong gender]. *MMW Fortschr Med*. 2014;156(12):38-39. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25369683

Hughes CK, McGarey P, Morrison D, Gawlik AE, Dominguez L, Dion GR. Vocal Fold Thinning in Transgender Patients. *J Voice*. 2021,

10.1016/j.jvoice.2021.06.026doi:10.1016/j.jvoice.2021.06.026 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34452779

Jacoby A, Rifkin W, Zhao LC, Bluebond-Langner R. Incidence of Cancer and Premalignant Lesions in Surgical Specimens of Transgender Patients. *Plast Reconstr Surg*. 2021;147(1):194-198. doi:10.1097/PRS.0000000000007452 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L633890506&from=export

Kearns S, O'Shea D, Neff K. Transgender and non-binary demographics, referrals, and comorbidities among young Irish adults (2014–2020). *Ir J Med Sci*. 2022;192:1679-1685. doi:10.1007/s11845-022-03163-y Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s11845-022-03163-y

Klein DA, Ellzy JA, Olson J. Care of a Transgender Adolescent. *Am Fam Physician*. 2015;92(2):142-148. Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26176373

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-254. doi:10.1080/00224499.2011.596954 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21797716

López JLJ, Guzmán MEM, Miranda NJ. Protocol care for patients with gender dysphoria : A case report. *Archivos de Neurociencias*. 2017;22(1):35-40. Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L621102318&from=export

MacDonald T, Noel-Weiss J, West D, et al. Transmasculine individuals' experiences with lactation, chestfeeding, and gender identity: A qualitative study. *BMC Pregnancy Childbirth*. 2016;16(1):106. doi:10.1186/s12884-016-0907-y Accessed September 15, 2023. Available at https://bmcpregnancychildbirth.biomedcentral.com/counter/pdf/10.1186/s12884-016-0907-y.pdf

Marchiano L. Gender detransition: a case study. *The Journal of analytical psychology*. 2021;66(4):813-832. doi:10.1111/1468-5922.12711 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9298887/pdf/JOAP-66-813.pdf

Marks DH, Hagigeorges D, Manatis-Lornell AJ, Dommasch E, Senna MM. Excess hair, hair removal methods, and barriers to care in gender minority patients: A survey study. *J Cosmet Dermatol*. 2020;19(6):1494-1498. doi:10.1111/jocd.13164 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31553137

Marsh C, McCracken M, Gray M, Nangia A, Gay J, Roby KF. Low total motile sperm in transgender women seeking hormone therapy. *J Assist Reprod Genet*. 2019;36(8):1639-1648. doi:10.1007/s10815-019-01504-y Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708020/pdf/10815_2019_Article_1504.pdf

Ristori J, Cocchetti C, Castellini G, et al. Hormonal Treatment Effect on Sexual Distress in Transgender Persons: 2-Year Follow-Up Data. *The journal of sexual medicine*. 2020;17(1):142-151. doi:10.1016/j.jsxm.2019.10.008 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31735612

Robertson BD, Lerner BS, Collen JF, Smith PR. The Effects of Transgender Hormone Therapy on Sleep and Breathing: A Case Series. *J Clin Sleep Med*. 2019;15(10):1529-1533. doi:10.5664/jcsm.7992 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31596219

Sam KQ, Severs FJ, Ebuoma LO, Chandandeep NS, Sedgwick EL. Granulomatous mastitis in a transgender patient. *Journal of Radiology Case Reports*. 2017;11(2):16-22. doi:10.3941/jrcr.v11i2.2934 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443635/pdf/jrcr-11-2-16.pdf

Strandjord SE, Ng H, Rome ES. Effects of treating gender dysphoria and anorexia nervosa in a transgender adolescent: Lessons learned. *Int J Eat Disord*. 2015;48(7):942-945. doi:10.1002/eat.22438 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/26337148

Taziaux M, Swaab DF, Bakker J. Sex differences in the neurokinin B system in the human infundibular nucleus. *J Clin Endocrinol Metab*. 2012;97(12):E2210-E2220. doi:10.1210/jc.2012-1554 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L366220088&from=export

Wrong Patient Population (eg, Patients with Sex Development Disorders)

Aziz NA, Mohd Ali MH, Ramli R. Hysterectomy in a phenotypic male with congenital adrenal hyperplasia (CAH). *BMJ Case Rep*. 2022;15(2)doi:10.1136/bcr-2021-246603 Accessed September 15, 2023. Available at https://casereports.bmj.com/content/15/2/e246603

Bosi IM, Holmes-Walker J, Lau NS, et al. Sexual identity in congenital adrenal hyperplasia. *J Paediatr Child Health*. 2021;57(4):581-583. doi:10.1111/jpc.14912 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32468703

Chuang J, Vallerie A, Breech L, et al. Complexities of gender assignment in 17beta-hydroxysteroid dehydrogenase type 3 deficiency: is there a role for early orchiectomy? *Int J Pediatr Endocrinol*. 2013;2013(1):15. doi:10.1186/1687-9856-2013-15 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24025597

Cocchetti C, Ristori J, Mazzoli F, et al. 5α-Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature. *J Endocrinol Invest*. 2020;43(8):1131-1136. doi:10.1007/s40618-020-01193-w Accessed September 15, 2023. Available at https://link.springer.com/article/10.1007/s40618-020-01193-w

Costa C, Castro-Correia C, Mira-Coelho A, et al. The dilemma of the gender assignment in a Portuguese adolescent with disorder of sex development due to 17beta-hydroxysteroid-dehydrogenase type 3 enzyme deficiency. *Endocrinology, diabetes & metabolism case reports*. 2014;2014(101618943):140064. doi:10.1530/EDM-14-0064 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25298885

Deeb A, Suwaidi HA, Ibukunoluwa F, Attia S. Phenotype, sex of rearing, gender re-assignment, and response to medical treatment in extended family members with a novel mutation in the SRD5A2 gene. *JCRPE Journal of Clinical Research in Pediatric Endocrinology*. 2016;8(2):236-240.

doi:10.4274/jcrpe.2782 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5096483/pdf/JCRPE-8-236.pdf

Gangaher A, Jyotsna VP, Chauhan V, John J, Mehta M. Gender of rearing and psychosocial aspect in 46 XX congenital adrenal hyperplasia. *Indian J Endocrinol Metab*. 2016;20(6):870-877. doi:10.4103/2230-8210.192922 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/27867895

Levy B, Teplitsky S, Kalaitzoglou E, Kahler S, Matheny JP, Saltzman AF. "Exogenous" 5 Alpha Reductase Deficiency: A Case Report". *Urology*. 2023;178(wsy, 0366151):147-150. doi:10.1016/j.urology.2023.05.001 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/37178876

Luy SCR, Ho F. A rare case of true hermaphrodite with features of klinefelter syndrome. *Phillippine Journal of Internal Medicine*. 2013;51(4)Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L372245520&from=export

T'Sjoen G, De Cuypere G, Monstrey S, et al. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2011;40(3):635-638. doi:10.1007/s10508-010-9624-1 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L362321508&from=export

Tunas SD, Dinc G, Goker Z, Uneri OS. Gender dysphoria in an adolescent diagnosed with Klinefelter syndrome over a follow-up period. *The European Research Journal*. 2017;4(1):48-51. doi:10.18621/eurj.313304 Accessed June 28, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626135868&from=export

Zainuddin AA, Mahdy ZA. The Islamic Perspectives of Gender-Related Issues in the Management of Patients With Disorders of Sex Development. *Arch Sex Behav*. 2017;46(2):353-360. doi:10.1007/s10508-016-0754-y Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L618034443&from=export

Wrong Intervention

Fisher CB, Fried AL, Desmond M, Macapagal K, Mustanski B. Perceived Barriers to HIV Prevention Services for Transgender Youth. *LGBT health*. 2018;5(6):350-358. doi:10.1089/lgbt.2017.0098 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145040/pdf/lgbt.2017.0098.pdf

Haley SG, Tordoff DM, Kantor AZ, Crouch JM, Ahrens KR. Sex Education for Transgender and Non-Binary Youth: Previous Experiences and Recommended Content. *J Sex Med*. 2019;16(11):1834-1848. doi:10.1016/j.jsxm.2019.08.009 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L2003126060&from=export

Hancock AB, Garabedian LM. Transgender voice and communication treatment: a retrospective chart review of 25 cases. *International journal of language & communication disorders / Royal College of Speech & Language Therapists*. 2013;48(1):54-65. doi:10.1111/j.1460-6984.2012.00185.x Accessed September 15, 2023. Available at https://onlinelibrary.wiley.com/doi/10.1111/j.1460-6984.2012.00185.x

Hardon A, Idrus NI, Hymans TD. Chemical sexualities: The use of pharmaceutical and cosmetic products by youth in South Sulawesi, Indonesia. *Reproductive Health Matters*. 2013;21(41):214-224. doi:10.1016/S0968-8080(13)41709-3 Accessed September 15, 2023. Available at https://www.tandfonline.com/doi/pdf/10.1016/S0968-8080%2813%2941709-3

Hill WJ, Shapiro MA. Transgender Youth in the Inpatient Psychiatric Setting: A Literature Review and Case Report. *J Psychiatr Pract*. 2017;23(4):290-293. doi:10.1097/PRA.0000000000000244 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28749834

Kattari SK, Bakko M, Hecht HK, Kinney MK. Intersecting Experiences of Healthcare Denials Among Transgender and Nonbinary Patients. *Am J Prev Med*. 2020;58(4):506-513. doi:10.1016/j.amepre.2019.11.014 Accessed September 15, 2023. Available at https://www.ajpmonline.org/article/S0749-3797(19)30538-0/fulltext

Katz-Wise SL, Budge SL, Orovecz JJ, Nguyen B, Nava-Coulter B, Thomson K. Imagining the future: Perspectives among youth and caregivers in the trans youth family study. *J Couns Psychol*. 2017;64(1):26-40. doi:10.1037/cou0000186 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5224913/pdf/nihms-828499.pdf

Nahata L, Campo-Engelstein LT, Tishelman A, Quinn GP, Lantos JD. Fertility Preservation for a Transgender Teenager. *Pediatrics*. 2018;142(3)doi:10.1542/peds.2017-3142 Accessed September 15, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30072573

Opsomer D, Gast KM, Ramaut L, et al. Creation of Clitoral Hood and Labia Minora in Penile Inversion Vaginoplasty in Circumcised and Uncircumcised Transwomen. *Plast Reconstr Surg*. 2018;142(5):729e-733e. doi:10.1097/PRS.0000000000004926 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L626511517&from=export

She J, McCall J, Pudwell J, Kielly M, Waddington A. An Assessment of the Mental Health History of Patients in a Transgender Clinic in Kingston, Ontario. *Can J Psychiatry*. 2020;65(4):281-283. doi:10.1177/0706743719901245 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/31961198

van der Miesen AIR, de Vries ALC, Steensma TD, Hartman CA. Autistic Symptoms in Children and Adolescents with Gender Dysphoria. *J Autism Dev Disord*. 2018;48(5):1537-1548. doi:10.1007/s10803-017-3417-5 Accessed September 15, 2023. Available at https://www.embase.com/search/results?subaction=viewrecord&id=L619498209&from=export

Wrong Study Design

Girardelli S, Albano L, Mangili G, et al. Meningiomas in Gynecology and Reproduction: an Updated Overview for Clinical Practice. *Reprod Sci*. 2022;29(9):2452-2464. doi:10.1007/s43032-021-00606-2 https://www.ncbi.nlm.nih.gov/pubmed/33970444

Grant AD, Kriegsfeld LJ. Continuous body temperature as a window into adolescent development. *Dev Cogn Neurosci*. 2023;60:101221. doi:10.1016/j.dcn.2023.101221 https://www.ncbi.nlm.nih.gov/pubmed/36821877

APPENDIX II.B: ROB SUMMARY OF TGNB VS TGNB OBSERVATIONAL STUDIES

Return to TOC

Table II.B.1. Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies

First author (year)	Criteria			
Arnoldussen (2022)[2]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average adolescent seeking GD treatment at the Center of Expertise on GD in the Netherlands	72 out of 119 eligible adolescents participated
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	b) structured interview	
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	IQ taken at initial assessment, gender affirming treatment given, then educational achievement was assessed.
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆	a) study controls for the most important confounder(s)	They looked at externalizing variables at start of treatment.
	Outcome			
	Outcome assessment		c) self-report	Participants completed a survey.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up occurred around 8 years after initial assessment
	Attrition	☆	a) complete follow up - all subjects accounted for	Based on data in results section, all patients are included in analysis
Asscheman (2011)[3]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB individual on CSHT in the Dutch community	Baseline and follow-up data of all transsexual subjects referred to their outpatient department since 1975 were entered into a cumulative database. The analysis on mortality aiming to measure longer term effects, only subjects who had started cross-sex hormone treatment before July 1, 1997, followed-up for at least 1 year and 2 MTF who had died the first year of hormone administration were included.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants who were never or former user and who were continuous user of ethinyl estradiol were recruited from the same clinic.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	Baseline and follow-up data of all TGNB subjects referred to the department since 1975 were entered into a cumulative database
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Data was collected from the time that the TGNB participants began CSHT at the clinic until death or end of study period
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆	a) study controls for the most important confounder(s)	In the Cox proportional hazard analysis of the type of estrogen treatment in MTF TGNB individuals, hazard ratio of mortality was adjusted for age, smoking status, and a starting date before 1990, although they also reported crude HR and HR adjusted for only age and smoking.

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; SBP, systolic blood pressure; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.1. Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies

First author (year)	Criteria			
	Outcome			
	Outcome assessment	☆	b) record linkage	The cause of death was ascertained by medical report or information from the family physician and was coded according to the International Classification of Disease (ICD-10, 10th revision 2007).
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Patients needed to be on CSHT for at least a year, and patients were followed for an average of was 19.3 ± 7.7 years in MTF cohort and 18.8 ± 6.3 years in FTM cohort
	Attrition	☆	a) complete follow-up-all patients accounted for	Due to the retrospective nature of the review, all patients that had a visit at the center were followed up. Of note, no patients on the waiting list were included in follow-up.
de Vries (2014)[4]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB adolescent in the Amsterdam gender identity clinic of the VUmc	Adolescents belonged to a group of consecutively referred adolescent, and then determined to be considered eligible for medical intervention.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	
	Ascertainment of exposure	☆	a) secure record (e.g., medical or surgical records)	Drawn from medical center
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Outcomes were checked again at follow-up with baseline information provided.
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆	b) study controls for any additional factor	Gender was addressed.
	Outcome			
	Outcome assessment		c) self-report	Outcomes were assessed using self-administered, validated questionnaires.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Follow-up was done at 1 year.
	Attrition		c) Follow-up rate ≥ 5% and no description of those lost	Only a portion finished the questionnaires.
Martinez-Martin (2023)[5]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average outpatient at the Gender Identity Clinic since its opening in March 2000	Most patients who are treated with estradiol plus LHRH agonists were previously treated with LHRH agonists as a puberty suppressor, and typically start estradiol therapy shortly after their 16th birthday, thus earlier than most other patients. (Note: Cyproterone acetate is banned in the US.)
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Drawn from the same community as exposed group: a local Outpatient Gender Identity Clinic (not in the US)

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; SBP, systolic blood pressure; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.1. Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies

First author (year)	Criteria			
	Ascertainment of exposure	☆	a) secure record (e.g., medical or surgical records)	Clinical records were retrospectively reviewed
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	Not specify in the article
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	For risk difference in incidence of HTN, adjusted for perceived gender, age, and calendar year at the onset of gender-affirming hormonal therapy, changes in body weight, fasting plasma glucose, creatinine, LDL-cholesterol, and triglycerides
	Outcome			
	Outcome assessment	☆	b) record linkage	SBP and diagnosis of HTN were obtained from clinical records.
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	They explored a 5-yr follow up.
	Attrition		c) Follow-up rate loss ≥ 5% and no description of those lost	Out of 811 records, 168 were lost to follow-up before completing 5 years of therapy
Wiepjes (2020)[6]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Dutch transgender individual in the community	No description of the study population is given within paper, but it includes all people that visited the center (most likely for gender-affirming care) within a span of 45 years. Description of cohort until 2015 is described in another paper, including data on percentage that had begun hormonal treatment. The fact that transgender people not seeking care were not included may be a source of confounding bias.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Comparisons were made within the cohort with some groups more clearly defined than others
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All participants that visited the center were included, as indicated by having a chart
	Outcome temporality requirements	☆	a) yes, study was designed to ensure that the timing of exposure measurement preceded the timing of outcome measurements	All data was collected from all people that visited the center, of which some received hormonal therapy until death or end of study period.
	Comparability			
	Comparability of (exposure/ comparator) cohorts		c) neither (a) nor (b)	No control of confounders is described; the study specifies that no information on psychological comorbidities or other psychological information (like social support) was obtained. Comparisons were made between gender and between those starting therapy before and after 18, but no controls besides the direct comparisons were used.
	Outcome			
	Outcome assessment	☆	b) record linkage	Verification of occurrence and cause of death of participants was obtained from the National Civil Record Registry of the Netherlands and the hospital registration system, medical, and psychological files for the transgender population.

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; SBP, systolic blood pressure; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.1. Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies

First author (year)	Criteria			
	Duration of follow-up	☆	a) yes, follow-up was long enough for outcome to occur	Suicide data was measured year to year from 1972-2018
	Attrition	☆	a) complete follow-up-all patients accounted for	Due to the retrospective nature of the review, all patients that had a visit at the center were followed up. Of note, no patients on the waiting list were included in follow-up.

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; SBP, systolic blood pressure; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.2. Newcastle-Ottawa Quality Assessment Scale (NOS) adapted for cross-sectional studies

First author (year)	Criteria			
Gomez-Gil (2021)[7]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB individual in the Spanish community	A sample of 200 TGNB individuals selected consecutively at the Gender Identity Team of the Hospital Clinic of Barcelona (Spain). The response rate was 93.5% of 200 patients who were invited to participate, resulting in a final study population of 187 TGNB individuals. This public hospital is the only center providing specialized and comprehensive psychiatric, psychological, endocrine, and surgical treatment for transsexual patients in Catalonia, Spain. However, does not mention how many were identified originally.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	Participants without cross-sex hormonal therapy and under cross-sex hormonal therapy were recruited from the same clinic.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	It is assumed that hormone treatment would be ascertained from their medical records based on selection criteria
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆ ☆	a) study controls for the most important confounder(s)	The relationship between SADS, HAD-Anxiety and HAD-Depression subscales and CSHT in TGNB patients were assessed, adjusting for age, gender, and educational level.
	Outcome			
	Outcome assessment		c) self-report	The data was collected from self-reported questionnaire responses.
	Duration of follow-up		N/A	
	Attrition		N/A	
Ott (2010)[8]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average TGNB MTF patient in Austria seeking CSHT	It is not clear if all patients that presented to the clinic are represented, but it seems to be a large cohort of those that were seen at the clinic to treat gender dysphoria
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	All patients were being seen at the same clinic
	Ascertainment of exposure	☆	a) secure record (e.g., medical or surgical records)	Records were reviewed for all interventions, treatments, and outcomes. All patients were seen before starting CSHT at the clinic, although some had been self-treating, and this was noted in the charts
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/ comparator) cohorts		c) neither (a) nor (b)	There were no confounders accounted for when comparing this subset except exposure to cyproterone acetate and/or ethinyl estradiol
	Outcome			
	Outcome assessment	☆	b) record linkage	Charts were used to assess all interventions, treatments, and outcomes

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HAD, Hospital Anxiety and Depression Scale; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; N/A, not applicable; SADS, Social Avoidance and Distress Scale; SBP, systolic blood pressure; SF-36, Short Form-36 Health Survey; SRS, sex-reassignment surgery; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.2. Newcastle-Ottawa Quality Assessment Scale (NOS) adapted for cross-sectional studies

First author (year)	Criteria			
	Duration of follow-up		N/A	
	Attrition		N/A	
Wierckx (2011)[9]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Dutch transgender man who had undergone reassignment surgery in the German community	Out of total population from hospital that underwent reassignment surgery (N=79), n= 47 participated in the study. So, it is somewhat representative of the total population at this site, and somewhat representative of men that have underwent surgery with previous hormone exposure.
	Selection of the nonexposed cohort		c) no description of the derivation of the non-exposed cohort	There is little information about the reference population except that they are a sample of Dutch-speaking, community dwelling men and women. No information if they are from the same community or ages of population.
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All Dutch-speaking transgender men that underwent SRS between 1987 and 2009 at the hospital were invited to the study, and all had previously been on hormonal therapy-it is assumed that the selection was made using chart or hospital records.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/ comparator) cohorts		c) neither (a) nor (b)	No control of confounders is described.
	Outcome			
	Outcome assessment		c) self-report	Self-perceived physical, social, and mental health was measured using the Dutch version of the Short Form-36 Health Survey (SF-36).
	Duration of follow-up		N/A	
	Attrition		N/A	
Wierckx (2012)[10]	**Selection**			
	Representativeness of the exposed cohort	☆	b) somewhat representative of the average Dutch transgender man who had undergone reassignment surgery in the German community	Out of the total population from hospital that underwent reassignment surgery (N=79), n= 47 participated in the study, in addition to 3 other men who were referred to study. So, it is somewhat representative of the total population at this site, and somewhat representative of TGNB men that have underwent surgery with previous hormone exposure.
	Selection of the nonexposed cohort	☆	a) drawn from the same community as the exposed cohort	TGNB men within the population who had children were compared to those that did not have children
	Ascertainment of exposure	☆	a) secure record (eg, medical or surgical records)	All Dutch-speaking transgender men that underwent SRS between 1987 and 2009 at the hospital were invited to the study, and all had previously been on hormonal therapy; it is assumed that the selection was made using chart or hospital records.
	Outcome temporality requirements		N/A	
	Comparability			
	Comparability of (exposure/ comparator) cohorts	☆	a) study controls for the most important confounder(s)	Subgroup analyses were performed to control for age and time since SRS; no differences were found.

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HAD, Hospital Anxiety and Depression Scale; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; N/A, not applicable; SADS, Social Avoidance and Distress Scale; SBP, systolic blood pressure; SF-36, Short Form-36 Health Survey; SRS, sex-reassignment surgery; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

Table II.B.2. Newcastle-Ottawa Quality Assessment Scale (NOS) adapted for cross-sectional studies

First author (year)	Criteria			
	Outcome			
	Outcome assessment		c) self-report	Self-perceived physical, social, and mental health was measured using the Dutch version of the Short Form-36 Health Survey (SF-36).
	Duration of follow-up		N/A	
	Attrition		N/A	

Abbreviations: CSHT, cross-sex hormone therapy; FTM, female-to-male; GnRH, gonadotropin-releasing hormone; HAD, Hospital Anxiety and Depression Scale; HTN, hypertension; ICD, International Classification of Disease; LDL, low-density lipoprotein; LHRH, luteinizing hormone-releasing hormone; MTF, male-to-female; N/A, not applicable; SADS, Social Avoidance and Distress Scale; SBP, systolic blood pressure; SF-36, Short Form-36 Health Survey; SRS, sex-reassignment surgery; TGNB, transgender, non-binary, and other gender-diverse; VUmc, Vrije University Medical Center

Return to TOC

APPENDIX II.C: ROB SUMMARY FOR LONGITUDINAL, PRE-POST DESCRIPTIVE STUDIES, OR SINGLE-ARM TRIALS

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
Arnoldussen (2022)[11]	1. Was the study question or objective clearly stated?	Yes	Self-perception changes over the course of irreversible medical gender-affirming treatments in TGNB adolescents was measured
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	Unclear-adolescents were only included if pretreatment data on self-perception was available, Out of 513 referred adolescents, 179 were eligible, and only 70 had pretreatment data on self-perception.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible candidates that also had the pretreatment data on self-perception were enrolled
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear. Did not report a power calculation.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	Some patients had received puberty suppression at pretreatment assessment, and some had not. Patients may have received a variety of GAH treatments and surgeries.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	all patients were evaluated on the same screening questionnaire-the SPSS
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All participants had received PS, CSH and gender affirming surgery
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Since data was retrospectively obtained, all patients had all data points
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P values and confidence intervals were calculated, and multilevel modeling was conducted to determine the effect of time. Possible confounders were also added to the model.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	ITS design was not used
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Asscheman (2011)[3]	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison, and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria clearly described
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	While we don't know how many subjects were excluded, there was a large population of TGNB participants included. Only selection criteria and number of subjects who met criteria were stated.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Subjects who met the inclusion criteria were included in analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention any information about power or sample size calculation. The only statement is that this study contains a larger study population compared to previous studies.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	The observed number of deaths in the study population was set against the expected numbers of deaths (except from AIDS and drug abuse) derived from the 2001 mortality data of the general population provided by the Central Bureau of Statistics of the Netherlands.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Not clearly stated
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Looks like all included participants had follow-up data. Baseline and follow-up data of all TGNB subjects referred to their outpatient department since 1975 were entered into a cumulative database.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Mortality data is pre-post. They did not report P value on that but did report 95% CI.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear	While data was assessed continually, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
De Blok (2021)[12]	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison, and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria clearly described
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Almost all participants that used hormone treatment were included, and this was a large sample size from the Dutch population
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Subjects who met the inclusion criteria were included in analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention any information about power/sample size calculation. But they did state that their study has large cohort.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Data about cause of death were retrieved from Statistics Netherlands (CBS) and were available since 1996. Cause of death was determined from the death certificates, which were filled out by the medical doctor at the time of death. If the cause of death was not known, it was registered on these forms as unknown. Each deceased person is registered with a single death cause (primary cause of death).
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Not clearly stated
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	One of the exclusion criteria is that people were excluded if there were no data available from at least one visit after the start of hormone treatment. Subjects included in analysis would not have loss to follow up issue.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Mortality data has pre post property in nature. They did not report P value on that but did report 95% CI.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear	While data was assessed continually, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
De Nie (2020)[19]	1. Was the study question or objective clearly stated?	Yes	"Objective: To assess the incidence of prostate cancer in trans women using hormone treatment."
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	General inclusion was mentioned; exclusion criteria were listed.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	They were seen in a gender identity clinic for treatment. Representative of TGNB individuals in the Dutch population who received CSHT for the treatment for GD
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	They had a total of 2307 individuals, with 2306 in the analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There was no mention of power. While this is a large sample size, the incidence of prostate cancer is very low
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	There was a switch of how estrogen therapy was provided over time, but it was consistent across the population
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Outcome was prostate cancer diagnosis obtained by a database linked to the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands and mortality data obtained from Statistics Netherlands
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No mention of blinding within the study
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	All eligible participants were included
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Cancer incidence data has pre post property in nature. They did not report P value on that but did report 95% CI.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	While data was assessed continually over time, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
De Vries (2014) [4]	1. Was the study question or objective clearly stated?	Yes	Can extract population, intervention, comparison, and outcome from the abstract.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Located on P2; other study provides additional detail on those who were eligible
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	First 70 were included, not the whole sample. Potential selection bias.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	Limited to the first 70
	5. Was the sample size sufficiently large to provide confidence in the findings?	Other	There were no power calculations.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Unclear	Some were on CSHT; the treatment regimen was not clearly provided.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	They used validated instruments to measure mental health outcomes and quality of life.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Participants answered validated surveys, but they knew what treatments they had received.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Noted when you look at the n provided by the individual results provided in the results tables.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-values were provided.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	There were three time periods, and a time linear quadratic P-value test was also provided. Multiple measurements not taken before intervention.
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	
Gooren (2013)[14]	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison, and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Eligibility criteria clearly described
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All participants who had started CSHT from 1975 through 2006 were included, at the largest transgender clinic in the Netherlands, representing the TGNB population who would desire and seek treatment
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Subjects who met the inclusion criteria were included in analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear if it is sufficiently large since they did not mention any information about power/sample size calculation. But they did state that their study has large cohort.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	The intervention was clearly described and delivered consistently across the population.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Cases of breast cancer were identified as baseline and follow-up data have been entered into a cumulative database since 1975. The incidence rate of breast cancer was calculated per 100,000 patient years of follow-up.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Unclear	Not clearly stated
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Those who were included in analysis were restricted to have available follow-up for at least 6 years.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Cancer incidence data is pre-post. They did not report P value on that but did report 95% CI.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear	While data was assessed continually, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
Gooren (2014)[15]	1. Was the study question or objective clearly stated?	Yes	"The aim of this study was to investigate the incidence of prostate cancer in a cohort of MTF individuals."
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	All charts for MTF treated TGNB patients between 1975 and 2006 were reviewed
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	All MTF participants who had started CSHT from 1975 to 2006 were included, at the largest transgender clinic in the Netherlands, representing the TGNB population who would desire and seek treatment
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	They had a total of 2307 individuals, with 2306 in the analysis.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There was no mention about power. While this is a large sample size, the incidence of prostate cancer is very low
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	There was a switch of how estrogen therapy was provided over time, but it was consistent across the population
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Outcome was prostate cancer diagnosis. They did describe how prostate cancer was diagnosed in the individual case, but it is not prespecified how prostate cancer would be diagnosed. They noted in the discussion that in their clinic, prostate cancer screening (either done by prostate surface antigen (PSA) or digital rectal examination (DRE) was not routinely done.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No mention of blinding within the study
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	There was only one individual out of 2307 that was not included in the analysis.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Unclear	Cancer incidence data has pre post property in nature. They did not report P-value on that but did report 95% CI.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	While data was assessed continually over time, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
Klink (2015)[16]	1. Was the study question or objective clearly stated?	Yes	Very clearly stated population, intervention, comparison, and objective
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Study subjects were included when they were at least 21 years of age, gonadectomy had taken place in the period from June 1998 to August 2012, and data on BMD at start of GnRH analog treatment, at start of CSHT, and at the age of 22 years were available. The 34 eligible subjects and their parents or legal representatives gave written consent for follow-up at start of treatment.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	This study was somewhat representative of the group. Some selection bias was likely introduced with a specific set of inclusion criteria and the need for specific metrics to have been included in past medical charts.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	It looks as if all patients who met criteria were included
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Unclear-no power calculation stated
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Patients all followed the same protocol
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Information was given about how all data was collected.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	All patients had been on the same treatment protocol
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No	Only 34 subjects were analyzed. No data provided about who was lost in follow-up.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Normally distributed data were compared with the paired sample T test with post-hoc Bonferroni correction. With data that were not normally distributed Wilcoxon Signed Rank test was used for comparison. For correlation analyses, the Pearson's correlation coefficient was calculated for normally distributed data. When data were not normally distributed the Spearman's rank correlation coefficient was calculated. P < .05 was considered statistically significant.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	While data was collected at 3 time points, there was no data collected at multiple time points before intervention
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No	
Nota (2018)[17]	1. Was the study question or objective clearly stated?	Yes	To assess the incidence of brain cancer in transgender individuals receiving cross-sex hormone treatment.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Inclusion and exclusion criteria were listed.
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	They were seen in a gender identity clinic for treatment. Representative of TGNB individuals who had received CSHT in the Dutch population for treatment for GD
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All eligible patients were enrolled in this retrospective review
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	There was no mention about power. While this is a large sample size, the incidence of certain cancers is very low
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	While there were different treatments for CSHT, there was a fairly standard protocol given to the population
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Outcome was prostate cancer diagnosis obtained by a database linked to the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands and data from mortality obtained from Statistics Netherlands
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No mention of blinding within the study
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	All eligible participants were included

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Cancer incidence data is pre-post in nature. They did not report P value on that but did report 95% CI.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	While data was assessed continually over time, the outcome measure is defined at one point in time by definition
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
Ott (2010)[8]	1. Was the study question or objective clearly stated?	Yes	To assess the incidence of thrombophilic events at baseline and to evaluate the incidence of VTE.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	All patients underwent screening for thrombophilia at the institution. A retrospective review was done for those presenting to the clinic from 1995 to 2007 who took CSHT
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	This cohort would be representative of TGNB individuals who seek out transgender care in Austria
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Unclear	251 patients presenting to the clinic from 1995 to 2007 were included, but it is unclear if this is the total population that presented to the clinic or a subset of that population
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	No mention of power within the study
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	All patients underwent the same screening for thrombophilia and participated in a standard CSHT protocol at the clinic
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Reviewed for a diagnosis of VTE
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No mention of blinding within the study
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Retrospective review, so no patient lost to follow-up
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	P-values and incidence comparisons were used
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	Although continually assessed for the outcome, only one measure was used
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A
Van der Loos (2021)[18]	1. Was the study question or objective clearly stated?	Yes	Clearly stated in abstract
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Listed under "Study Design and Population"

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	These patients were all who visited the gender clinic between 1972 and 2018
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Noted in text
	5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear	Power calculation was not provided.
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	There is a treatment protocol at this clinic.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes, patients were chosen that had the outcomes available. Measures were consistent across patient population.
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	Blinding was not noted.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Having appropriate measures was an inclusion criterion.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Implicitly; P-values do not seem to be provided but confidence intervals are.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	Only three time points
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No	
Wiepjes (2020)[6]	1. Was the study question or objective clearly stated?	Yes	The study sought to determine overall suicide death rate, incidence over time, and stage in transition where suicide deaths were observed in transgender people seen at the Center of Expertise on Gender Dysphoria of the Amsterdam UMC between 1972 and 2017.
	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	All people that once visited the center between 1972 and 2017 were included. No information on exclusion criteria is given. The article states that the selection of the study population is described in a previous study (Wiepjes 2018)[20].
	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	The study did not include transgender people that were not seeking care at the clinic.
	4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	All people that came to the clinic at any point during the study period (1972-2017) were included.
	5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	N = 8263; FTM = 5107, MTF = 3156
	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No	Participants were at different stages of their transition, but all sought care at the center at least once. Those that received hormone therapy were under a standard treatment protocol.
	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	A retrospective chart study was performed on all people that came to the center between 1972 and 2017, which included adults, adolescents, and children. Information on death occurrence and time was obtained by cross-checking the National Civil Record Registry for date of birth and death, and the hospital registration system, medical, and psychological files for cause of death.

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

Table II.C.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First Name (year)	Question	Answer	Details and notes
	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	This was a retrospective cohort study using existing records and all patients were TGNB individuals seeking care.
	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	No participants seem to be lost to follow-up, as the review was retrospective, but it was not addressed specifically.
	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Cox regressions were performed to calculate reported hazard ratios. No p-values were given, but 95% confidence intervals were.
	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	The outcome was death by suicide
	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A

Abbreviations: BMD, bone mineral density; CBS, Statistics Netherlands; CI, confidence interval; CSHT, cross-sex hormone therapy; DRE, digital rectal examination; FTM, female-to-male; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; MTF, male-to-female; N/A, not applicable; PSA, prostate surface antigen; TGNB, transgender, non-binary, and other gender-diverse; VTE, venous thromboembolism

Return to TOC

APPENDIX II.D: INCLUDED STUDIES

Studies with Long-term Data that Underwent Data Extraction

Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry*. 2022;27(4):1069-1076. doi:10.1177/13591045221091652 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35638479

Abstract: BACKGROUND: Concerns exist regarding effects of puberty suppression on neurodevelopment. Intelligence is strongly correlated with educational achievement in the general population. This study aimed to examine the association between pre-treatment intelligence and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents to contribute to the emerging understanding of the effect that gender-affirming treatment including puberty suppression may have on cognitive development. METHODS: IQ was measured in 72 adolescents (45 trans boys, 27 trans girls) at clinical entry (mean age 12.78 years), educational achievement was evaluated after gender-affirming treatment (mean age 20.40 years). RESULTS: IQ pre-treatment and educational achievement post-treatment were positively associated (Nagelkerke R = 0.71). DISCUSSION: The association between IQ pre-treatment and educational achievement post-treatment in transgender adolescents who received gender-affirming medical treatment including puberty suppression appears to be similar to the general population. This may reflect that gender-affirming medical treatment including puberty suppression does not negatively affect the association between IQ and educational achievement.

Annotation: Examines changes in IQ and educational achievement after puberty suppression with GnRH agonists and GAHT in TGNB adolescents from a gender specialty clinic

Arnoldussen M, van der Miesen AIR, Elzinga WS, et al. Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT health*. 2022;9(4):238-246. doi:10.1089/lgbt.2020.0494 Accessed September 15, 2023. Available at https://www.liebertpub.com/doi/pdf/10.1089/lgbt.2020.0494?download=true

Abstract: Purpose: Early medical treatment for transgender adolescents should contribute to healthy psychological development, including the development of positive self-perception. However, at present, there are no longitudinal studies that have examined whether current treatment approaches meet this expectation. Therefore, the aim of this single-arm retrospective study was to examine transgender adolescents' self-perception changes over the course of irreversible medical gender-affirming treatment. Methods: The total study sample consisted of 70 adolescents (49 trans men and 21 trans women). Self-perception was assessed before the start of gender-affirming hormone treatment (mean age = 14.65, standard deviation (SD) = 2.08) and at least 6 months after gender-affirming surgeries (mean age = 20.70, SD = 1.49) by Self-Perception Profile for Adolescents (SPPA). The SPPA is a self-report measure that examines self-perception on seven different domains: Scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, close friendship, and global self-worth. Multilevel modeling (random intercepts model) was conducted to determine the effect of time for all domains of self-perception. Results: It was found that the domains of physical appearance

and global self-worth improved significantly over the course of treatment. No domain worsened significantly over the course of treatment. The domains of scholastic competence, social acceptance, athletic competence, and close friendship remained stable over time. Conclusion: This study provides the first suggestive evidence that irreversible gender-affirming treatment for adolescents could contribute to the development of a more positive self-perception.

Annotation: Examines changes in psychosocial outcomes in TGNB adolescents before (while on hormonal treatments only) vs after gender-affirming surgery.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;164(4):635-642. doi:10.1530/EJE-10-1038 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21266549

Abstract: OBJECTIVE: Adverse effects of long-term cross-sex hormone administration to transsexuals are not well documented. We assessed mortality rates in transsexual subjects receiving long-term cross-sex hormones. DESIGN: A cohort study with a median follow-up of 18.5 years at a university gender clinic. Methods Mortality data and the standardized mortality rate were compared with the general population in 966 male-to-female (MtF) and 365 female-to-male (FtM) transsexuals, who started cross-sex hormones before July 1, 1997. Follow-up was at least 1 year. MtF transsexuals received treatment with different high-dose estrogen regimens and cyproterone acetate 100 mg/day. FtM transsexuals received parenteral/oral testosterone esters or testosterone gel. After surgical sex reassignment, hormonal treatment was continued with lower doses. RESULTS: In the MtF group, total mortality was 51% higher than in the general population, mainly from increased mortality rates due to suicide, acquired immunodeficiency syndrome, cardiovascular disease, drug abuse, and unknown cause. No increase was observed in total cancer mortality, but lung and hematological cancer mortality rates were elevated. Current, but not past ethinyl estradiol use was associated with an independent threefold increased risk of cardiovascular death. In FtM transsexuals, total mortality and cause-specific mortality were not significantly different from those of the general population. CONCLUSIONS: The increased mortality in hormone-treated MtF transsexuals was mainly due to non-hormone-related causes, but ethinyl estradiol may increase the risk of cardiovascular death. In the FtM transsexuals, use of testosterone in doses used for hypogonadal men seemed safe.

Annotation: Longitudinal, retrospective, descriptive study examining long-term mortality rates in a mixed population of TGNB adolescents and adults; comparisons were made to a reference population. This was also a cohort study comparing mortality risks in MTF patients receiving different estrogen compounds.

de Blok CJ, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol*. 2021;9(10):663-670. doi:10.1016/S2213-8587(21)00185-6 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/34481559

Abstract: BACKGROUND: Increased mortality in transgender people has been described in earlier studies. Whether this increased mortality is still present over the past decades is unknown. Therefore, we aimed to investigate trends in mortality over five decades in a large cohort of adult transgender people in addition to cause-specific mortality. METHODS: We did a retrospective cohort study of adult transgender people who visited the gender identity clinic of

Amsterdam University Medical Centre in the Netherlands. Data of transgender people who received hormone treatment between 1972 and 2018 were linked to Statistics Netherlands. People were excluded if they used alternating testosterone and oestradiol treatment, if they started treatment younger than age 17 years, or if they had ever used puberty-blockers before gender-affirming hormone treatment. Standardised mortality ratios (SMRs) were calculated using general population mortality rates stratified by age, calendar period, and sex. Cause-specific mortality was also calculated. FINDINGS: Between 1972 and 2018, 8831 people visited the gender identity clinic. 4263 were excluded from the study for a variety of reasons, and 2927 transgender women and 1641 transgender men were included in the study, with a total follow-up time of 40 232 person-years for transgender women and 17 285 person-years for transgender men. During follow-up, 317 (10.8%) transgender women died, which was higher than expected compared with general population men (SMR 1.8, 95% CI 1.6-2.0) and general population women (SMR 2.8, 2.5-3.1). Cause-specific mortality in transgender women was high for cardiovascular disease, lung cancer, HIV-related disease, and suicide. In transgender men, 44 people (2.7%) died, which was higher than expected compared with general population women (SMR 1.8, 95% CI 1.3-2.4) but not general population men (SMR 1.2, 95% CI 0.9-1.6). Cause-specific death in transgender men was high for non-natural causes of death. No decreasing trend in mortality risk was observed over the five decades studied. INTERPRETATION: This observational study showed an increased mortality risk in transgender people using hormone treatment, regardless of treatment type. This increased mortality risk did not decrease over time. The cause-specific mortality risk because of lung cancer, cardiovascular disease, HIV-related disease, and suicide gives no indication to a specific effect of hormone treatment, but indicates that monitoring, optimising, and, if necessary, treating medical morbidities and lifestyle factors remain important in transgender health care. FUNDING: None.

Annotation: Longitudinal, retrospective, pre-post descriptive study examining long-term mortality rates over time in a mixed population of hormone treated TGNB adolescents and adults; comparisons were made to a reference population of both natal and chosen gender.

de Nie I, de Blok CJM, van der Sluis TM, et al. Prostate Cancer Incidence under Androgen Deprivation: Nationwide Cohort Study in Trans Women Receiving Hormone Treatment. *J Clin Endocrinol Metab*. 2020;105(9):e3293-3299. doi:10.1210/clinem/dgaa412 https://www.ncbi.nlm.nih.gov/pubmed/32594155

Abstract: CONTEXT: Trans women (male sex assigned at birth, female gender identity) mostly use antiandrogens combined with estrogens and can subsequently undergo vaginoplasty including orchiectomy. Because the prostate remains in situ after this procedure, trans women are still at risk for prostate cancer. OBJECTIVE: To assess the incidence of prostate cancer in trans women using hormone treatment. The incidence of prostate cancer in trans women using hormone treatment. DESIGN: In this nationwide retrospective cohort study, data of participants were linked to the Dutch national pathology database and to Statistics Netherlands to obtain data on prostate cancer diagnosis and mortality. SETTING: Gender identity clinic. PARTICIPANTS: Trans women who visited our clinic between 1972 and 2016 and received hormone treatment were included. MAIN OUTCOME MEASURES: Standardized incidence ratios (SIRs) were calculated using the number of observed prostate cancer cases in our cohort and the number of expected cases based on age-specific incidence numbers from the Netherlands Comprehensive Cancer Organization. RESULTS: The study population consisted of 2281 trans women with a median follow-up time of 14 years (interquartile range 7-24), and a total follow-up time of 37 117 years. Six prostate cancer cases were identified after a median 17 years of hormone

treatment. This resulted in a lower prostate cancer risk in trans women than in Dutch reference males (SIR 0.20, 95% confidence interval 0.08-0.42). CONCLUSIONS: Trans women receiving androgen deprivation therapy and estrogens have a substantially lower risk for prostate cancer than the general male population. Our results support the hypothesis that androgen deprivation has a preventive effect on the initiation and development of prostate cancer.

Annotation: Longitudinal, retrospective, pre-post descriptive study examining long-term mortality rates over time in a mixed population of hormone treated TGNB adolescents and adults; comparisons were made to a reference population of both natal and chosen gender.

de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25201798

Abstract: BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach. METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated. RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being. CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults.

Annotation: A cohort study examining psychosocial functioning after GnRHas, cross-sex hormones, and surgery among TGNB adolescents.

Gomez-Gil E, Zubiaurre-Elorza L, Esteva I, et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;37(5):662-670. doi:10.1016/j.psyneuen.2011.08.010 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21937168

Abstract: INTRODUCTION: The aim of the present study was to evaluate the presence of symptoms of current social distress, anxiety and depression in transsexuals. METHODS: We investigated a group of 187 transsexual patients attending a gender identity unit; 120 had undergone hormonal sex-reassignment (SR) treatment and 67 had not. We used the Social Anxiety and Distress Scale (SADS) for assessing social anxiety and the Hospital Anxiety and Depression Scale (HADS) for evaluating current depression and anxiety. RESULTS: The mean

SADS and HADS scores were in the normal range except for the HAD-Anxiety subscale (HAD-A) on the non-treated transsexual group. SADS, HAD-A, and HAD-Depression (HAD-D) mean scores were significantly higher among patients who had not begun cross-sex hormonal treatment compared with patients in hormonal treatment (F=4.362, p=.038; F=14.589, p=.001; F=9.523, p=.002 respectively). Similarly, current symptoms of anxiety and depression were present in a significantly higher percentage of untreated patients than in treated patients (61% vs. 33% and 31% vs. 8% respectively). CONCLUSIONS: The results suggest that most transsexual patients attending a gender identity unit reported subclinical levels of social distress, anxiety, and depression. Moreover, patients under cross-sex hormonal treatment displayed a lower prevalence of these symptoms than patients who had not initiated hormonal therapy. Although the findings do not conclusively demonstrate a direct positive effect of hormone treatment in transsexuals, initiating this treatment may be associated with better mental health of these patients.

Annotation: Observational study comparing symptoms of current social distress, anxiety, and depression between a mixed population of adolescent and adult hormone treated TGNB vs untreated TGNB participants

Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014;46(10):1156-1160. doi:10.1111/and.12208 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24329588

Abstract: Male-to-female transsexual persons (MtoF) undergo treatment with antiandrogens and oestrogens followed by bilateral orchiectomy. The aim of this study was to investigate the incidence of prostate cancer (PCa) in a cohort of MtoF individuals. Medical records 2306 MtoF treated between 1975 and 2006 of the Amsterdam Gender Clinic were reviewed. Mean age at initiation of treatment was 29.3 +/- 12.7 years (range 16-83). Mean follow-up was 21.4 years, resulting in a combined total of 51 173 person-years of exposure and follow-up. Follow-up more than 20 years was available for 303 individuals, including follow-up of more than 30 years in 151 individuals. A single case of PCa was identified in this group. The overall incidence of PCa in this population was 0.04% and 0.13% for individuals who had initiated hormonal treatment after at 40 years or later. PCa in this large MtoF population was rare. However, underdiagnosis is likely due to lack of close prostate monitoring and suppression of PSA due to androgen deprivation. In addition, only a limited number of MtoF individuals have yet reached old age when PCa becomes more common. When diagnosed in this population, there appears to be a tendency for PCa to behave aggressively. Prostate monitoring should be considered in these individuals beginning at age 50 years.

Annotation: Longitudinal, retrospective, pre-post descriptive study examining the incidence of prostate cancer in transgender women who received antiandrogens and estrogens followed by a bilateral orchiectomy as an adolescent and/or an adult as part of their treatment.

Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *J Sex Med*. 2013;10(12):3129-3134. doi:10.1111/jsm.12319 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/24010586

Abstract: INTRODUCTION: Transsexual people receive cross-sex hormones as part of their treatment, potentially inducing hormone-sensitive malignancies. AIM: To examine the

occurrence of breast cancer in a large cohort of Dutch male and female transsexual persons, also evaluating whether the epidemiology accords with the natal sex or the new sex. MAIN OUTCOME MEASURE: Number of people with breast cancer between 1975 and 2011. METHODS: We researched the occurrence of breast cancer among transsexual persons 18-80 years with an exposure to cross-sex hormones between 5 to >30 years. Our study included 2,307 male-to-female (MtF) transsexual persons undergoing androgen deprivation and estrogen administration (52,370 person-years of exposure), and 795 female-to-male (FtM) subjects receiving testosterone (15,974 total years of exposure). RESULTS: Among MtF individuals one case was encountered, as well as a probable but not proven second case. The estimated rate of 4.1 per 100,000 person-years (95% confidence interval [CI]: 0.8-13.0) was lower than expected if these two cases are regarded as female breast cancer, but within expectations if viewed as male breast cancer. In FtM subjects, who were younger and had shorter exposure to cross-sex hormones compared with the MtF group, one breast cancer case occurred. This translated into a rate of 5.9 per 100,000 person-years (95% CI: 0.5-27.4), again lower than expected for female breast cancer but within expected norms for male breast cancer. CONCLUSIONS: The number of people studied and duration of hormone exposure are limited but it would appear that cross-sex hormone administration does not increase the risk of breast cancer development, in either MtF or FtM transsexual individuals. Breast carcinoma incidences in both groups are comparable to male breast cancers. Cross-sex hormone treatment of transsexual subjects does not seem to be associated with an increased risk of malignant breast development.

Annotation: Longitudinal, retrospective, pre-post descriptive study examining the incidence of breast cancer in a TGNB population who received CSHT as an adolescent and/or an adult as part of their treatment; incidence rate was compared to the expected incidence for the Dutch population.

Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;100(2):E270-275. doi:10.1210/jc.2014-2439 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/25427144

Abstract: CONTEXT: Sex steroids are important for bone mass accrual. Adolescents with gender dysphoria (GD) treated with gonadotropin-releasing hormone analog (GnRHa) therapy are temporarily sex-steroid deprived until the addition of cross-sex hormones (CSH). The effect of this treatment on bone mineral density (BMD) in later life is not known. OBJECTIVE: This study aimed to assess BMD development during GnRHa therapy and at age 22 years in young adults with GD who started sex reassignment (SR) during adolescence. DESIGN AND SETTING: This was a longitudinal observational study at a tertiary referral center. PATIENTS: Young adults diagnosed with gender identity disorder of adolescence (DSM IV-TR) who started SR in puberty and had undergone gonadectomy between June 1998 and August 2012 were included. In 34 subjects BMD development until the age of 22 years was analyzed. INTERVENTION: GnRHa monotherapy (median duration in natal boys with GD [transwomen] and natal girls with GD [transmen] 1.3 and 1.5 y, respectively) followed by CSH (median duration in transwomen and transmen, 5.8 and 5.4 y, respectively) with discontinuation of GnRHa after gonadectomy. MAJOR OUTCOME MEASURES: How BMD develops during SR until the age of 22 years. RESULTS AND CONCLUSION: Between the start of GnRHa and age 22 years the lumbar areal BMD z score (for natal sex) in transwomen decreased significantly from -0.8 to -1.4 and in transmen there was a trend for decrease from 0.2 to -0.3. This suggests that the BMD was below their

pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated.

Annotation: Examines patient characteristics and bone outcomes over time in GnRH agonist- and CSHT-treated adolescents in a gender specialty clinic

Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. *Hypertens Res*. 2023;46(1):219-225. doi:10.1038/s41440-022-01067-z Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36229533

Abstract: In order to assess the risk of hypertension development, we performed a retrospective analysis of the clinical records of consecutive transgender patients who began gender-affirming hormonal therapy in our Outpatient Gender Identity Clinic with <30 years of age and had a follow-up >5 years. 149 transgender women treated with estradiol and 153 transgender men treated with testosterone were included; 129 of the transgender women received also androgen blockers (54 spironolactone, 49 cyproterone acetate and 26 LHRH agonists). The annual incidence of hypertension in young transgender men (1.18%) seemed comparable to that of the general population. In young transgender women, it seemed higher (2.14%); we found that the choice of androgen blocker had a remarkable effect, with a highly significant increase in patients treated with cyproterone acetate (4.90%) vs. the rest (0.80%); the adjusted hazard-ratio was 0.227 ($p = 0.001$). Correlation, logistic regression and mediation analyses were performed for the associations of the available clinical variables with the increase in systolic blood pressure and the onset of hypertension, but besides the use of cyproterone acetate, only the ponderal gain was found significant (Spearman's r: 0.361, $p < 0.001$); with a 36.7% mediation effect (31.2-42.3%). Cyproterone acetate has additional known risks, such as meningioma; although we cannot conclusively prove that it has a role in the development of hypertension, we conclude that the use of cyproterone acetate for this indication should be reconsidered.

Annotation: A cohort study comparing blood pressure outcomes in young transgender patients receiving different hormone therapies.

Nota NM, Wiepjes CM, de Blok CJM, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. *Brain*. 2018;141(7):2047-2054. doi:10.1093/brain/awy108 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29688280

Abstract: Benign brain tumours may be hormone sensitive. To induce physical characteristics of the desired gender, transgender individuals often receive cross-sex hormone treatment, sometimes in higher doses than hypogonadal individuals. To date, long-term (side) effects of cross-sex hormone treatment are largely unknown. In the present retrospective chart study we aimed to compare the incidence of common benign brain tumours: meningiomas, pituitary adenomas (non-secretive and secretive), and vestibular schwannomas in transgender individuals receiving cross-sex hormone treatment, with those reported in general Dutch or European populations. This study was performed at the VU University Medical Centre in the Netherlands and consisted of 2555 transwomen (median age at start of cross-sex hormone treatment: 31 years, interquartile range 23-41) and 1373 transmen (median age 23 years, interquartile range 18-31) who were followed for 23 935 and 11 212 person-years, respectively. For each separate

brain tumour, standardized incidence ratios with 95% confidence intervals were calculated. In transwomen (male sex assigned at birth, female gender identity), eight meningiomas, one non-secretive pituitary adenoma, nine prolactinomas, and two vestibular schwannomas occurred. The incidence of meningiomas was higher in transwomen than in a general European female population (standardized incidence ratio 4.1, 95% confidence interval 1.9-7.7) and male population (11.9, 5.5-22.7). Similar to meningiomas, prolactinomas occurred more often in transwomen compared to general Dutch females (4.3, 2.1-7.9) and males (26.5, 12.9-48.6). Noteworthy, most transwomen had received orchiectomy but still used the progestogenic anti-androgen cyproterone acetate at time of diagnosis. In transmen (female sex assigned at birth, male gender identity), two cases of somatotrophinomas were observed, which was higher than expected based on the reported incidence rate in a general European population (incidence rate females = incidence rate males; standardized incidence ratio 22.2, 3.7-73.4). Based on our results we conclude that cross-sex hormone treatment is associated with a higher risk of meningiomas and prolactinomas in transwomen, which may be linked to cyproterone acetate usage, and somatotrophinomas in transmen. Because these conditions are quite rare, performing regular screenings for such tumours (e.g. regular prolactin measurements for identifying prolactinomas) seems not necessary.

Annotation: Longitudinal, retrospective pre-post study examining the occurrence of benign brain tumors in a mixed population of adolescent and adult TGNB patients who received CSHT. A standardized incidence ratio was calculated using incidence data of general Dutch or European reference populations.

Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267-1272. doi:10.1016/j.fertnstert.2008.12.017 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/19200981

Abstract: OBJECTIVE: To evaluate the incidence of venous thromboembolism (VTE) in transsexual patients and the value of screening for thrombophilia in this population. DESIGN: Retrospective cohort study. SETTING: Academic research institution. PATIENT(S): Two hundred fifty-one transsexuals (162 male-to-female [MtF] and 89 female-to-male [FtM] transsexuals). INTERVENTION(S): Screening for activated protein C (aPC) resistance, antithrombin III, free protein S antigen, and protein C deficiency. MAIN OUTCOME MEASURE(S): Incidence of thrombophilic defects and VTE during cross-sex hormone therapy. RESULT(S): Activated protein C resistance was detected in 18/251 patients (7.2%), and protein C deficiency was detected in one patient (0.4%). None of the patients developed VTE under cross-sex hormone therapy during a mean of 64.2 +/- 38.0 months. There was no difference in the incidence of thrombophilia comparing MtF and FtM transsexuals (8.0% [13/162] vs. 5.6% [5/89], respectively). CONCLUSION(S): VTE during cross-sex hormone therapy is rare. General screening for thrombophilic defects in transsexual patients is not recommended. Cross-sex hormone therapy is feasible in MtF as well as in FtM patients with aPC resistance.

Annotation: Longitudinal, retrospective, pre-post study examining the incidence of thrombophilia and VTE in a mixed pediatric and adult TGNB population using CSHT, as well as a cohort study comparing MTF and FTM TGNB participants, and a comparison of incidence of VTE to reference population.

van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *J Bone Miner Res*. 2021;36(5):931-941. doi:10.1002/jbmr.4262 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33507568

Abstract: Bone geometry can be described in terms of periosteal and endocortical growth and is partly determined by sex steroids. Periosteal and endocortical apposition are thought to be regulated by testosterone and estrogen, respectively. Gender-affirming hormone (GAH) treatment with sex steroids in transgender people might affect bone geometry. However, in adult transgender people, no change in bone geometry during GAH was observed. In this study, we investigated changes in bone geometry among transgender adolescents using a gonadotropin-releasing hormone agonist (GnRHa) and GAH before achieving peak bone mass. Transgender adolescents treated with GnRHa and subsequent GAH before the age of 18 years were eligible for inclusion. Participants were grouped based on their Tanner stage at the start of GnRHa treatment and divided into early, mid, and late puberty groups. Hip structure analysis software calculating subperiosteal width (SPW) and endocortical diameter (ED) was applied to dual-energy X-ray absorptiometry scans performed at the start of GnRHa and GAH treatments, and after >/=2 years of GAH treatment. Mixed-model analyses were performed to study differences over time. Data were visually compared with reference values of the general population. A total of 322 participants were included, of whom 106 were trans women and 216 trans men. In both trans women and trans men, participants resembled the reference curve for SPW and ED of the experienced gender but only when GnRHa was started during early puberty. Those who started during mid and late puberty remained within the reference curve of the gender assigned at birth. A possible explanation might be sought in the phenomenon of programming, which conceptualizes that stimuli during critical windows of development can have major consequences throughout one's life span. Therefore, this study adds insights into sex-specific bone geometry development during puberty of transgender adolescents treated with GnRHa, as well as the general population. (c) 2021 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

Annotation: Reports on bone changes over time in TGNB adolescents seen in a gender specialty clinic. Reports the size of the ACOG as 8210 patients in 2018, up from 6793 patients in 2015.

Wiepjes CM, den Heijer M, Bremmer MA, et al. Trends in suicide death risk in transgender people: results from the Amsterdam Cohort of Gender Dysphoria study (1972-2017). *Acta Psychiatr Scand*. 2020;141(6):486-491. doi:10.1111/acps.13164 https://www.ncbi.nlm.nih.gov/pubmed/32072611

Abstract: OBJECTIVE: This study explored the overall suicide death rate, the incidence over time, and the stage in transition where suicide deaths were observed in transgender people. METHODS: A chart study, including all 8263 referrals to our clinic since 1972. Information on death occurrence, time, and cause of death was obtained from multiple sources. RESULTS: Out of 5107 trans women (median age at first visit 28 years, median follow-up time 10 years) and 3156 trans men (median age at first visit 20 years, median follow-up time 5 years), 41 trans women and 8 trans men died by suicide. In trans women, suicide deaths decreased over time, while it did not change in trans men. Of all suicide deaths, 14 people were no longer in treatment, 35 were in treatment in the previous two years. The mean number of suicides in the years 2013-2017 was higher in the trans population compared with the Dutch population.

CONCLUSIONS: We observed no increase in suicide death risk over time and even a decrease in suicide death risk in trans women. However, the suicide risk in transgender people is higher than in the general population and seems to occur during every stage of transitioning. It is important to have specific attention for suicide risk in the counseling of this population and in providing suicide prevention programs.

Annotation: Longitudinal, retrospective, pre-post study examining trends in suicide death risk in a mixed pediatric and adult TGNB population. Incidence compared to a reference Dutch population.

Wierckx K, Van Caenegem E, Elaut E, et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;8(12):3379-3388. doi:10.1111/j.1743-6109.2011.02348.x Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21699661

Abstract: INTRODUCTION: Although sexual health after genital surgery is an important outcome factor for many transsexual persons, little attention has been attributed to this subject. AIMS: To provide data on quality of life and sexual health after sex reassignment surgery (SRS) in transsexual men. METHODS: A single-center, cross-sectional study in 49 transsexual men (mean age 37 years) after long-term testosterone therapy and on average 8 years after SRS. Ninety-four percent of the participants had phalloplasty. MAIN OUTCOME MEASURES: Self-reported physical and mental health using the Dutch version of the Short Form-36 Health Survey; sexual functioning before and after SRS using a newly constructed specific questionnaire. RESULTS: Compared with a Dutch reference population of community-dwelling men, transsexual men scored well on self-perceived physical and mental health. The majority reported having been sexually active before hormone treatment, with more than a quarter having been vaginally penetrated frequently before starting hormone therapy. There was a tendency toward less vaginal involvement during hormone therapy and before SRS. Most participants reported an increase in frequency of masturbation, sexual arousal, and ability to achieve orgasm after testosterone treatment and SRS. Almost all participants were able to achieve orgasm during masturbation and sexual intercourse, and the majority reported a change in orgasmic feelings toward a more powerful and shorter orgasm. Surgical satisfaction was high, despite a relatively high complication rate. CONCLUSION: Results of the current study indicate transsexual men generally have a good quality of life and experience satisfactory sexual function after SRS.

Annotation: Observational cohort study examining quality of life, sexual health, and satisfaction of surgical results among transgender men after SRS who had started CSHT as an adolescent or adult with QOL scores compared to a Dutch sample population. Also, a longitudinal, descriptive pre-post study comparing sexual functioning before and after hormone therapy and SRS.

Wierckx K, Van Caenegem E, Pennings G, et al. Reproductive wish in transsexual men. *Hum Reprod*. 2012;27(2):483-487. doi:10.1093/humrep/der406 Accessed September 15, 2023. Available at https://watermark.silverchair.com/der406.pdf

Abstract: BACKGROUND: Hormonal therapy and sex reassignment surgery (SRS) in transsexual persons lead to an irreversible loss of their reproductive potential. The current and future technologies could create the possibility for female-to-male transsexual persons (transsexual men) to have genetically related children. However, little is known about this topic. The aim of this study is to provide information on the reproductive wishes of transsexual men after SRS.

METHODS: A self-constructed questionnaire was presented to 50 transsexual men in a single-center study. RESULTS: The majority (64%) of transsexual men were currently involved in a relationship. Eleven participants (22.0%) reported having children. For eight participants, their female partner was inseminated with donor sperm, whereas three participants gave birth before hormonal therapy and SRS. At the time of interview, more than half of the participants desired to have children (54%). There were 18 participants (37.5%) who reported that they had considered freezing their germ cells, if this technique would have been available previously. Participants without children at the time of investigation expressed this desire more often than participants with children ($\chi 2$ test: P = 0.006). CONCLUSIONS: Our data reveal that the majority of transsexual men desire to have children. Therefore, more attention should be paid to this topic during the diagnostic phase of transition and to the consequences for genetic parenthood after starting sex reassignment therapy.

Annotation: Descriptive study examining the reproductive wishes of transgender men following CHST and SRS as an adolescent and/or adult, as well as a cohort study comparing transgender men with and without children and their quality of life.

Studies with Long-term Data but Lacking High-priority Outcomes (Bibliography Only)

Cohen A, Gomez-Lobo V, Willing L, et al. Shifts in Gender-Related Medical Requests by Transgender and Gender-Diverse Adolescents. *J Adolesc Health*. 2023;72(3):428-436. doi:10.1016/j.jadohealth.2022.10.020 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/36529618

Abstract: PURPOSE: Gender-affirming hormones and/or surgeries seeking to change the body can have potentially lasting effects. Changes in requests for these therapies among gender-diverse youth are not well-understood. The study aim is to characterize factors associated with shifts in gender-related medical requests. METHODS: This mixed-methods study used retrospective chart review and qualitative interviews with clinicians. Of 130 youth receiving clinical gender care at Children's National Hospital, 68 met inclusion criteria. Qualitative interview analysis was performed to identify patterns and themes around shifts in gender-related medical requests over time. Statistical analysis employed chi-square and t-tests to compare characteristics in the shift versus no-shift groups and kappa statistics to calculate qualitative coding agreement. RESULTS: Of the 68 youth followed over time (mean age 15.11 years, 47% autistic, 22% nonbinary), 20 (29%) reported a shift in request. No significant differences were found by age, autism status, or designated sex at birth. More youth with shifts were nonbinary (p = .012). Six shift profiles were identified from qualitative interviews with excellent reliability (kappa = 0.865). Four of the profiles reflect shifts in request prior to starting treatment (85% sample); two involved shifts after commencing treatment (15%). The most common profile reflected a medical request that was made, withdrawn, and re-requested (45%). DISCUSSION: Shifts in gender-affirming medical requests by gender-diverse youth may not be uncommon during the adolescent's gender discernment process, and may more likely occur among nonbinary youth. Many individuals who experience shifts away from medical treatment may later resume the request.

Annotation: A case-control study examining potential predictors of GD treatment discontinuation in TGNB adolescents in a gender services program. Only natal sex (29 AMAB and 39 AFAB) and transbinary/nonbinary were reported.

Imhof RL, Davidge-Pitts CJ, Miest RYN, Nippoldt TB, Tollefson MM. Dermatologic disorders in transgender patients: A retrospective cohort of 442 patients. *J Am Acad Dermatol*. 2020;83(5):1516-1518. doi:10.1016/j.jaad.2020.06.074 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32593637

Abstract: None

Annotation: Longitudinal, retrospective, pre-post study examining dermatologic treatment and outcomes in a mixed pediatric and adult TGNB population.

Kempf AM, Burns ZT, Guss CE, et al. Clinical outcomes and considerations of gender-affirming care for transgender and gender-diverse pediatric and young adult patients with cancer. *Pediatr Blood Cancer*. 2023;70(1):e29851. doi:10.1002/pbc.29851 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/35713118

Abstract: None

Annotation: Longitudinal, retrospective, pre-post descriptive study examining clinical outcomes of pediatric and young adult TGNB patients with cancer.

Leinung MC, Joseph J. Changing Demographics in Transgender Individuals Seeking Hormonal Therapy: Are Trans Women More Common Than Trans Men? *Transgend Health*. 2020;5(4):241-245. doi:10.1089/trgh.2019.0070 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/33644314

Abstract: Introduction: The number of individuals seeking sex hormone therapy for gender dysphoria has been increasing. The prevalence gender dysphoria has recently been estimated as high as 390 to 460 per 100,000 with a consistently greater prevalence of trans women (MTF) than trans men (FTM). We report here the changing demographics encountered in our experience over the past 2 decades. Methods: We collected data on individuals receiving hormonal therapy in the transgender clinic at Albany Medical Center in upstate New York from 1990 to 2017. We analyzed temporal changes in the number, age, and gender identity of transgender individuals. Results: Through June 2017, a total of 421 transgender individuals were seen who initiated hormonal therapy after 1990. Over the past 25 years, there has been a significant increase in the number of individuals seen. The mean age at initiation has remained higher in MTF than in FTM but has decreased steadily in both groups with the overall average dropping <30 years since 2015 (27.5+/-10.6). Since 1990, there has been a steady increase in the percentage of FTM such that it is now equivalent to MTF. Conclusion: Consistent with many reports, we are seeing an increasing number of gender dysphoric individuals seeking hormonal therapy. The age at initiation has been dropping over the past 25 years, and we have seen a steady increase in the number of FTM such that the incidence now equals that of MTF. Possible reasons for these changes are discussed.

Annotation: Longitudinal, pre-post study examining changing demographics over time in TGNB pediatric and adult patients seeking hormonal therapy.

Swendiman RA, Vogiatzi MG, Alter CA, Nance ML. Histrelin implantation in the pediatric population: A 10-year institutional experience. *J Pediatr Surg*. 2019;54(7):1457-1461. doi:10.1016/j.jpedsurg.2018.08.048 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/30262200

Abstract: PURPOSE: To perform the largest review of the safety and clinical management practices of histrelin implantation in children. METHODS: A retrospective cohort study was performed including all patients (age </= 20) that underwent histrelin implant insertion, replacement, or removal by a single surgeon at a large pediatric tertiary care center (2008-2017). Data analyzed included patient demographics, procedure details, and complications. RESULTS: A total of 377 patients, with a mean age of 9.3 +/- 2.4 years, underwent 866 unique procedures (352 insertions, 329 replacements, and 185 removals) for a diagnosis of either central precocious puberty (343 patients, 821 cases) or gender identity disorder (34 patients, 45 cases). There were 271 (72%) female patients, 72 (19%) male patients, and 34 (9%) children in gender transition. Procedures were performed in three settings: 415 (47.9%) in the outpatient clinic, 401 (46.3%) in a sedation unit, and 50 (5.8%) in the operating room. The preferred setting shifted over time to more clinic-based procedures (9.4% vs. 62.9% in the first five vs. second five years, respectively). Complications were rare (1% of cases). CONCLUSION: Histrelin implantation in the pediatric population is safe, with minimal morbidity. Implantation and removal in the clinic setting are appropriate for the majority of patients. LEVEL OF EVIDENCE: Treatment study; Level IV.

Annotation: Longitudinal, retrospective, pre-post study reviewing safety and clinical management practices of histrelin implantation in the pediatric population.

Wierckx K, Elaut E, Van Caenegem E, et al. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011;165(2):331-337. doi:10.1530/EJE-11-0250 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21602316

Abstract: OBJECTIVE: To describe sexual desire in female-to-male transsexual persons post sex reassignment surgery (SRS). The associations between serum androgen levels and sexual desire are examined. DESIGN: Single center cross-sectional study. METHODS: Forty-five female-to-male transsexual persons post SRS completed a standardized questionnaire assessing sexual desire (Sexual Desire Inventory). In addition, participants were asked questions on sexual desire before starting hormone treatment and having SRS. Serum levels of testosterone, LH and sex hormone-binding globulin were measured on fasting morning serum samples. RESULTS: In retrospect, 73.9% of the participants reported an increase in sexual desire after hormone treatment and SRS. Solitary sexual desire scores were significantly correlated with frequency of masturbation ($r=0.835$; $P<0.001$), whereas frequency of sexual intercourse with a partner was not. No direct associations were found between testosterone and solitary or dyadic sexual desire. However, ANOVA showed an independent effect of LH on solitary sexual desire ($P<0.001$). Post hoc analysis revealed that female-to-male transsexual persons with elevated levels of LH, indicating suboptimal testosterone therapy, reported significantly lower solitary sexual desire levels (than those with low LH levels; $P=0.007$). Suppressed LH levels were also associated with having a higher need for sexual activities ($P=0.009$) and a higher frequency of excessive sexual desire ($P=0.007$). CONCLUSION: Most female-to-male transsexual persons report on a marked increase in sexual desire after testosterone treatment and SRS. No direct associations between levels of

testosterone and solitary or dyadic sexual desire were found. However, measures of sexual desire were inversely associated with LH levels.

Annotation: Longitudinal descriptive study examining sexual desire in a mixed adolescent and adult transgender male population in relation to hormone treatment and SRS.

Studies with Long-term Data that were Neither Observational Nor Descriptive (Bibliography Only)

Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav*. 2020;49(7):2611-2618. doi:10.1007/s10508-020-01660-8 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/32152785

Abstract: Gonadotropin-releasing hormone analogues (GnRHa) are recommended as initial treatment for adolescents diagnosed with gender dysphoria, providing time to follow gender identity development and consider further treatment wishes without distress caused by unwanted pubertal changes. This has been described as an extended diagnostic phase. However, there are also concerns about the physical, neurocognitive, and psychosocial effects of this treatment. In this retrospective study, we document trajectories after the initiation of GnRHa and explore reasons for extended use and discontinuation of GnRHa. Treatment was considered appropriate in 143 (67%) of the 214 adolescents eligible for GnRHa treatment by virtue of their age/pubertal status, and all started GnRHa (38 transgirls, 105 transboys; median age, 15.0 years [range, 11.1-18.6] and 16.1 years [range, 10.1-17.9]). After a median duration of 0.8 years (0.3-3.8) on GnRHa, 125 (87%) started gender-affirming hormones (GAH). Nine (6%) discontinued GnRHa, five of whom no longer wished gender-affirming treatment. Thirteen had used GnRHa for longer than required by protocol for reasons other than logistics and regularly met with a mental health professional during this time, supporting the use of GnRHa treatment as an extended diagnostic phase. In conclusion, the vast majority who started GnRHa proceeded to GAH, possibly due to eligibility criteria that select those highly likely to pursue further gender-affirming treatment. Due to the observational character of the study, it is not possible to say if GnRHa treatment itself influenced the outcome. Few individuals discontinued GnRHa, and only 3.5% no longer wished gender-affirming treatment.

Annotation: A Dutch descriptive study examining GnRHa treatment trajectories in n=143 TGNB adolescents

Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011;40(4):843-847. doi:10.1007/s10508-011-9758-9 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/21503817

Abstract: Puberty suppression by means of gonadotropin releasing hormone (GnRH) analogs is considered a diagnostic aid in gender dysphoric adolescents. However, there are also concerns about potential risks, such as poor outcome or post-surgical regret, adverse effects on metabolic and endocrine status, impaired increment of bone mass, and interference with brain development. This case report is on a 22-year follow-up of a female-to-male transsexual, treated with GnRH analogs at 13 years of age and considered eligible for androgen treatment at age 17, and who had gender reassignment surgery at 20 and 22 years of age. At follow-up, he indicated

no regrets about his treatment. He was functioning well psychologically, intellectually, and socially; however, he experienced some feelings of sadness about choices he had made in a long-lasting intimate relationship. There were no clinical signs of a negative impact on brain development. He was physically in good health, and metabolic and endocrine parameters were within reference ranges. Bone mineral density was within the normal range for both sexes. His final height was short as compared to Dutch males; however, his body proportions were within normal range. This first report on long-term effects of puberty suppression suggests that negative side effects are limited and that it can be a useful additional tool in the diagnosis and treatment of gender dysphoric adolescents.

Annotation: A case report following a Dutch adolescent who received puberty suppresion 22 years earlier.

Maxwell S, Noyes N, Keefe D, Berkeley AS, Goldman KN. Pregnancy Outcomes After Fertility Preservation in Transgender Men. *Obstet Gynecol*. 2017;129(6):1031-1034. doi:10.1097/AOG.0000000000002036 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/28486372

Abstract: BACKGROUND: Transgender individuals, individuals whose gender identity does not align with their sex assigned at birth, undergoing gender-affirming hormonal or surgical therapies may experience loss of fertility. Assisted reproductive technologies have expanded family-building options for transgender men who were assigned female at birth. CASES: Three transgender men underwent oocyte cryopreservation before gender-affirming hormonal therapy. One patient underwent fertility preservation as an adolescent. Two adult patients had children using their cryopreserved oocytes, with the pregnancies carried by their sexually intimate partners. CONCLUSION: Transgender men with cryopreserved gametes can build families in a way that affirms their gender identity. Obstetrician-gynecologists should be familiar with the fertility needs of transgender patients so appropriate discussions and referrals can be made.

Annotation: A New York-based case series reporting on pregnancy outcomes in 3 transgender men (1 adolescent) who underwent fertility preservation

Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *J Sex Med*. 2018;15(4):582-590. doi:10.1016/j.jsxm.2018.01.016 Accessed June 28, 2023. Available at https://www.ncbi.nlm.nih.gov/pubmed/29463477

Abstract: BACKGROUND: Over the past decade, the number of people referred to gender identity clinics has rapidly increased. This raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions. AIM: To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment. METHODS: The medical files of all people who attended our gender identity clinic from 1972 to 2015 were reviewed retrospectively. OUTCOMES: The number of (and change in) people who applied for transgender health care, the percentage of people starting with gender-affirming hormonal treatment (HT), the estimated prevalence of transgender people receiving gender-affirming treatment, the percentage of people who underwent gonadectomy, and the percentage of people who regretted gonadectomy, specified separately

for each year. RESULTS: 6,793 people (4,432 birth-assigned male, 2,361 birth-assigned female) visited our gender identity clinic from 1972 through 2015. The number of people assessed per year increased 20-fold from 34 in 1980 to 686 in 2015. The estimated prevalence in the Netherlands in 2015 was 1:3,800 for men (transwomen) and 1:5,200 for women (transmen). The percentage of people who started HT within 5 years after the 1st visit decreased over time, with almost 90% in 1980 to 65% in 2010. The percentage of people who underwent gonadectomy within 5 years after starting HT remained stable over time (74.7% of transwomen and 83.8% of transmen). Only 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy were identified as experiencing regret. CLINICAL IMPLICATIONS: Because the transgender population is growing, a larger availability of transgender health care is needed. Other health care providers should familiarize themselves with transgender health care, because HT can influence diseases and interact with medication. Because not all people apply for the classic treatment approach, special attention should be given to those who choose less common forms of treatment. STRENGTHS AND LIMITATIONS: This study was performed in the largest Dutch gender identity clinic, which treats more than 95% of the transgender population in the Netherlands. Because of the retrospective design, some data could be missing. CONCLUSION: The number of people with gender identity issues seeking professional help increased dramatically in recent decades. The percentage of people who regretted gonadectomy remained small and did not show a tendency to increase. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018;15:582-590.

Annotation: First describes the Dutch ACOG cohort, adults, adolescents, and children with a GD/TGNB diagnosis and at least one CEGD visit. Examines temporal trends in diagnosis, treatment, and surgical interventions, as well as reporting on the proportions of subjects who reported regret after gonadectomy in N=6793 transgender patients, including N=812 adolescents.

APPENDIX II.E: EVIDENCE TABLES FOR TGNB VERSUS TGNB LONG-TERM OUTCOMES

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
Mental Health Outcomes						
de Vries (2014)[4] [redacted] the Netherlands)	**N=55 TGNB adults** Eligibility criteria: Prescribed puberty suppression at the clinic as an adolescent with GD, and received gender reassignment surgery between 2004 and 2011 Sampling method: This group of adolescents belonged to a larger group of adolescents (n = 196) who were referred for treatment between 2000 and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery Subset definition: Comparisons were made between transgender women (n = 22) and transgender men (n = 33)	Mean age at assessment before treatment is started, yr (SD): Transgender women: 13.6 (1.8) Transgender men: 13.7 (2.0) Mean age at start of GnRH analogs, yr (SD): Transgender women: 14.8 (2.0) Transgender men: 14.9 (1.9) Mean age at start of CSH, yr (SD): Transgender women: 16.5 (1.3) Transgender men: 16.8 (1.0) Mean age at gender reassignment surgery, yr (SD): Transgender women: 19.6 (0.9) Transgender men: 19.0 (0.8) Mean age at assessment after gender reassignment surgery, yr (SD): Transgender women: 21.0 (1.1) Transgender men: 20.5 (0.8)	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Depression, Anger and Anxiety Depression was assessed using self-reported BDI scores Anger was assessed using self-reported TPI scores Anxiety was measured using self-reported STAI scores Cohort: outcomes were measured before the start of puberty suppression (pre-treatment; T0), at the start of CSHT (T1), and at least 1 year after gender reassignment surgery (T2)[a] Mean age change between assessment pre and post treatment is 7.1 years	Over time, trans men showed reduced anger and anxiety, whereas trans women were more stable. There was not a significant effect between sex on depression scores. **Mean depression (BDI) score (SD):** Mean pre-treatment BDI score (SD): Transgender women (n = 12): 4.73 (4.20) Transgender men (n = 20): 10.09 (8.34) At least 1 year after gender reassignment surgery (T2): Transgender women: 3.38 (4.40) Transgender men: 6.95 (9.83) Time X sex: Linear effect, P = .66, Quadratic effect, P = .49 **Mean anger (TPI) score (SD):** Mean pre-treatment anger TPI score (SD): Transgender women (n = 12): 14.17 (3.01) Transgender men (n = 20): 19.55 (5.96) At least 1 year after gender reassignment surgery (T2): Transgender women: 5.58 (3.92) Transgender men: 16.56 (6.06) Time X sex: Linear effect, P = .04, Quadratic effect, P = .12 **Mean anxiety (STAI) score (SD):** Mean pre-treatment anxiety (STAI) score (SD): Transgender women (n = 12): 31.87 (7.42) Transgender men (n = 20): 44.41 (9.06) At least 1 year after gender reassignment surgery (T2): Transgender women: 35.83 (10.22) Transgender men: 39.20 (10.53) Time X sex: Linear effect, P = .05, Quadratic effect, P = .52

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
Gomez-Gil (2012)[7] [redacted] Spain) the [redacted] Spain) was invited to participate in the study	**N= 187 TGNB individuals** Eligibility criteria: A sample of 200 transsexuals selected consecutively at Sampling method: The response rate was 93.5% of 200 patients who were invited to participate. The most common reasons for declining were refusal to participate or incomplete answers on the scale questionnaires. This resulted in 187 participants, 67 transsexuals without hormonal treatment and 120 transsexuals under hormonal treatment. Subset definition: Of N=187 TGNB individuals, n=67 in TGNB group were not under hormonal treatment and n=120 in TGNB group were under hormonal treatment	Full cohort (N = 187) mean (SD) age of the participants was 29.87 (9.15), range15–61 years. TGNB cohort without hormonal treatment (N = 67): The mean (SD) age of the participants was 25.9 (7.5). The n (%) of MTF was 29 (43%) and FTM was 38 (57%). A total of 2 participants (n = 1 in MTF and n = 1 in FTM) had at least one sex reassignment surgery. TGNB cohort under hormonal treatment (N = 120): The mean (SD) age of the participants was 33.6 (9.1) and was 24.6 (8.1) at onset of hormonal therapy. The n (%) of MTF was 84 (70%) and FTM was 36 (30%). A total of 77 participants (n = 49 in MTF and n = 28 in FTM) had at least one sex reassignment surgery.	CSHT treated TGNB patients. Hormonal treatment for treated MTF patients consisted of estrogens either via the oral route (conjugated estrogens 1.8-2.4 mg/day or estradiol valerate 2—4 mg/day) or transdermal treatment for treated MF transsexuals consisted of estrogens either via the oral route (conjugated estrogens 1.8-2.4 mg/day or estradiol valerate 2-4 mg/day) or transdermal estradiol patches (3 mg twice per week, delivering 100 mg/day), generally in association with oral cyproterone acetate (25—50 mg/day), except for patients who had undergone vaginoplasty. The androgen administration schedule in FTM patients consisted of testosterone administered either as intramuscular injections of a testosterone esters depot (1000 mg every 10—14 weeks), or daily transdermal testosterone gel (50 mg per day), according to the patient's preference.	TGNB patients not on hormonal treatment	Anxiety and Depression Anxiety was assessed by self-report using the Hospital anxiety and depression scale (HAD-A) Depression was assessed by self-report using the Hospital Anxiety and Depression Scale (HAD-D) Cross sectional: Exposure and outcomes were measured at the same time. Average length (SD) of hormonal treatment was 4.7 (5.2) years, range 1-46 years, in FTM cohort; and 11.0 (9.9), range 1-46 years, in MTF cohort.	**Mean Anxiety (HAD-A) score (SD)** TGNB participants without hormonal treatment had significantly higher anxiety scores with a HAD-A score of 9 (4.0) vs 6.4 (3.7) in the treated cohort. P = .001, effect size .075 26 (39%) of TGNB participants without hormonal therapy had a HAD-A score of 0-7 (no symptoms) vs 81 (67%) in the treated cohort. 41 (61%) of TGNB participants without hormonal therapy had HAD-A score of 8-21 (symptoms) vs 39 (33%) in the treated cohort. There was a significant difference in the prevalence of symptoms, P = .001, effect size .278 **Mean depression (HAD-D) score (SD)** TGNB participants without hormonal treatment had significantly higher depression scores with a HAD-D score of 5.2 (4.2) vs 3.3 (3.2) in the treated cohort, P = .002, effect size .050 46 (69%) of TGNB participants without hormonal treatment had HAD-D scores of 0-7 (no symptoms) vs 110 (92%) in the treated cohort. 21 (31%) of the untreated cohort that had HAD-D score of 8-21 (symptoms) vs 10 (8%) of the treated cohort. There was a significant difference in the prevalence of symptoms, P = .001, effect size .297
Psychosocial Outcomes						
Arnoldussen (2022)[2] [redacted]	**TGNB adolescents (N = 72)** Eligibility: referred prior to 2010, met GD diagnostic criteria, started PS	Full cohort: • Gender	Lower pre-treatment IQ score (total, verbal and performance IQ)	Higher pre-treatment IQ score (total, verbal and performance IQ)	IQ was measured using the WISC	Total IQ Score:

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]*

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
[redacted]	before the age of 17 years followed by cross-sex hormonal treatment and gender-affirming surgery Sampling method: 72 out of 119 eligible participated Subset: transgender men (n = 45) transgender women (n = 27)	○ 62.5% are transgender males ○ 37.5% are transgender females • Adolescent living situation prior to treatment, ○ 72.2% lived with both biological parents, ○ 26.4% lived with other ○ 1.4% were unknown • Age, mean (SD) ○ at baseline: 12.78 years (1.48) ○ at the start of puberty suppression: 13.77 years (1.46) ○ at the start of CSH: 16.22 years (0.82) ○ at the start of GAS: 18.70 years (0.77) ○ at the evaluation of educational achievement: 20.40 years (1.03) ○ between start puberty suppression and start of CSH was 2.40 years (1.08) • IQ, mean (SD) ○ total IQ: 100.29 (15.07) ○ verbal IQ: 99.53 (15.01) ○ performance IQ: 100.72 (14.26) ○ *P* = NS between trans men and trans women • Education level achieved ○ 37 were vocational educated (51.4%) ○ 35 were higher vocational educated (48.6%).	Transgender men	Transgender women	Educational achievement later in life after gender affirming treatment (PS, CSHT and gender-affirming surgery) was measured via survey question. Educational level was dichotomized into "vocational educated" and "higher vocational educated/academic educated" Cohort study: Outcomes were measured after a mean duration of 7.6 years of gender-affirming treatment	For each increase of one point in total IQ score, the chance of being higher educated increased with 1.170 odds.[c] (β = 0.157, P < .001, 95% CI 1.074, 1.275) Verbal IQ score: For each increase of one point in verbal IQ score, the chance of being higher educated increased with 1.164 odds c (β = 0.152, P = .001, 95% CI 1.068, 1.268) Performance IQ score For each increase of one point in performance IQ score, the chance of being higher educated increased with 1.127 odds.[c] (β = 0.120, P < .001, 95% CI 1.054, 1.206) Results similar to general population. There was no significant difference in total, verbal or performance IQ scores between transgender men and transgender women, P = NS There was no significant difference between educational levels achieved between transgender men and transgender women

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]*

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
		P = NS between trans men and trans women				
de Vries (2014)[4] [redacted] the Netherlands)	**N=55 TGNB adults** Eligibility criteria: Prescribed puberty suppression at the clinic as an adolescent with GD, and received gender reassignment surgery between 2004 and 2011 Sampling method: This group of adolescents belonged to a larger group of adolescents (n = 196) who were referred for treatment between 2000 and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery Subset definition: Comparisons were made between transgender women (n = 22) and transgender men (n = 33)	Mean age at assessment before treatment is started, yr (SD): Transgender women: 13.6 (1.8) Transgender men: 13.7 (2.0) Mean age at start of GnRH analogs, yr (SD): Transgender women: 14.8 (2.0) Transgender men: 14.9 (1.9) Mean age at start of CSHT (yr, SD): Transgender women: 16.5 (1.3) Transgender men: 16.8 (1.0) Mean age at gender reassignment surgery, yr (SD): Transgender women: 19.6 (0.9) Transgender men: 19.0 (0.8) Mean age at assessment after gender reassignment surgery, yr (SD): Transgender women: 21.0 (1.1) Transgender men: 20.5 (0.8)	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Psychological functioning Psychological functioning was assessed by physician report using CGAS scores Cohort: outcomes were measured before the start of puberty suppression (pre-treatment; T0), at the start of CSHT (T1), and at least 1 year after gender reassignment surgery (T2)[a] Mean age change between assessment pre and post treatment is 7.1 years	**Mean CGAS score (SD):** There was no significant difference in CGAS scores between natal males and females Mean pre-treatment CGAS score (SD): Transgender women (n = 12): 74.33 (7.53) Transgender men (n = 20): 67.65 (11.87) At least 1 year after gender reassignment surgery (T2): Transgender women: 82.40 (8.28) Transgender men: 76.29 (14.48) ▪ Time X sex: Linear effect, P = .89, Quadratic effect, P = .68
Gomez-Gil (2012)[7] [redacted] Spain) the [redacted] (Spain) was invited to participate in the study	**N= 187 TGNB individuals** Eligibility criteria: A sample of 200 transsexuals selected consecutively at Sampling method: The response rate was 93.5% of 200 patients who were invited to participate. The most common reasons for declining were refusal to participate or incomplete answers on the scale questionnaires.	Full cohort (N = 187) mean (SD) age of the participants was 29.87 (9.15) with a range of 15–61 years. MTF cohort (N = 113) Average length of time that the treated MF patients had been on hormone therapy was 11.0 years (S.D: 9.9; range 1—46 years). FTM cohort (N = 74)	CSHT treated TGNB patients Hormonal treatment for treated MTF patients consisted of estrogens either via the oral route (conjugated estrogens 1.8—2.4 mg/day or estradiol valerate 2—4 mg/day) or transdermal treatment for treated MF transsexuals consisted of estrogens either via the oral route (conjugated estrogens	TGNB patients not on hormonal treatment	Social Distress Social anxiety and distress were assessed by self-report using the social anxiety and distress scale (SADS) Cross sectional: Exposure and outcomes were measured at the same time. Average length (SD) of hormonal treatment was	**Mean social distress (SADS) score (SD)** TGNB participants without hormonal treatment had significantly higher social distress scores with a SADS score of 11 (7.3) vs 8.5 (7.8) in the treated cohort, P = .038, effect size 0.24.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]*

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
	This resulted in 187 participants, 67 transsexuals without hormonal treatment and 120 transsexuals under hormonal treatment. Subset definition: Of 187 TGNB individuals, n=113 MTFs and n=74 FTMs Of 187 TGNB individuals, n=67 in TGNB group were not under hormonal treatment and n=120 in TGNB group were under hormonal treatment	Average length of time that the treated FM patients had been on hormone therapy was 4.7 years (S.D: 5.2; range 1—22 years). TGNB cohort without hormonal treatment (N = 67): The mean (SD) age of the participants was 25.9 (7.5). The n (%) of MTF was 29 (43%) and FTM was 38 (57%). A total of 2 participants (n = 1 in MTF and n = 1 in FTM) had at least one sex reassignment surgery. TGNB cohort under hormonal treatment (N = 120): The mean (SD) age of the participants was 33.6 (9.1) and was 24.6 (8.1) at onset of hormonal therapy. The n (%) of MTF was 84 (70%) and FTM was 36 (30%). A total of 77 participants (n = 49 in MTF and n = 28 in FTM) had at least one sex reassignment surgery.	1.8—2.4 mg/day or estradiol valerate 2—4 mg/day) or transdermal estradiol patches (3 mg twice per week, delivering 100 mg/day), generally in association with oral cyproterone acetate (25—50 mg/day), except for patients who had undergone vaginoplasty. The androgen administration schedule in FTM patients consisted of testosterone administered either as intramuscular injections of a testosterone esters depot (1000 mg every 10—14 weeks), or daily transdermal testosterone gel (50 mg per day), according to the patient's preference.		4.7 (5.2) years, range 1-46 years, in FTM cohort; and 11.0 (9.9), range 1-46 years, in MTF cohort.	
Wierckx (2012)[10] [redacted] [redacted]Belgium	**N=50 FTM TGNB adults** Eligibility criteria: All Dutch-speaking transgender men who underwent sex reassignment surgery (SRS) (mastectomy, hysterectomy, and bilateral oophorectomy) between 1987 and 2009 at the[redacted] Belgium were invited to participate in the study. Participants had to have SRS at least 1 year before the start of the study.	mean age (SD): 37 (8.2) years, range 22-54 years age at time of SRS: 30 (8.2) years, range 16-49 years on testosterone therapy: 100% duration of testosterone therapy: 9.9 (5.8), range 3.2 - 27.5 years	Transgender men treated with testosterone therapy who had children	Transgender men treated with testosterone therapy who had not had children	Quality of Life Quality of life was measured using the Dutch version of the short form-36 Health survey (SF-36). These scores were converted into a 0–100 summary score for each section: vitality, physical functioning, bodily pain, general health, physical role functioning, emotional	**Quality of Life, median (1st-3rd quartile)** Bodily pain TGNB men with children had a score of 77.6 (55.1 - 100.0), which was comparable to the score of 77.6 (57.1 - 100.0) in TGNB men without children, P = NS General health TGNB men with children had a score of 75.0 (70.0 - 80.0), which was comparable to the score of 75.0 (55.0 - 85.0) in TGNB men without children, P = NS Vitality

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]*

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
	Sampling method: Participants were invited to the study by letter and confirmed their participation by telephone or email. Three additional participants that weren't treated in the listed setting offered to participate in the study. Subset definition: Of 50 FTM TGNB adults, n=11 had children, and n=39 did not have children				role functioning, social role functioning, and mental health, with higher scores indicating higher levels of well-being. Internal consistency with the SF-36 was high (Cronbach's alpha = 0.81).	TGNB men with children had a score of 80.0 (75.0 - 80.0) which was significantly higher than the score of 60.0 (50.0 - 70.0) in TGNB men without children, P = 0.004 Role - social TGNB men with children had a score of 100.0 (100.0 - 100.0) which was non significantly higher than the score of 87.5 (75.0 - 100.0) in TGNB men without children, P = 0.058 Role - emotional TGNB men with children had a score of 100.0 (100.0 - 100.0), which was comparable to the score of 100.0 (66.7 - 100.0) in TGNB men without children, P = NS Mental health TGNB men with children had a score of 88.0 (80.0 - 92.0), which was significantly higher than the score of 70.0 (60.0 - 84.0) in TGNB men without children, P = 0.009 Physical functioning TGNB men with children had a score of 95.0 (80.0 - 100.0), which was non significantly higher than the score of 90.0 (77.5 - 100.0) in TGNB men without children, P = NS Role - physical TGNB men with children had a score of 100.0 (100.0 - 100.0), which was comparable to the score of 100.0 (100.0 - 100.0) in TGNB men without children, P = NS
Body Image Outcomes						
de Vries (2014)[4] [redacted] the Netherlands)	**N=55 TGNB adults** Eligibility criteria: Prescribed puberty suppression at the clinic as an adolescent with GD, and received gender reassignment surgery between 2004 and 2011 Sampling method: This group of adolescents belonged to a larger group of adolescents (n = 196) who were referred for treatment between 2000	Mean age at assessment before treatment is started, yr (SD): Transgender women: 13.6 (1.8) Transgender men: 13.7 (2.0) Mean age at start of GnRH analogs (yr, SD): Transgender women: 14.8 (2.0) Transgender men: 14.9 (1.9) Mean age at start of CSH, yr (SD):	Transgender women who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 22)	Transgender men who had received puberty suppression during adolescence, and completed gender reassignment surgery (n = 33)	Self-reported measures: UGDS questionnaire BIS Cohort: outcomes were measured before the start of puberty suppression (pre-treatment; T0), at the start of CSHT (T1), and at	**Body satisfaction:** Trans women reported more satisfaction over time with primary sex characteristics than trans men and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Trans men reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. **Mean UGDS score (SD):** Mean pre-treatment UGDS (SD): Transgender women (n = 11): 47.07 (11.05)

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
	and 2008. Participants were recruited for the study between 2008 and 2012, at least 1 year post gender reassignment surgery Subset definition: Comparisons were made between transgender women (n = 22) and transgender men (n = 33)	Transgender women: 16.5 (1.3) Transgender men: 16.8 (1.0) Mean age at gender reassignment surgery, yr (SD): Transgender women: 19.6 (0.9) Transgender men: 19.0 (0.8) Mean age at assessment after gender reassignment surgery, yr (SD): Transgender women: 21.0 (1.1) Transgender men: 20.5 (0.8)			least 1 year after gender reassignment surgery (T2)[a] Mean age change between assessment pre and post treatment is 7.1 years	Transgender men (n = 22): 56.74 (3.74) At least 1 year after gender reassignment surgery (T2): Transgender women: 17.27 (2.57) Transgender men: 15.08 (2.64) **Mean BIS score (SD):** Primary sex characteristics (pre-treatment): Transgender women (n = 17): 4.03 (0.68) Transgender men (n = 28): 4.18 (0.53) Primary sex characteristics at least 1 year after gender reassignment surgery (T2): Transgender women: 2.07 (0.74) Transgender men: 2.89 (0.71) ▪ Time X sex: Linear effect, P = .01, Quadratic effect, P = .45 Secondary sex characteristics (pre-treatment): Transgender women (n = 17): 2.63 (0.60) Transgender men (n = 28): 2.80 (0.72 Secondary sex characteristics at least 1 year after gender reassignment surgery (T2): Transgender women: 1.93 (0.63) Transgender men: 2.48 (0.40) ▪ Time X sex: Linear effect, P = .10, Quadratic effect, P < .001 Neutral body characteristics (pre-treatment): Transgender women (n = 17): 2.57 (0.70) Transgender men (n = 28): 2.21 (0.64) Neutral body characteristics at least 1 year after gender reassignment surgery (T2): Transgender women: 2.09 (0.56) Transgender men: 2.32 (0.44) ▪ Time X sex: Linear effect, P = .007, Quadratic effect, P = .01

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
Cardiovascular Health						
Martinez-Martin (2023)[5] [redacted] (Spain)	**TGNB subjects (N = 302)** Eligibility criteria: Subjects who started CSHT at the clinic since it opened in March 2000 and < 30 years of age, with at least 5 years of follow-up. Patients were excluded if they were only treated with LHRH analogs, discontinued hormonal therapy, or switched to androgen blockers due to having pre-existing HTN, or refused to give informed consent Sampling method: 811 medical records were reviewed. After excluding 509 patients, 302 were included in the study Subset definition: Comparisons were made between transgender women taking estradiol + spironolactone (n = 54) and transgender women taking estradiol + an LHRH analog (n = 26)	Mean age (yrs, SD): Spironolactone: 17.1 (4.1) LHRH analog: 16.2 (1.1) Mean weight (kg, SD): Spironolactone: 68.5 (11.6) LHRH analog: 65.6 (10.1) Mean glucose (mmol/L, SD): Spironolactone: 5.2 (0.6) LHRH analog: 4.9 (0.4) Mean cLDL (mmol/L, SD): Spironolactone: 2.4 (0.6) LHRH analog: 2.3 (0.7) Mean triglycerides (mmol/L, SD): Spironolactone: 1.6 (0.8) LHRH analog: 1.5 (0.9) Mean SBP (mmHg, SD): Spironolactone: 121 (12) LHRH analog: 119 (13)	Transgender women taking estradiol + spironolactone (n = 54)	Transgender women taking estradiol + an LHRH analog (n = 26)	5-yr follow-up of baseline cardiovascular risk factors Incidence of HTN Cohort: outcomes were measured at baseline and at the 5-yr follow-up	**HTN risk** Spironolactone and LHRH analog use were nonsignificant predictors for the development of HTN Spironolactone was shown to have a marginally protective effect (OR: 0.632, P = NS), but LHRH analog use did not (OR: 1.103, P = NS) **Mean weight change at 5-yr follow-up (kg, SD), P < .05:** Spironolactone: 5.3 (3.2) LHRH analog: 8.4 (6.5) **Mean glucose change at 5-yr follow-up (mmol/L, SD), P = NS:** Spironolactone: 0.3 (0.3) LHRH analog: 0.5 (0.4) **Mean cLDL change at 5-yr follow-up (mmol/L, SD), P = NS:** Spironolactone: 0.4 (0.3) LHRH analog: 0.5 (0.4) **Mean triglycerides change at 5-yr follow-up (mmol/L, SD), P = NS:** Spironolactone: 0.4 (0.2) LHRH analog: 0.6 (0.4) **Mean SBP change at 5-yr follow-up (mmHg, SD), P < .05:** Spironolactone: 2 (1) LHRH analog: 6 (2) **Those who had HTN at the 5-yr follow-up (n, %), P = NS:** Spironolactone: 1 (1.8) LHRH analog: 2 (7.7%) **Yearly incidence of HTN (%, 95% CI), P = NS:** Spironolactone: 0.37 (0.00 to 0.74) LHRH analog: 1.54 (0.45 to 2.63)
Ott (2010)[8]	**N=162 TGNB MTF individuals**	mean age (SD): 36.6 years (10.9) mean (SD) BMI: 22.7 kg/m2 (3.9)	MTF TGNB individuals who self-treated with cyproterone	MTF TGNB individuals who self-treated with cyproterone acetate and/or ethinyl	Incidence of thrombophilia and venous thrombosis	Significantly more aPC-resistant than non-aPC-resistant MTF TGNB individuals reported former self-administration of cyproterone acetate. While 37% of MTF TGNB individuals (60 of 162) reported

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
[redacted] Austria (1995–2007)	Eligibility criteria: all patients diagnosed with transsexualism who started CSHT (as all were screened for aPC-resistance, antithrombin III activity, free protein S antigen, and protein C activity before receiving CSHT) Sampling method: All eligible participants were included Subset definition: Of the N=162 MTF TGNB individuals, n=13 had a thrombophilic defect (aPC resistance)	5 (3.1%) have had a previous thrombophilic event 8 (6.3%) had a family Hx of thrombosis 96 (59.3%) have a Hx of smoking 35 (21.6%) have a Hx of HTN 62 (38.3%) have a Hx of dyslipidemia 2 (1.2%) have a Hx of DM 60 (37.0%) have a Hx of previous CSHT 24 (14.8%) have a Hx of cross-sex surgery before initiation of CSHT	acetate and/or ethinyl estradiol	estradiol with thrombophilic defect	Venous blood was obtained at first visit and screened for aPC resistance, protein C activity and protein S antigen for routine thrombophilia screening. Cross sectional: exposures and outcomes were measured at the same time	former hormone self-treatment with cyproterone acetate and/or ethinyl estradiol for a median of 15 months (range, 5-21 months) before initiation of therapy at the clinic, 69.2% of MTF TGNB individuals with thrombophilic defect (9 of 13) reported former hormone self-treatment. The difference was statistically significant, P = .04
Mortality Outcomes						
Asscheman (2011)[3] [redacted] the Netherlands	**N= 964 MTF TGNB individuals** Eligibility: Included only subjects who had started cross-sex hormone treatment before July 1, 1997, followed-up for at least 1 year Sampling method: Baseline and follow-up data of all TGNB subjects referred to outpatient department since 1975 were entered into a cumulative database. 2 MTF who had died the first year of hormone administration were also included. Subset definition: Of the N=966 MTF TGNB individuals, n= 596 MTF individuals never or formerly used ethinyl estradiol and n=368 FTM individuals continuously used ethinyl estradiol	mean age of 31.4 years at the start of cross-sex hormones (range: 16–76 years) 18,678 patient-years of follow-up.	MTF TGNB individuals with continuous use of ethinyl estradiol (n=368)	MTF TGNB individuals who never or formerly used ethinyl estradiol (n=596)	Mortality risk Cause of death was ascertained by medical report or information from family physician according to ICD-10 code Data was adjusted for confounding variables such as age, smoking status, and a starting date before 1990 (because before 1990, ethinyl estradiol was the standard estrogen prescribed) and adjusted for Cox proportional hazard models by incrementally including them as covariates. Cohort: Outcomes were measured year to year from 1975 until July 1, 2007	**Mortality, hazard ratio (95% CI)** Current and continuous use of ethinyl estradiol was not significantly associated with an increased risk of all-cause mortality. All-cause mortality was n=51 (13.9%) in the continuous ethinyl estradiol use cohort, and n=69 (11.6%) in the ever or former use cohort. Continuous use of ethinyl estradiol had a fully adjusted HR of 1.28 (0.88-1.86), P = NS Current and continuous use of ethinyl estradiol was significantly associated with cardiovascular mortality with a fully adjusted HR of 3.12 (1.28 - 7.63), P = .01 Current and continuous use of ethinyl estradiol was not significantly associated with mortality due to external causes with a fully adjusted HR of 1.36 (0.60-3.10), P = NS Current and continuous use of ethinyl estradiol was not significantly associated with mortality due to non-cardiovascular mortality with a fully adjusted HR of 1.15 (0.71-1.83), P = NS Current use of ethinyl estradiol was not significantly associated with increased cancer mortality with a fully adjusted HR of 1.35 (0.61 - 3.00), P = NS.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]*

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

Table II.E.1. Clinical Studies with Between-TGNB-group Comparisons

Study first author (publication year) Setting	Population	Select Baseline Characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
					Mean follow-up period (SD) of subjects receiving CSHT was 19.3 (7.7) years	
Wiepjes (2020)[6] [redacted] the Netherlands between 1972-2017	**N=8263 TGNB individuals** Eligibility criteria: All people that once visited the center between 1972 and 2017 were included. Sampling method: A retrospective chart study was performed on all people that came to the center between 1972 and 2017, which included adults, adolescents, and children. Information on death occurrence and time was obtained by cross-checking the National Civil Record Registry for date of birth and death, and the hospital registration system, medical, and psychological files for cause of death. Subset definition: Of N= 8263 TGNB individuals, n=5107 are MTF and n=3156 are FTM	FTM (n= 3156) median (range) age at first visit: 20 (4-73) years median (range) follow-up time: 4.8 (0-45.5) years Total follow up of was 27,940 person years MTF (n = 5107) median (range) age at first visit: 25 (4-81) years median (range) follow-up time: 10.2 (0-45.5) years Total follow up was 64,287 person years	Transgender women who had visited the center. Unspecified number were treated with CSHT and surgical interventions.[b] (Cohort until 2015 described in Wiepjes 2018)[20]	Transgender men who had visited the center Unspecified number were treated with CSHT and surgical interventions.[b] (Cohort until 2015 described in Wiepjes 2018)[20]	Suicide death rate Information on death occurrence, time, and cause of death was obtained by cross-checking multiple sources: The National Civil Record Registry and the hospital registration system. Cohort: outcomes were measured year to year 1972-2017	Suicide death risk, hazard ratio (95% CI) Transgender women had a higher overall suicide death risk than transgender men, HR 2.26 (1.06-4.82)
			TGNB individuals referred to the clinic before the age of 18	TGNB individuals referred to the clinic as adults		Suicide death risk, hazard ratio (95% CI) Four suicide deaths occurred in individuals who were referred to the clinic before the age of 18 (0.2%), which is a lower risk than those referred as adults (0.7%), P = .010
			TGNB suicide death rate compared yearly 1972-2017	TGNB suicide death rate compared yearly 1972-2017		Suicide death rate, hazard ratio per year (95% CI) Overall suicide deaths did not increase over the years: HR per year 0.97 (0.94-1.00) In transgender women, suicide death rates decreased slightly over time with per year HR of 0.96 (0.93-0.99) In transgender men, there was no significant change in suicide death rates over time with a per year HR of 1.10 (0.97-1.25)

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.J of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018)[18]

Abbreviations: aPC, activated protein C; BIS, Body Image Scale; BDI, Beck Depression Inventory; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FTM, female transitioning to male; HAD-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAD-D, Hospital Anxiety and Depression Scale-Depression subscale; HR, hazard ratio; HTN hypertension; Hx, history; ICD-10, International Classification of Diseases, 10th edition; LDL, LHRH, Luteinizing hormone-releasing hormone; LDL, low-density lipoprotein; MTF, male transitioning to female; SADS, Social Anxiety Distress Scale; SBP, systolic blood pressure; SD, standard deviation; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; WISC, Weschsler Intelligence Scale For Children

Return to TOC

APPENDIX II.F: EVIDENCE TABLES FOR TGNB VERSUS CISGENDER PEER LONG-TERM OUTCOMES

Return to TOC

Table II.F.1. Clinical Studies with TGNB vs Peer Comparisons

Study first author (publication year) and setting	Population	Select baseline characteristics: n (%, unless otherwise noted) and p-value (if reported)	Exposure/Intervention	Comparator	Outcome Measures and Timing	Results
Mental Health and Psychosocial Outcomes						
Wierckx (2011)[9] [redacted] Belgium	**N = 47 transgender men** **N = 976 cisgender men** **N= 976 cisgender women[a]** Transgender cohort: Eligibility criteria: All Dutch-speaking transgender men who underwent sex reassignment surgery (SRS) (hystero-oophorectomy, mastectomy) between 1987 - 2009 (at least 1 year before inclusion in the study) at [redacted] Belgium, were eligible. At least one year must have passed after SRS. All participants started hormonal therapy >2 years before SRS. Sampling method: All eligible participants were invited to the study by letter; if they did not reply within 1 month, they were contacted by telephone, and were left a voice message as a reminder. Participants were contacted a second time if needed. Cisgender cohort (Aaronson 1998)[21]: Eligibility criteria: No information in study, information found in cited source. Survey was mailed to random households in the Netherlands. Participants needed to be over 16 years old. No other information given. Sampling method: SF-36 was mailed to 2800 households; 1771 surveys were returned with 1742 being from respondents 16 years or older.	Transgender men: Average age, mean (SD): 37 (8.2) years, range 22-54 years Average age (SD) at SRS: 30 (8.2) years, range 16-49 Average of 8 years after SRS (range 2-22 years) metoidioplasty: 18.4% phalloplasty: 93.9% erection prosthesis: 65.3% Testosterone therapy: 100% Cisgender population[21] Age, mean (SD): 40.4 (18.0) years, range 16-94 years Gender Male (56%) Female (44%) Chronic health conditions None (48%) One (29%) >1 (23%)	Transgender men who underwent SRS and had hormonal therapy	Cisgender men and cisgender women	Mental and physical health Self-perceived physical, social, and mental health was measured using the Dutch version of the SF-36. Scores were converted into a 0–100 summary score for each section: vitality, physical functioning, bodily pain, general health, physical role functioning, emotional role functioning, social role functioning, and mental health, with higher scores indicating higher levels of well-being. Internal consistency with the SF-36 was high (Cronbach's alpha = 0.81) Cross-sectional: Outcome measures and exposure measured at the same time TGNB respondents were an average of 8 years post-surgery (range 2-22 years) with all having had CSHT >2 years prior to surgery.	Physical functioning, mean (SD) Transgender men had a comparable score of 85.9 (15.0), vs 85.4 (21.0) in cisgender men, P = .795 Transgender men had a significantly higher score of 85.9 (15.0) vs 80.4 (24.2) in cisgender women, P = .015 Role-physical, mean (SD) Transgender men had a nonsignificant higher score of 83.3 (33.2) vs 78.7 (34.1) in cisgender men, P = .338 Transgender men had a nonsignificant higher score of 83.3 (33.2) vs 73.8 (38.5) in cisgender women, P= .052 Bodily pain, mean (SD) Transgender men had a comparable score of 75.8 (20.8) vs 77.3 (22.7) in cisgender men, P = .617 Transgender men had a nonsignificant higher score of 75.8 (20.8) vs 71.9 (23.8) in cisgender women, P = 0.192 General health, mean (SD) Transgender men had a comparable score of 70.9 (19.4) vs 71.6 (20.6) in cisgender men, P = .807 Transgender men had a nonsignificant higher score of 70.9 (19.4) vs 69.9 (20.8) in cisgender women, P = .715 Vitality, mean (SD) Transgender men had a significantly lower score of 62.1 (20.7) vs 71.9 (18.3) in cisgender men, P = .002 Transgender men had a nonsignificant lower score of 62.1 (20.7) vs 64.3 (19.7) in cisgender women, P = .475 Social functioning, mean (SD) Transgender men had a comparable score of 85.5 (19.5) vs 86.0 (21.1) in cisgender men, P = .847 Transgender men had a nonsignificant higher score of 85.5 (19.5) vs 82.0 (23.5) in cisgender women, P = .220 Role-emotional, mean (SD) Transgender men had a nonsignificant lower score of 83.0 (34.1) vs 85.5 (29.9) in cisgender men, P = .609 Transgender men had a nonsignificant higher score of 83.0 (34.1) vs 78.5 (35.7) in cisgender women, P = .361 Mental health, mean (SD) Transgender men had a significantly lower score of 72.6 (19.2) vs 79.3 (16.4) in cisgender men, P = .020 Transgender men had a nonsignificant lower score of 72.6 (19.2) vs 73.7 (18.2) in cisgender women, P = .690

[a] Sampled population from Aaronson (1998).[19] Discrepancy in number of female participants reported: 766 cisgender female participants reported in referenced study.

Abbreviations: CSHT, Cross-sex hormone therapy; SD, standard deviation; SF-36, Short Form-36 Health Survey; SRS, sex-reassignment surgery.

Return to TOC

APPENDIX II.G: EVIDENCE TABLES FOR PRE-POST LONG-TERM OUTCOMES

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
Mental Health Outcomes						
de Vries (2014)[4] [redacted]	**N = 55 TGNB youth** Eligibility: adolescents with GD prescribed puberty suppression between 2004 and 2011 Sampling method: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011 Subset definition: N = 55 TGNB adolescents, with n = 22 MTF and n = 33 FTM)	Full cohort: mean age (SD) at assessment pretreatment was 13.6 (1.9) (range: 11.1–17.0) mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5) mean age (SD) at the start of CSHT was 16.7 (1.1) (range: 13.9–19.0) mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3) mean age (SD) at assessment post treatment was 20.7 (1.0) (range: 19.5–22.8) mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)	CSHT and GRS	N/A	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS)[a] BDI used to assess depressive symptoms TPI administered to assess the tendency to respond with anger to a threatening or annoying situation. (Scale ranges from 1-4) STAI administered to assess the tendency to respond with anxiety to a threatening or annoying situation. (Scale ranges from 1-4) General linear models examined the repeated measures with an analysis of variance-based model. A linear effect signifies an overall change across T0 to T2.	BDI (depression) (n = 32), mean (SD) Scores showed a nonsignificant decrease from 7.89 (7.52) at intake to 5.44 (8.40) at post treatment, P = NS Linear effect (time) P = .23, Significant quadratic effect (time) P = .04 TPI (Anger) (n = 32), mean (SD) Scores showed a nonsignificant decrease from 17.55 (5.72) at intake to 16.01 (5.28) at post treatment, P = .20 linear effect (time) P = NS, quadratic effect (time) P = NS STAI (Anxiety) (n = 32), mean (SD) Scores showed a nonsignificant decrease from 39.57 (10.53) at intake to 37.61 (10.39) at post treatment, P = NS linear effect (time) P = NS, quadratic effect (time) P = NS ▪ effect (time) P = NS

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
					Quadratic effect signifies change was not continuous.	
Psychosocial Outcomes						
Arnoldussen (2022)[11] [redacted] the Netherlands	**Population: N = 70 adolescents** • Eligibility: Adolescents who were referred between 2000 and 2013, who met the criteria for a "Gender Identity Disorder" diagnosis according to the DSM-IV-TR27 (because that was the DSM used during these years), who received puberty suppression and subsequent gender-affirming hormone treatment, and were at least 6 months post gender- affirming surgery could be included in the larger evaluation study. There were no exclusion criteria. Adolescents were included in the current study if their pretreatment data on self-perception were available. • Sampling Method: Between 2000 and 2013, 513 adolescents were referred consecutively to the CEGD. Of these 513 adolescents, a total of 179 were eligible for the larger evaluation study,	• Gender, N (%) ○ Trans men: 49 (70.0%) ○ Trans women: 21 (30.0%) • Age at assessment in years, M (SD) ○ Pre-irreversible gender-affirming treatment (pretreatment assessment): 14.65 (2.08), range 11.23–19.74 ○ Post-irreversible gender-affirming treatment (post treatment assessment): 20.70 (1.49), range 18.97–26.28 • Age at gender-affirming surgery in years: 19.23 (1.27), range 17.98–24.75	PS, CSH and gender-affirming surgery	N/A	• The SPPA was used to examines self-perception on seven different domains: Scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, close friendship, and global self-worth at pre-treatment assessment, before any CSHT, and at least 6 months after gender-affirming surgeries. Time between assessments was 6.05 (1.82) years (range 2.77-10.63 years)	• Multilevel modeling (adjusted for gender, age at pretreatment and post treatment assessment, use of puberty suppression at pretreatment assessment, full-scale IQ and living situation) revealed that the domains of physical appearance ($P < .001$) and global self-worth ($P < 0.001$) improved significantly over time. For the domains of scholastic competence, social acceptance, athletic competence, and close friendship, no significant change over time was found (no significant increase nor decrease, all $P > .05$). Only for the domain of behavioral conduct, an interaction effect for gender was found; a significant improvement was only observed for trans men ($P = .003$). • **Self-Perception Descriptive Scores for total sample**, mean (95% CI) ○ Scholastic competence (N = 70), ▪ Pre-irreversible gender-affirming treatment: 14.26 (13.54–14.98) ▪ Post- irreversible gender-affirming treatment: 14.96 (14.22–15.69) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.56 (0.64), $P < .05$; Adjusted 7.14 (5.26), P = NS ▪ Time: Unadjusted 0.70 (0.38), P = NS; Adjusted 0.71 (0.39), P = NS ○ Social acceptance (N = 70), P = NS ▪ Pre-irreversible gender-affirming treatment: 14.81 (14.05–15.58) ▪ Post- irreversible gender-affirming treatment: 15.23 (14.48–15.98) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 14.40 (0.76), $P < .05$; Adjusted 22.34 (5.10), $P < .05$ ▪ Time: Unadjusted 0.41 (0.46), P = NS; Adjusted 0.43 (0.48), P = NS

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
	among whom 107 participated. Of the 107 people who participated in the larger evaluation study, pretreatment data on self-perception were available for 70 of them and they were therefore included in the current study. As 70 individuals of the 179 eligible were eventually included in this study, the participation rate was 39.1%. Subset definition: n = 49 trans men and n = 21 trans women	• Post-surgical years at post treatment assessment: 1.47 (0.67), range 0.69–4.79 • Living situation of the adolescent at the pretreatment assessment, N(%) ○ Living with both biological parents: 43 (61.4%) ○ Other: 27 (38.6%) Full-scale IQ, M (SD): 99.63 (14.23), range 72–135				○ Athletic competence (N = 69), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 12.86 (11.87–13.84) ▪ Post- irreversible gender-affirming treatment: 12.54 (11.62–13.46) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.16 (0.73), *P* < .05; Adjusted 12.98 (7.54), *P* = NS ▪ Time: Unadjusted -0.31 (0.39), *P* = NS; Adjusted -0.25 (0.40), *P* = NS ○ Physical appearance (N = 69), *P* < .001 ▪ Pre-irreversible gender-affirming treatment: 10.16 (9.37–10.95) ▪ Post- irreversible gender-affirming treatment: 12.81 (11.92–13.70) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 7.48 (0.72), *P* < .05; Adjusted 21.57 (5.20), *P* < .05 ▪ Time: Unadjusted 2.66 (0.42), *P* < .05; Adjusted 2.65 (0.42), *P* < .05 ○ Behavioral conduct (N = 70), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 15.81 (15.17–16.46) ▪ Post- irreversible gender-affirming treatment: 16.83 (16.23–17.43) ○ Close friendship (N = 70), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.87 (16.18–17.57) ▪ Post- irreversible gender-affirming treatment: 17.30 (16.57–18.03) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 16.44 (0.66), *P* < .05; Adjusted 21.39 (4.97), *P* < .05 ▪ Time: Unadjusted 0.43 (0.40), *P* = NS; Adjusted 0.49 (0.41), *P* = NS ○ Global self-worth (N = 68), *P* < .001

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
						▪ Pre-irreversible gender-affirming treatment: 12.01 (11.13–12.90) ▪ Post- irreversible gender-affirming treatment: 14.19 (13.32–15.06) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 9.71 (0.87), *P* < .05; Adjusted 14.24 (5.53), *P* < .05 ▪ Time: Unadjusted 2.23 (0.54), *P* < .05; Adjusted 2.27 (0.55), *P* = NS • **Self-perception descriptive scores for trans women**, mean (95% CI) o Scholastic competence (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.29 (13.06–15.51) ▪ Post- irreversible gender-affirming treatment: 15.95 (14.61–17.29) o Social acceptance (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.91 (13.66–16.15) ▪ Post- irreversible gender-affirming treatment: 15.71 (14.64–16.79) o Athletic competence (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 11.91 (10.32–13.49) ▪ Post- irreversible gender-affirming treatment: 11.19 (9.41–12.97) o Physical appearance (N = 21), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 12.29 (10.65–13.92) ▪ Post- irreversible gender-affirming treatment: 14.95 (13.48–16.42) o Behavioral conduct (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.86 (16.04–17.68) ▪ Post- irreversible gender-affirming treatment: 16.71 (15.71–17.72) ▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 17.00 (0.85), *P* < .05; Adjusted 17.51 (7.99), *P* < .05

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
						▪ Time: Unadjusted -0.14 (0.52), *P* = NS; Adjusted -0.05 (0.57), *P* = NS ○ Close friendship (N = 21), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 17.48 (16.46–18.49) ▪ Post- irreversible gender-affirming treatment: 17.67 (16.07–19.27) ○ Global self-worth (N = 21), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 13.57 (11.63–15.51) ▪ Post- irreversible gender-affirming treatment: 15.33 (13.99–16.68) • **Self-Perception Descriptive Scores for trans men**, mean (95% CI) ○ Scholastic competence (N = 49), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.25 (13.33–15.16) ▪ Post- irreversible gender-affirming treatment: 14.53 (13.65–15.41) ○ Social acceptance (N = 49), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 14.78 (13.80–15.75) ▪ Post- irreversible gender-affirming treatment: 15.02 (14.03–16.01 ○ Athletic competence (N = 48), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 13.27 (12.01–14.53) ▪ Post- irreversible gender-affirming treatment: 13.13 (12.06–14.19) ○ Physical appearance (N = 48), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 9.23 (8.44–10.02) ▪ Post- irreversible gender-affirming treatment: 11.88 (10.85–12.90 ○ Behavioral conduct (N = 49), *P* = .003 ▪ Pre-irreversible gender-affirming treatment: 15.37 (14.53–16.20) ▪ Post- irreversible gender-affirming treatment: 16.88 (16.11–17.64)

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
						▪ Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±SE) Without and With Adjustment for Possible Confounders: ▪ Intercept: Unadjusted 13.86 (0.80), *P* < .05; Adjusted 6.16 (5.06), *P* = NS ▪ Time: Unadjusted 1.51 (0.49), *P* < .05; Adjusted 1.51 (0.49), *P* < .05 o Close friendship (N = 49), *P* = NS ▪ Pre-irreversible gender-affirming treatment: 16.61 (15.71–17.51) ▪ Post- irreversible gender-affirming treatment: 17.14 (16.32–17.97) o Global self-worth (N = 47), *P* < .05 ▪ Pre-irreversible gender-affirming treatment: 11.32 (10.39–12.24) ▪ Post- irreversible gender-affirming treatment: 13.68 (12.58–14.78)
de Vries (2014)[4] [redacted]	**N = 55 TGNB youth** Eligibility: adolescents with GD prescribed puberty suppression between 2004 and 2011 Sampling method: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011 Subset: N = 55 TGNB adolescents, with N = 22 MTF and N = 33 FTM)	Full cohort: mean age (SD) at assessment pretreatment was 13.6 (1.9) (range: 11.1–17.0) mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5) mean age (SD) at the start of CSHT was 16.7 (1.1) (range: 13.9–19.0) mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3) mean age (SD) at assessment post	CSHT and GRS	N/A	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS)[a] CGAS used to assess Psychosocial functioning CBCL/ABCL and YSR/ASR used to assess behavioral and emotional problems using the total, internalizing, and externalizing T scores as well as the clinical range	CGAS (Psychosocial functioning) (n = 32), mean (SD) Scores significantly increased from 71.13 (10.46) at intake to 79.94 (11.56) at post treatment, P < .001 Significant linear effect (time) P < 0.001, Quadratic effect (time) P = NS CBCL /ABCL (Behavioral and emotional problems) (n = 40) Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 60.20 (12.66) at intake to 48.10 (9.30) at post treatment, P < .001 ▪ Significant linear effect (time) P < .001, quadratic effect (time) P = NS Internalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 60.83 (12.36) at intake to 50.45 (10.04) at post treatment, P < .001 ▪ Significant linear effect (time) P < 0.001, quadratic effect (time) P = 0.42 Externalizing T-Score, mean (SD) ▪ Scores showed a significant decrease from 57.85 (13.73) at intake to 47.85 (8.59) at post treatment, P < .001

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
		treatment was 20.7 (1.0) (range: 19.5–22.8) mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)			scores for the indices (T score > 63) General linear models examined the repeated measures with an analysis of variance-based model. A linear effect signifies an overall change across T0 to T2. Quadratic effect signifies change was not continuous. Mean age change between assessment pre and post treatment is 7.1 years	▪ Significant linear effect (time) P < .001, quadratic effect (time) P = NS YSR/ ASR (Behavior and emotional problems) (n = 43) Total T-Score, mean (SD) ▪ Scores showed a significant decrease from 54.72 (12.08) at intake to 48.53 (9.46) at post treatment, P < .005 ▪ Significant linear effect (time) P < .005, quadratic effect (time) P = NS Internalizing T-Score, mean (SD); ▪ Scores showed a significant decrease from 55.47 (13.08) at intake to 50.07 (11.15) at post treatment, P < .03 ▪ Significant linear effect (time) P < .03, Significant quadratic effect (time) P < .008 Externalizing T-Score, mean (SD) ▪ Scores showed a nonsignificant decrease from 52.77 (12.47) at intake to 49.44 (9.37) at post treatment with a P value of 0.14 ▪ linear effect (time) P = NS, quadratic effect (time) P = NS
Cardiovascular Health Outcomes						
Ott (2010)[8] [redacted] Austria (1995–2007)	**N=251 TGNB individuals** Eligibility criteria: all patients diagnosed with transsexualism who started CSHT (as all were screened for aPC-resistance, antithrombin III activity, free protein S antigen, and protein C activity before receiving CSHT) Sampling method: All eligible participants were included	MTF: mean age (SD): 36.6 years (10.9) mean (SD) BMI: 22.7 kg/m2 (3.9) 5 (3.1%) have had a previous thrombophilic event 8 (6.3%) had a family Hx of thrombosis,	CSHT MTF: transdermal 17ß-estradiol (2 x 100 mcg/week), oral cyproterone acetate (50 mg/day), and oral finasteride (5 mg every other day) and is reduced to transdermal 17ß-estradiol (2 x 100 mcg/week) after sex-reassignment surgery	Incidence if VTE in asymptomatic individuals with aPC resistance reported from Langlois (2003)[22]	Incidence of thrombophilia and venous thrombosis Venous blood was obtained at first visit and screened for aPC resistance, protein C activity and protein S antigen for routine thrombophilia screening. To assess incidence of VTE, patients were	**Venous thrombosis (VTE)** 0 incidences of VTE during CSHT hormone therapy 18 patients had a thrombophilic defect. 18 had aPC resistance and 1 patient had a protein C deficiency in addition. There were no incidents of VTE within this cohort. The expected incidence for those with aPC resistance was 2.4% over 64-month follow-up (0.43/18 patients),[22] which did not differ significantly from expected incidence (P = .5) **Thrombophilic defects** Of the 9 MTF patients with aPC-resistance that reported previous hormone use; 33% of these patients were found to have normal aPC resistance levels after a mean of 61.6 ± 41.8 months.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
	Subset definition: of the N=251 TGNB individuals, n=162 were MTF and n=89 were FTM	96 (59.3%) have a Hx of smoking 35 (21.6%) have a Hx of HTN 62 (38.3%) have a Hx of dyslipidemia 2 (1.2%) have a Hx of DM 60 (37.0%) have a Hx of previous CSHT 24 (14.8%) have a Hx of cross-sex surgery before initiation of CSHT FTM: mean age (SD): 26.9 years (7.3) mean (SD) BMI was 23.1 kg/m2 (4.1) 0 (0%) have had a previous thrombophilic event 3 (3.4%) had a family Hx of thrombosis 62 (69.7%) have a Hx of smoking 14 (15.7%) have a Hx of HTN	FTM: Standard FTM cross-sex hormone therapy includes IM T undecanoate (1000 mg every 12 weeks) and oral lynestrenol (5 mg daily) and is reduced to T undecanoate (1000 mg every 12 weeks) after sex-reassignment surgery		specifically asked for clinical symptoms of thrombosis at each visit as part of routine follow-up care. Mean length (SD) of follow-up was 64.2 (38.0) months	

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
		29 (32.6%) have a Hx of dyslipidemia 0 (0%) have a Hx of DM 2.2% have a Hx of previous CSHT 6.7% have a Hx of cross-sex surgery before initiation of CSHT				
Body Change Outcomes						
van der Loos (2021)[18] [redacted]	**N = 322 TGNB adolescents** Eligibility criteria: minimum duration of 6 months of GnRH analogs monotherapy; started therapy before 18 years of age, DEXA scan was available within a 6-month range before or after the start of GnRH analogs (baseline), the start of CSH, and/or after greater than equal to 2 years since the start of CSH Sampling method: all patients who visited the gender clinic in between 1972 and December 2018 Subset: Transgender male (n = 216) ▪ early puberty (n = 8) ▪ mid-puberty (n = 22) ▪ late puberty (n = 186)	Age at start of GnRH analogs: Median (interquartile range) Transgender women early puberty: 13.1 (12.5;13.5) mid puberty: 13.4 (12.9;14.9) late puberty: 15.5 (14.3;16.6) Transgender men early puberty: 11.9 (11.8;12.0) mid puberty: 12.5 (12.1;13.0) late puberty: 15.7 (14.6;16.8)	Adolescents diagnosed with GD were started with subcutaneous triptorelin (GnRH analog) 3.75 mg every 4 weeks or 11.25 mg every 12 weeks. The criterion for commencement was having a Tanner breast stage 2 or more for trans boys or Tanner genital stage 2–3 or more for trans girls, commonly around the age of 12 years. Around the age of 16 years, CSHT was added in incremental dosages to induce novel puberty.	N/A	Data was collected at the start of GnRH analog therapy, at the start of CSHT, and then ≥ 2 years after CSHT.[b] The outcome was 2 geometric parameters: subperiosteal width and endocortical diameter. They were obtained by running an HAS option on previously produced DXA images of the non-dominant proximal femur. Mean duration of mono GnRH analog therapy ranged from 1.0-3.7 years between cohorts, followed by GAH	**Transgender women/Early puberty** Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.44 (0.23, 0.65) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.38 (0.17, 0.60) **Transgender women/Mid puberty** Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.57 (0.39, 0.75) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.55 (0.37, 0.72) **Transgender women/Late puberty** Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27 (0.16; 0.39) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27 (0.15, 0.40) **Transgender men/Early puberty**

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
	Transgender female (n = 106) ▪ early puberty (n = 32) ▪ mid-puberty (n = 30) ▪ late puberty (n = 44)	Age at start of CSH: Median (interquartile range) Transgender women early puberty: 15.7 (15.3;16.0) mid puberty: 16.0 (15.8;16.6) late puberty: 16.4 (16;17.4) Transgender men early puberty: 15.9 (15.7;15.9) mid puberty15.9 (15.4;16.0) late puberty: 16.5 (16.0;17.5)	Trans girls were prescribed oral 17-beta-estradiol, usually starting at 5 µg/kg body weight. This was increased up to a daily maintenance dose of 2 to 4 mg. Trans boys were usually prescribed an ester mixture of 25 mg/m² body surface area intramuscular testosterone. Dosage was increased up to a maintenance of 250 mg every 3 to 4 weeks. Eligibility for gonadectomy was determined at the age of 18 years after receiving at least 1 year of CSH. Further, GnRH analogs were discontinued after gonadectomy.		therapy. Duration of GAH therapy ranged from 3.7-4.3 years between cohorts.	Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.79 (0.72, 0.85) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.73 (0.67, 0.79) **Transgender men/Mid puberty** Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.31(0.11, 0.50) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.27(0.06, 0.48) **Transgender men/Late puberty** Subperiosteal width; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.15 (0.04, 0.26) Endocortical diameter; mean difference (95% CI) ▪ Significant Δ between the start of GnRH analogs and after ≥ 2 years of CSH: 0.17 (0.05, 0.28)
Body Image Outcomes						
de Vries (2014)[4] [redacted]	**N = 55 TGNB youth** Eligibility: adolescents with GD prescribed puberty suppression between 2004 and 2011	Full cohort: mean age (SD) at assessment pretreatment	CSHT and GRS	N/A	Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at	**UGDS (GD) (n = 33), mean (SD)** Scores showed a significant decrease from 53.51 (8.29) at intake to 15.81 (2.78) at post treatment, P < .001 [T0- 53.51 (8.29), T1- 54.39 (7.70), T2- 15.81 (2.78)] Significant linear effect (time) P < .001, Significant quadratic effect (time) P < .001

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
[redacted]	Sampling method: first 70, and then filtered to those who were prescribed puberty suppression and continued with GRS between 2004 and 2011 Subset: N = 55 TGNB adolescents, with n = 22 MTF and n = 33 FTM	was 13.6 (1.9) (range: 11.1–17.0) mean age (SD) at the start of GnRH analogs was 14.8 (1.8) (range: 11.5–18.5) mean age (SD) at the start of CSHT was 16.7 (1.1) (range: 13.9–19.0) mean age (SD) at the start of GRS was 19.2 (0.9) (range: 18.0–21.3) mean age (SD) at assessment post treatment was 20.7 (1.0) (range: 19.5–22.8) mean full scale intelligence (SD) was 99.0 (14.3) (range: 70–128)			initiation of CSH), and post treatment (T2, 1 year after GRS)[a] UGDS was used to measure GD BIS used to measure dissatisfaction with body characteristics General linear models examined the repeated measures with an analysis of variance-based model. A linear effect signifies an overall change across T0 to T2. Quadratic effect signifies change was not continuous. Mean age change between assessment pre and post treatment is 7.1 years	GD persisted from T0-T1 but then decreased significantly **BIS (body image) (n = 45)** Primary sex characteristics, mean (SD) There was a significant decrease in body dissatisfaction of primary sex characteristics from 4.13 (0.59) at intake to 2.59 (0.82) post treatment, P < .001 T0- 4.13 (0.59), T1- 4.05 (0.60), T2- 2.59 (0.82) Significant linear effect (time) P < 0.001, significant quadratic effect (time) P < .001 Secondary sex characteristics, mean (SD) There was a significant decrease in body dissatisfaction of secondary sex characteristics from 2.73 (0.72) at intake to 2.27 (0.56) post treatment, P < .001 T0- 2.73 (0.72), T1- 2.86 (0.67), T2- 2.27 (0.56) significant linear effect (time) P < .001, significant quadratic effect (time) P < .001 Neutral body characteristics, mean (SD) There was a non-significant decrease in body dissatisfaction of neutral body characteristics, P = NS T0- 2.35 (0.68), T1- 2.49 (0.53), T2- 2.23 (0.49) linear effect (time) P = .29, significant quadratic effect (time) P = .01
Bone Health Outcomes						
Klink (2015)[16] [redacted] the Netherlands	**N = 34 TGNB adolescents** Eligibility criteria: Study subjects were included when they were at least 21 years of age, gonadectomy had taken place in the period from June 1998 to August 2012, and data	Transgender women Median age ± SD (in years) start of GnRH analogs: 14.9 ± 1.9	GnRH analog monotherapy (median duration in natal boys with GD [trans women] and natal girls with GD [trans men] 1.3 and 1.5 y,	Z-scores were calculated using UK reference population.	Baseline data were collected at start of GnRH analogs, start of CSHT and at follow-up near age 22[c]	**BMAD and BMD** At age 22 years, LS aBMD z scores were lower compared with start GnRH analogs, but this was not significant. Scores significantly declined from start of GnRH analogs to start of CSH, but then improved from the start of CSHT to age 22 Transgender women Mean ±SD or median [interquartile range]

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
	on BMD at start of GnRH analog treatment, at start of CSHT, and at the age of 22 years were available. The 34 eligible subjects and their parents or legal representatives gave written consent for follow-up at start of treatment. Sampling method: Patients that met criteria were included Subset definition: of the total population (N = 34) there were (n = 15) trans women and (n = 19) trans men	start of CSHT: 16.6 ± 1.4 22-year follow-up: 22.1 ± 0.9 Median duration (in years) GnRH analogs monotherapy: 1.3 years (range, 0.5–3.8) CSHT: 5.8 years (range, 3.0–8.0) Combined GnRH analog and CSHT therapies: 3.1 years (range, 2.1– 4.5) Transgender men Median age ±SD (in years) Start of GnRH analogs: 15.0 ± 2.0 Start of CHST: 16.4 (2.3) 22-year follow-up: 21.9 ± 0.5 Median duration (in years) GnRH analogs monotherapy: 1.5 years (range, 0.25–5.2) CSHT: 5.4 years (range, 2.8–7.8)	respectively) followed by CSHT (median duration in trans women and trans men, 5.8 and 5.4 y, respectively) with discontinuation of GnRH analogs after gonadectomy. Treatment protocol: Triptorelin (Decapeptyl-CR) 3.75 mg every 4 weeks s.c. was started in patients diagnosed with gender identity disorder (DMS IV-TR) in the age range from 11.4 –18.3 years. In the age range from 15.6 –19 years trans-women were prescribed incremental dosing of 17-beta-estradiol orally and trans men were given in mixed T esters (Sustanon 250 mg/ml) every 2–4 weeks in incremental dosages. At a minimum age of 18 years, after gonadectomy, GnRH analog treatment was terminated and CSHT therapy continued. During the entire treatment		BMAD and aBMD with accompanying z-scores of lumbar spine and femoral region were measured. aBMD of the LS and FN was measure by dual energy X-ray absorptiometry	Start of GnRH analogs to age 22 ▪ There was a significant increase in LS aBMD from start of GnRH analogs to age 22 (0.84 g/cm3 ± 0.13 to 0.93 g/cm3 ± 0.10, P = 0.06,) but the corresponding z-score had significantly declined from the start of treatment from -0.77 ± 0.89 to -1.36 ± 0.83 at age 22, P = .003 ▪ LS and FN BMAD and FN aBMD showed no significant change from start of GnRH analogs to age 22 Transgender men Mean ±SD or median [interquartile range] From start of GnRH analogs to age 22 ▪ There was no significant change in LS BMAD and their corresponding z-score or absolute aBMD. ▪ There was also no significant change in FN BMAD and its corresponding z-score or aBMD and its corresponding z-score. ▪ The only significant change was a decrease in the LS aBMD z-score from 0.17 ± 1.18 to -0.33 ± 1.12, P = .02

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
		Combined GnRH analog and CSHT therapies: 2.2 years (range, 1.4 –3.1)	patients were advised on calcium intake and weight- bearing physical exercise			
Cancer Outcomes						
Gooren (2013)[14] [redacted] the Netherlands from 1975 to 2012	**N=3102 TGNB individuals** Eligibility criteria: Baseline and follow-up data were available in the database, had started cross-sex hormone treatment from 1975 to December 31, 2006, with follow-up duration of at least 6 years Sampling method: Baseline and follow-up data of all TGNB individuals referred to the clinic who met the eligibility criteria were included. Subset definition: Of the N=3102 TGNB individuals, n=2307 were MTF and n=795 were FTM	MTF cohort: mean age (SD) was 29.3 (12.7) years at the start of cross-sex hormone administration (range 16–83 years). mean follow-up period (SD) of subjects receiving anti-androgens and estrogens or only estrogens was 21.4 (8.7) years (median 17.6, range 6.0–43.5 years). FTM cohort The mean age (SD) at the start of testosterone treatment was 23.2 (6.5) years (range 16-65 years.) mean follow-up period (SD) was 20.1 (7.3) years (median 16.8, range 6.0–36 years).	TGNB individuals who had started CSHT	Dutch general population	Breast cancer incidence: The incidence rate of breast cancer was calculated per 100,000 patient years of follow-up. The 95% confidence interval for FTM subjects was calculated using the model proposed by Byar because of the small number of cases. The expected incidence of breast cancer was calculated based on Dutch incidence numbers for men and women and were standardized for the age distribution of transgender subjects in the cohort. Follow up on hormone treatment (SD) in MTF cohort was 21.4 (8.7)	Breast cancer incidence: Three cases of cancer have occurred in this population including 2 MTF subjects (1 unproven) and 1 FTM subject. The incidence rate of breast cancer in MTF cohort was 4.1 per 100,000 person-years. The 95% confidence interval of the incidence ranged from 0.8 to 13.0 per 100,000 patient-years. For comparison, the calculated expected incidence of breast cancer in biologic women would be 170.0 per 100,000 person-years of follow-up. In the sample, the incidence of breast cancer in MTF subjects more closely approximate the expected incidence of breast cancer of 1.2 per 100,000 patient-years that would occur in biologic men. The incidence rate of breast cancer in FTM individuals was 5.9 per 100,000 person-years, with a 95% confidence interval of 0.5 to 27.4 per 100,000 person years. For comparison, the expected incidence of breast cancer would be 154.7 per 100,000 person-years for biologic women and 1.1 per 100,000 person years for biologic men.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
					years and 20.1 (7.3) years in the FTM cohort.	
Gooren (2014)[15] [redacted] the Netherlands from 1975 to 2006	**N=2307 MTF TGNB individuals** Eligibility criteria: MTF TGNB patients treated with cross-sex hormone treatment at the [redacted] between 1975 and 2006 Sampling method: Medical records were reviewed for all participants who met the criteria Subset definition: Of the N=2307 transgender women, n=749 were over the age of 40 at the time of medical review.	mean age (SD) at the start of CSHT was 29.3 (12.7) years (range 16-83) Age groups (n, %) 426 (18.4) age 15-24 1132 (49.0) age 25-39 702 (32.4) age 40-64 47 (2.0) age 65-80 mean follow-up (SD) was 21.4 years (8.7) follow-up time (% of sample) by years were: 0.5% (125) for less than 5 years 16.3% (375) for 5-10 years 26.6% (614) for 10-15 years 24.0% (570) for 15-20 years 13.1% (303) for 20–25 years 169 (7.1%) for 25–30 years 151 (6.3%) for >30 years	CSHT antiandrogens (usually cyproterone acetate 100 mg/day) + estrogens (1975-1993 ethinyl estradiol 100 mcg/day, 1993-2006 estradiol 4 mg/day or transdermal 17beta-oesterdiol 100 mcg/day) and then bilateral orchiectomy)	US men data derived from SEER cancer statistics 1975-2009	Prostate cancer incidence The incidence of prostate cancer diagnosis was calculated using medical records and/or family physician information. Follow up on hormone treatment was a minimum of 6 years, with a mean follow-up (SD) of 21.4 (8.7) years representing 51,173 person years	Prostate cancer incidence: The overall incidence of prostate cancer in the total population was 0.04% (1/2307) For those who initiated hormone treatment after 40 years old, the overall incidence of prostate cancer was 0.13% Compared to SEER cancer statistics, the rate of .13% in men after 40 was lower than 10 -year incident rate of 3.18% for 40-60 years US men

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
De Nie (2020)[13] [redacted] the Netherlands from 1975-2016	**N=2281 MTF TGNB individuals** Eligibility criteria: MTF TGNB patients who received hormone therapy; excluded if start dates of hormone therapy were unknown, if under 18 years old at the time of the study, if both male and female hormones were used, and if last visit to clinic was before 1991. Sampling method: Medical records were reviewed for all participants who attended the clinic between 1972 and 2016 who met the criteria Subset definition: Of the N=2281 transgender women, n=1572 underwent an orchiectomy while n=709 did not.	median age (IQR) at the time of study is 50 years (37 to 59) Median age (IQR) at the start of hormonal treatment was 31 years (23 to 41) Median age at time of study (IQR) was 50 (37-59) years median BMI (IQR) is 22.7 kg/m2 (20.5 to 25.6), 96.7% were of Caucasian ethnicity 39% were former smokers, 1572 (68.9%) had an orchiectomy	CSHT Combination of antiandrogens and estrogen therapy spironolactone therapy used rarely	Dutch cis males' general population data from the Netherlands Comprehensive Cancer Organization	Prostate cancer incidence The incidence of prostate cancer diagnosis was calculated using follow-up time (as defined as years from the start date of hormone treatment until either prostate cancer diagnosis, date of death, or end of the study period-12/24/2019) To calculated standardized incidence ratios (SIRs), observed cases of cancer and the expected cases based on age-specific incidence rates obtained from the Netherlands Comprehensive Cancer Organization were used. 95% Cis were calculated using a mid-exact P-test Median follow up after hormonal treatment (IQR) was 14 (7-24) years with a total follow-up	Prostate cancer incidence (95% CI) Compared to the general male population of similar age, there was a 5-fold decrease in prostate cancer risk in transgender women using hormone treatment with a standardized incidence ratio of 0.20 (0.08-0.42). In all age categories, the prostate cancer risk in the TGNB cohort was lower than in Dutch cis males. The SIR for participants from ages 45-59 was 0.14 (0.01-0.70) with 1 observed case, ages 60-74 was 0.20 (0.06-0.48) with 4 observed cases and over age 74 was 0.33 (0.02-1.64) which was lower, but not statistically significant, with 1 observed case. Transgender women who were treated with hormones and an orchiectomy had a significantly lower prostate cancer risk with an SIR of 0.17 (0.05-0.40), while those who were hormone treated without an orchiectomy had a lower SIR of 0.44 (0.07-1.47) but was not statistically significant.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
					time in years of 31,117 person years	
Nota 2018[17] [redacted] the Netherlands	**N=3928 TGNB individuals** Eligibility criteria: seen at the gender clinic of the [redacted] between February 1972 and December 2015, were prescribed cross-sex hormones by this clinic or an affiliate with a known start date of therapy, those were excluded if they used female and male sex hormones alternately or discontinued for an extended period of time Sampling method: Medical records were reviewed for all participants who attended the clinic between 1972 and 2015 who met the criteria Subset definition: Of the N=3928 TGNB individuals, n=2555 were transgender women and n=1373 were transgender men.	Transgender women: median age (IQR) at start of cross-sex hormone treatment: 31 years (23–41) Transgender men: median age (IQR) at start of cross-sex hormone treatment: 23 years (18–31)	CSHT	Dutch or European general population	Benign brain tumor incidence Number of new cases of each separate brain tumor that occurred (observed cases) was determined. Total person-time of observation in years was determined based on follow-up period after beginning CSHT. The expected cases, based on reported incidence from rates in general Dutch or European populations (if Dutch data wasn't available) and the total person-time of observation was calculated When different incidence rates were reported for males and females, incidence rate was calculated twice using each rate. SIRs	Benign brain tumor incidence, SIR (95% CI) **Transgender women** In total, 20 cases of new benign brain tumor were identified. Expected incidence of cancer occurred in most tumor types. Transgender women showed significantly more cases of meningiomas than could be expected based on the incidence rate of European (French) female and male populations. Also, more prolactinomas were identified in transwomen than in general Dutch female and male populations. ▪ Meningioma: There were 8 observed cases. The expected cases in females is 1.97, resulting in an SIR of 4.1 (1.9-7.7). The expected cases in males is 0.67 resulting in an SIR of 11.9 (5.5-22.7). ▪ Non-secretive pituitary adenoma: There was 1 observed case. The expected cases in females and males is 0.13, resulting in an SIR of 7.7 (0.4-37.9). ▪ Secretive pituitary adenoma: 1. Prolactinoma (Total): There were 9 observed cases. The expected cases for females is 2.08, resulting in an SIR of 4.3 (2.1-7.9). The expected cases for males is 0.34, resulting in an SIR of 26.5 (12.9-48.6). 2. Prolactinoma (Symptomatic): There were 5 observed cases. The expected cases for females is 2.08, resulting in an SIR of 2.4 (0.9-5.3). The expected cases for males is 0.34, resulting in an SIR of 14.7 (5.4-32.6) 3. Somatotropinoma: There were no observed cases. The expected cases for both males and females is 0.18 4. Corticotropinoma: There were no observed cases. The expected cases for females is 0.06 and for males is 0.02. 5. Thyrotropinoma: There were no observed cases. The expected cases for both males and females is 0.01

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
					were calculated using a mid-P exact test with 95% CI for each type of tumor.	▪ Vestibular schwannoma: There were 2 observed cases. The expected cases for both females and males Is 0.90. The SIR, mean (95% CI) compared to both reference male and female was 2.2 (0.4–7.3) Transgender men In total, 3 cases of benign brain tumors were identified. The case of prolactinoma was not different from the number expected using the incidence rates from general Dutch female and male populations. Somatotropinomas occur very rarely, so the 2 cases were significantly higher than expected. ▪ Meningioma: There were no observed cases. The expected cases for females is 0.92 and for males is 0.32. ▪ Non-secretive pituitary adenoma: There were no observed cases. The expected cases for females and males is 0.06. ▪ Secretive pituitary adenoma: 1. Prolactinoma: There was 1 observed case. The expected cases in females is 0.98, resulting in an SIR of 1.02 (0.1–5.0). The expected cases in males is 0.16, resulting in a Sir of 6.3 (0.3–30.8). 2. Somatotropinoma: There were 2 observed cases: The expected cases in females is 0.09, resulting in an SIR of 22.2 (3.7–73.4). The expected cases in males is 0.09, resulting in an SIR of 22.2 (3.7–73.4) 3. Corticotropinoma: There were no observed cases. The expected cases for females is 0.03 and is 0.01 for males. 4. Thyrotropinoma: There were no observed cases. The expected cases for females and males is 0.00 ▪ Vestibular schwannoma: There were no observed cases. The expected cases for females and males is 0.42.
Mortality Outcomes						
Asscheman (2011)[3] [redacted]	**N= 1331 TGNB individuals** Eligibility: Included only subjects who had started cross-sex hormone	MTF (n=966) mean age of 31.4 years at the start of cross-sex	TGNB individuals who received CSHT	General Dutch population data compared from	Mortality The observed number of deaths in the study	**MTF cohort (n=966) mortality, SMR (95% CI)** 122 (12.6%) out of 966 subjects had died during follow-up.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
[redacted] the Netherlands	treatment before July 1, 1997, followed-up for at least 1 year Sampling method: Baseline and follow-up data of all TGNB subjects referred to outpatient department since 1975 were entered into a cumulative database. 2 MTF who had died the first year of hormone administration were also included. Subset definition: Of total population of TGNB individuals (N=1331), n= 966 were MTF and n=365 were FTM	hormones (range: 16–76 years) 18,678 patient-years of follow-up. 365 (27.4%) FTM (n=365) mean age 26.1 years (range: 16–57 years) at the start of hormone therapy 6,866 patient-years of follow-up MTF cohort was older when they started CSHT (31.4±11.4 years) than FTM (26.1±7.4 years; P < .001). In the MTF group, 207 subjects (21.4%) were over 40 years of age, and nine subjects (0.9%) were even over 65 years of age, whereas only few FTM (n=16, 4.4%) were over 40 years of age at the start of CSHT The mean duration of follow-up was not significantly different between MTF and FTM	MTF individuals received treatment with different high-dose estrogen regimens and cyproterone acetate 100 mg/day. FTM individuals received parenteral/oral testosterone esters or testosterone gel.	the 2001 mortality data of the general population provided by the Central Bureau of statistics of the Netherlands	population was set against the expected numbers of deaths derived from the 2001 mortality data of the general population provided by the Central Bureau of Statistics of the Netherlands stratified per age group and natal sex. Numbers of deaths were adjusted for the years of follow-up on cross-sex hormone treatment. The risk was expressed as standardized mortality ratio (SMR), and the 95% CIs were calculated by regarding the observed number as a Poisson variable with tables based on Poisson distribution. Cause of death was ascertained by medical report or information from family physician according to ICD-10 code Mean follow-up period of subjects receiving	When compared with the adjusted expected mortality in the general population, the MTF cohort had a significantly increased mortality with a SMR of 1.51 (1.47–1.55). In the 25–39 years of age group, the SMR of total mortality was increased (4.47; 4.04–4.92) and was mainly due to the relatively high numbers of suicides (in six), drugs-related death (in four), and death due to AIDS (in 13 subjects). In 40–64-year age group, the SMR of total mortality was increased to 1.42 (1.35–1.48) and was mainly due to the higher rate of suicides (in eight) and cardiovascular disease (in 17) In over 65 years of age, the total mortality was not increased with a SMR of 0.95 (0.86–1.06). Ischemic heart disease was the cause of death in 18 subjects, with a significantly increased mortality with a SMR of 1.64 (1.43–1.87) Five MTF subjects died from stroke with a statistically nonsignificant increase in the SMR of 1.26 (0.93–1.64) The observed total number of deaths due to malignant neoplasm (n=28) was not increased compared with the general population with a SMR of 0.98 (0.88-1.08) ▪ Lung cancer (n=13) showed a statistically significant increased SMR of 1.35 (1.14–1.58). ▪ The risk of death from leukemia/ lymphoma, with six deaths (one acute myeloid leukemia, one chronic lymphoid leukemia, one unclassified leukemia, and three non-Hodgkin lymphomas,) was significantly increased with a SMR of 2.66 (1.93–3.60). ▪ There was a reduced mortality risk of digestive tract malignant neoplasms with an SMR of 0.42 (0.28-0.60) External causes of death were increased almost eightfold due to suicide and illicit drug use with a SMR of 7.67 (6.84–8.56) ▪ Suicide rate increased sixfold with a SMR of 5.70 (4.93–6.54) ▪ Death due to illicit drugs was increased 13 times; SMR 13.2 (9.70 - 17.6). Sixteen MTF transsexual subjects died from AIDS between 1986 and 2006 (SMR = 30.2; 26.0–34.7). **FTM cohort (n=365) mortality, SMR (95% CI)** 12 out of 365 (3.4%) died during follow-up.

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
		subjects (19.4±7.7 vs 18.8±6.3 years; P = 0.12). The rate of sex reassignment surgery was significantly lower in MTF compared to FTM subjects (86.7 vs 94.0%, P < .001)			CSHT (years ± SD) was 19.3 ± 7.7 years in MTF cohort and 18.8 ± 6.3 years in FTM cohort	When compared with the adjusted expected mortality in the general population, the SMR of 1.12 (0.89–1.59) was not significantly increased. External causes of death were increased due to one death by illicit drug abuse (SMR 25; 6-32.5). Total number of cancer deaths was not different from the expected number (SMR 0.99; 0.65-1.44). ▪ No deaths due to breast cancer was observed, and in other cancer categories: lung (SMR 1.06; 0.26-3.19), digestive tract (SMR 2.41; 0.90-5.18), hematological (SMR 2.86; 0.69-8.57), brain (0 cases) and other (SMR 0.77; 0.25-1.77) mortality risk was not statistically significantly different from those expected Ischemic heart disease was increased compared to expected values but not statistically significant with a SMR of 1.19 (0.39-2.74).
De Blok (2021)[12] [redacted] the Netherlands between 1972 and 2018	**N=4568 TGNB individuals** Eligibility criteria: People were included if they had started hormone treatment between 1972 and 2018 and were excluded if they used alternating testosterone and estradiol treatment, if they started treatment younger than age 17 years, if they ever used puberty-blockers (ie, gonadotropin hormone releasing hormone analogues) before gender-affirming hormone treatment, or if they were lost to follow-up. Additionally, people were excluded if there were no data available from at least one visit after the start of hormone treatment. Sampling method: Between 1972 and 2018, 8831 people visited the	Transgender women: Median age at the start of hormone treatment was 30 years (IQR 24–42) Median follow-up time was 11 years (IQR 4–22) Total follow-up time of 40 232 person-years. The majority was white (n = 1967/2171, 90.6%) and ever-smokers (n = 815/1861, 43.8%). Transgender men: Median age at the start of hormone treatment was 23 years (IQR 20–32).	CSHT treatment Transgender women: either cyproterone acetate or spironolactone as an antiandrogen; In addition to antiandrogens, estrogen, conjugated estrogens, estradiol patches, implants, injections, valerate, or gel. Transgender men: either testosterone gel, intramuscular testosterone esters, or testosterone undecanoate. For those who experienced persistent menstrual	General Dutch population men and women – data from CBS	Overall mortality Data were retrieved from medical files and were linked to Statistics Netherlands (CBS), a Dutch governmental institution that gathers statistical information about the Netherlands and its inhabitants. Trends in overall mortality over 5 decades in transgender women and transgender men, compared with general population men and women. Standardized mortality ratios (SMRs) were calculated using an actuarial life table	Mortality, SMR (95% CI) Overall mortality: During follow-up, 317 (10.8%) of 2927 transgender women and 44 (2.7%) of 1641 transgender men died Overall mortality of 628 deaths per 100000 person-years. The overall mortality risk in transgender women was increased compared with general population men (SMR 1.8; 1.6–2.0) and general population women (SMR 2.8; 2.5–3.1). The increased overall mortality risk compared with general population men was mainly because of increased mortality risk in people who started hormone treatment between 2010 and 2018. The overall mortality risk in transgender men was increased significantly compared with general population women (SMR 1.8; 1.3-2.4) and not significant compared to general population men (SMR 1.2; 0.9-1.6). The increased overall mortality risk compared with general population women was mainly because of increased mortality risk in people who started hormone treatment between 1990 and 2000. Cumulative mortality shows impaired survival in transgender women compared with general population men and women. However, in transgender men the cumulative mortality shows impaired survival but the changes over time was not as significant as in transgender women. Cause-specific mortality (From 1996-2018)

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
	gender identity clinic, of which 5350 were birth-assigned males and 3481 were birth-assigned females. 4263 people were excluded from the study for a variety of reasons including not using hormone treatment or using hormone treatment younger than age 17 years. Subset definition: Of N=4568 TGNB individuals, n=2927 were transgender women and n=1641 were transgender men	Median follow-up time was 5 years (2–17) Total follow-up time of 17 285 person-years The majority was white (n = 1307/1411, 92.6%) and ever-smokers (n = 503/ 1138, 44.2%).	blood loss during testosterone therapy were treated with additional progestogens such as lynestrenol.		approach as described by Dickman and colleagues. Cause-specific mortality: Data about cause of death were retrieved from CBS and were available since 1996. Median follow up time in years (IQR) was 11 (4-22) years for transgender women and 5 (2-17) years for transgender men. Transgender women who died during follow-up received hormone treatment for a median of 16 (7-25) years, while transgender men received treatment for a median of 13 (7-24) years.	Compared with general population men, transgender women died more frequently because of either cardiovascular disease (SMR 1.4; 1.0–1.8), lung cancer (SMR 2.0; 1.4–2.8), infection (SMR 5.4; 2.9–8.7), or non-natural causes of death (SMR 2.7; 1.8–3.7). SMR was high for HIV related deaths (SMR 14.7; 1.8-40.9) and other infections (SMR 4.8; 2.4-8.0). For non-natural causes of death, SMR was highest for suicide deaths (3.1; 1.8-4.7) and significant for other causes (SMR 2.3; 1.2-3.6). There was no increased mortality risk for myocardial infarction (SMR 1.1; 0.7-17), or cancer (SMR 1.3; 1.0-1.6), including cancer of the digestive tract (SMR 1.0; 0.6-1.5) or other cancers (SMR1.1; 0.7-1.6) Compared with general population women, transgender women died more frequently because of either cardiovascular disease (SMR 2.6; 1.9–3.4), lung cancer (SMR 3.1; 2.1–4.2), infection (SMR 8.7; 4.7–14.1), or non-natural causes of death (SMR 6.1; 4.2–8.4). In the cardiovascular disease category, risk of death because of myocardial infarction (SMR 3.0; 1.7-4.5) showed the largest SMR. HIV-related disease (SMR 47.6, 5.8–132.6) resulted in the largest SMR in the infection category with other infections also having a high SMR of 7.6 (3.8-12.7). Suicide (SMR 6.8, 4.1–10.3) showed the largest SMR in the non-natural causes category, with other causes having an SMR of 5.2 (2.9-8.4). Transgender men had a higher risk of death from non-natural causes (SMR 3.3; 1.2–6.4) compared with general population women although neither subcategory had a significant increased risk of death with suicide having a SMR of 2.8 (0.6-6.8) and other causes having a SMR of 4.0 (0.8-9.7), with both having large confidence intervals. There was no significant increased mortality risk from cardiovascular disease(SMR 1.6; 0.5-3.2) including myocardial infarction (SMR 1.0; 0.0-3.7) and other CV deaths (SMR 1.8; 0.5-4.0); no increased risk of cancer (SMR 0.8; 0.4-1.4), including lung (SMR 1.1; 0.2-2.7), digestive tract (SMR 0.4; 0.0-1.6), and other cancers (0.8; 0.3-1.6); and an increased SMR in the other causes of death category (2.8; 1.6-4.5) Compared with general population men, transgender men had no increased risk of mortality. SMR compared to the general population of men was: cardiovascular disease (SMR 0.8; 0.3-1.6) including myocardial infarction (SMR 0.4; 0.0-1.4) and other CV deaths (SMR 1.1; 0.3-2.3); cancer (SMR 0.8; 0.4-1.4), including lung (SMR 1.0; 0.2-2.3), digestive tract (SMR 0.3; 0.0-1.0), and other cancers (1.1; 0.4-2.2); non natural causes (SMR 1.3; 0.5-2.5), including suicide(SMR 1.2; 0.3-3.0) and other non-natural causes (SMR 1.3; 0.3-3.2); other causes of death category (SMR 1.9; 1.0-3.0)

[a] *Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[b] *Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[c] *Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.*

[d] *Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]*

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC

Table II.G.1. Clinical studies with before and after (pre-post) comparisons

First Author (Publication year) and Setting	Population	Select Baseline Characteristics	Exposure/Intervention	Reference Population Comparator (if applicable)	Outcome Measures and Timing	Results
Wiepjes (2020)[6] [redacted] the Netherlands between 1972-2017	**N=8263 TGNB individuals** Eligibility criteria: All people that once visited the center between 1972 and 2017 were included. Sampling method: A retrospective chart study was performed on all people that came to the center between 1972 and 2017, which included adults, adolescents, and children. Information on death occurrence and time was obtained by cross-checking the National Civil Record Registry for date of birth and death, and the hospital registration system, medical, and psychological files for cause of death. Subset definition: Of N= 8263 TGNB individuals, n=5107 are MTF and n=3156 are FTM	FTM (n= 3156) median (range) age at first visit: 20 (4-73) years median (range) follow-up time: 4.8 (0-45.5) years Total follow up of was 27,940 person years MTF (n = 5107) median (range) age at first visit: 25 (4-81) years median (range) follow-up time: 10.2 (0-45.5) years Total follow up was 64, 287 person years	Transgender individuals who had visited the center. Unspecified number were treated with CSHT and surgical interventions.[d] Study cohort until 2015 described in Wiepjes 2018[20]	Dutch general population data from the National Civil Record Registry	Suicide death rate Information on death occurrence, time, and cause of death was obtained by cross-checking multiple sources: The National Civil Record Registry and the hospital registration system. Patients followed from the time they had their first appointment at the clinic until death or end of study period Median follow-up time was 4.8 years for FTM and 10.2 years for MTF participants	**Suicide deaths** 41 transgender women and 8 transgender men died by suicide Of all suicide deaths, 14 people were no longer in treatment and 35 were in treatment in the previous 2 years, with 17 participants in the diagnostic or hormonal phase, 2 in the surgical phase and 16 receiving only medical follow-up care. Median follow-up time between first visit and suicide death was 6.7 years in both transgender men and women **At time of death, Mean number of suicides in years 2013-2017** The mean number of suicides was higher in the transgender population at 40/100,000 person years compared with the Dutch population in the same time frame of 11/100,000 person years The mean number of suicides was higher in the transgender woman population at 43/100,000 person years compared with the Dutch population in the same time frame of 15/100,000 person years for men and 7/100,000 person years for women. The mean number of suicides was higher in the transgender men population at 34/100,000 person years compared with the Dutch population in the same time frame of 15/100,000 person years for men and 7/100,000 person years for women.

[a] Data is reported from intake appointment pre-treatment (T0) to post-treatment, 1 year after GRS (T2). Interim data (T0-T1 and T1-T2 [de Vries 2014][3]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[b] Data is reported from start of GnRH analog therapy (T0) to ≥ 2years after CSHT (T2). Interim data (T0-T1 and T1-T2 [van der Loos 2021][16]) can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[c] Data is reported from start of GnRH analogs to follow-up near age 22. Interim data, measurements from start of CSHT (T1 [Klink 2015][14]), can be found in Appendix I.L of the original report, Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria, submitted to the Utah Department of Health.

[d] Study cohort treatment demographics in 2015: In adults >18 years, 69.9% of study population reported starting CSHT, with 77.7% undergoing a gonadectomy. In adolescents aged 12-17, 41.0% had started PS, 1.9% had stopped PS, 32.2% had started CSHT without PS, and 78.2% had undergone a gonadectomy. In children <12 years, 40.3% had started PS (Wiepjes 2018).[18]

Abbreviations: ABCL, adult behavior checklist; aBMD, areal bone mineral density; aPC, activated protein C; ASR, adult self-report; BIS, Body Image Scale; BDI, Beck Depression Inventory; BMAD, bone mineral apparent density; BMI, body mass index; BMD, bone mineral density; CBCL, Children's behavior checklist; CBS, Statistics Netherlands; CI, confidence interval; CGAS, Children's Global Assessment Scale; CSH, cross sex hormone; CSHT, cross-sex hormone treatment; DM, diabetes mellitus; FN, femoral neck; FTM, female transitioning to male; GD, gender dysphoria; GnRH, gonadotropin releasing hormone; GRS, gender reassignment surgery; Hx, history; HTN hypertension; ICD-10, International Classification of Diseases, 10th edition; IQR, interquartile range; LS, lumbar spine; MTF, male transitioning to female; PS, puberty suppression; SD, standard deviation; SEER, The Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPPA, Harter Self-Perception Profile for Adolescents; STAI, Spielberger's Trait Anxiety Scale; TGNB, transgender, non-binary or gender diverse; TPI, Spielberger's trait Anger Scale; UGDS, Utrecht Gender Dysphoria Scale; US, United States; VTE, venous thrombosis; YSR, youth self-report

Return to TOC