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TRANSGENDER HEALTH

The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets

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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.**

Key Words: Transgender; Prevalence; Regret; Gender-Affirming Hormones; Gender-Affirming Surgery

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INTRODUCTION

Gender dysphoria (GD) refers to the distress related to a marked incongruence between one's assigned sex at birth and the experienced gender later in life.[1] In this study, we define transwomen as having a male birth assignment and transmen as having a female birth assignment who might receive medical treatment to adapt their physical characteristics to their experienced gender. This treatment can include puberty suppression (PS), gender-affirming hormonal treatment (HT), and gender-affirming surgery.

It has been widely observed that the transgender population is growing and broadening.[2,3] This increase in the transgender population raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions.

There are no reliable estimations of the current prevalence of transgender people who actually have received gender-affirming treatment (including HT), because most recent studies are based on questionnaires[4,5] or data about gender-affirming surgery only.[6,7] In most countries transgender care is performed by multiple health care providers (eg, university clinics or general practitioners), which makes it difficult to provide these numbers. In contrast, in the Netherlands, more than 95% of the transgender population has received treatment in only 1 center, the gender identity clinic at the VU University Medical Center (VUmc; Amsterdam, the Netherlands), currently known as the Center of Expertise on Gender Dysphoria.[8–10] This center started treating adults in 1972. From 1987 to 2002, children and adolescents were seen by a mental health specialist in the Utrecht University Medical Center (Utrecht, the Netherlands). After they were considered eligible, they could receive medical treatment in the VUmc, which consisted of PS (usually by gonadotropin-releasing hormone analogues), followed by HT (see Kreukels and Cohen-Kettenis[11] for the treatment protocol for adolescents diagnosed with GD). After 2002, the Utrecht clinic stopped seeing adolescents and the diagnostics were performed in the VUmc. Adult people are referred to a psychologist or psychiatrist for the diagnostic phase after an initial screening. People diagnosed with GD can start HT if they are considered eligible. HT consists of testosterone for transmen and estrogens, often combined with antiandrogens, for transwomen. In the 1st year of HT, checkups are performed every 3 months. After a minimum of 12 months of HT, gender-affirming surgery can be performed, including mastectomy and hysterectomy with oophorectomy in transmen and breast augmentation and vaginoplasty (including orchiectomy) in transwomen. After gonadectomy (oophorectomy or orchiectomy), people are usually seen every 1 to 2 years for clinical follow-up.

In the present study we included the complete population seen at the gender identity clinic of the VUmc from 1972 through December 2015 to assess the current prevalence of transgender people who received medical treatment, the frequency of specific medical treatments performed, and the numbers of people who received HT in line with their sex assigned at birth because they regretted undergoing gonadectomy.

METHODS

Study Design and Patient Selection

After approval of the local ethics committee, a retrospective medical record review was performed to identify all people seen in our gender identity clinic from 1972 until December 2015. Data were collected from the hospital registries of the VUmc. The total study population was defined as people who had been diagnosed with 1 of the following *International Classification of Diseases* diagnoses: 302.5 (transsexualism), 302.6 (gender identity disorder not otherwise specified), or 302.85 (gender identity disorder in adolescent or adult) according to the 9th edition or F64 (gender identity disorders) according to the 10th edition.[12] In addition, the administrative employees of our gender identity clinic registered everyone who was referred to our gender identity clinic since the early 1970s. People reported on this list also were included in the study population. Some people of this study population have been described in previous studies.[9,13–18] People were excluded from the study if they had been registered at our gender identity clinic but had actually never visited the clinic or if they had presented with other complaints than gender identity issues. Because of the retrospective design and the large study population, necessity for informed consent was waived by our local ethics committee.

Hospital Registries

The hospital registries store clinical data obtained during regular patient care performed in our center, including medical diagnoses (since 1985), medication prescriptions (since 2000), surgical interventions (since 2006), laboratory test results (since 2004), radiology results (since 1993), and visit dates (since 2007). The 1st visit was defined as the 1st appointment with the psychologist, psychiatrist, pediatrician, endocrinologist, or gynecologist for health care related to gender identity.

Clinical Data Collection

Not all data were available from the hospital registries, particularly older data or surgeries performed in other centers. To generate the most reliable results, the medical records of all people who composed the study population were checked. All people were classified as transwomen or transmen (based on the sex assigned at birth), and date of birth and death were noted. The following categories were included: the individual was in the diagnostic stage, the individual did not start HT, or the individual was on HT. Start of HT was defined as the 1st date gender-affirming hormones were prescribed by a physician in our gender identity clinic after a confirmed GD diagnosis, irrespective of previous gender-affirming hormone use. Of the people who started HT, baseline and follow-up data, including

1st visit, medical history, medication use, prior gender-affirming hormone use, start date and type of PS and HT, and date of gonadectomy, were collected. Some people regretted the interventions they had undergone. Transwomen who started testosterone treatment after vaginoplasty or transmen who started estrogen treatment after oophorectomy and expressed regret were categorized as those who experienced regret. Reasons for regret as reported in their medical records were noted. Dates were set to the 1st of the month and personal identification data were removed from the research database.

Statistical Analysis

The total number of people visiting the clinic each year and their median age were reported separately for transwomen and transmen and were stratified for age at the 1st visit: children were younger than 12 years, adolescents were 12 to 18 years old, and adults were at least 18 years old. The percentage of people who started HT within 5 years after the 1st visit was reported for each year. The prevalence was calculated for people at least 12, at least 16, 12 to 18, 18 to 30, 30 to 50, and at least 50 years old by using the total number of people in these age groups who received medical treatment in our center until 2015, excluding deceased people. The total populations of these age groups in the Netherlands in 2015 were provided by the Central Bureau of Statistics of the Netherlands. The percentage of people who underwent gonadectomy within 5 years after starting HT was reported. For calculation of the total percentage of the study population who had undergone gonadectomy, only people at least 18 years old who used HT for at least 1.5 years were included, because these were requirements for surgery. People who regretted their medical transition are reported as the percentage of the total population of transwomen and transmen who underwent gonadectomy. In adults, time from 1st visit to start of HT or gonadectomy, if applicable, are expressed as median days with interquartile range (IQR). Total follow-up time was calculated for every individual who started HT and was expressed as years from the 1st visit to the last visit. Prevalence with 95% CI was calculated using OpenEpi.[19] All other analyses were performed using STATA 13.1 (StataCorp, College Station, TX, USA).

RESULTS

1st Visit

6,793 people presented for gender-affirming treatment, with more transwomen (65.2%) than transmen (34.8%; Table 1). The number of people attending the gender identity clinic increased over time (Table 2), whereas the median age of adults at the time of their 1st visit decreased (Figure 1). The median age at the 1st visit was younger for adult transmen (25 years; IQR = 21–35 years) than for adult transwomen (33 years; IQR = 25–42 years). Although historically more transwomen than transmen presented for treatment, more transmen than

Table 1. Treatment patterns of total study population, stratified for age groups and for transwomen and transmen*

	Transwomen	Transmen	Total	Ratio of transwomen to transmen
Total study population, N (%)	4,432 (65.2)	2,361 (34.8)	6,793 (100)	1.9:1
Adults (≥18 y)	3,809	1,624	5,433	2.3:1
Age (y)†, median (IQR; max)	33 (25–42; 81)	25 (21–35; 73)	31 (23–41; 81)	
Started HT§, %	68.9	72.9	69.9	
Underwent gonadectomy‖, %	75.3	83.8	77.7	
Adolescents (12–18 y)	330	482	812	0.7:1
Age (y)†, median (IQR)	16 (15–17)	16 (15–17)	16 (15–17)	
Started PS‡, %	28.7	50.8	41.0	
Stopped PS, %	4.1	0.7	1.9	
Started HT§ without PS, %	33.9	30.8	32.2	
Underwent gonadectomy‖, %	79.5	77.2	78.2	
Children (<12 y)	293	255	548	1.1:1
Age (y)†, median (IQR)	8 (7–10)	9 (8–11)	9 (7–10)	
Started PS‡,¶, %	33.6	49.1	40.3	
Regret#, % (n)	0.6 (11)	0.3 (3)	0.5 (14)	2.0:1

HT = gender-affirming hormonal therapy; IQR = interquartile range; max = maximum; PS = puberty suppression.
*From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.
†Age is defined as the age at the 1st visit to the VU University Medical Center, Amsterdam.
‡Only those who reached the age of eligibility (usually ≥12 years old) could undergo PS.
§Only in people at least 16 years old.
‖Only people treated with gender-affirming hormones for at least 1.5 years and at least 18 years old (orchiectomy in transwomen and oophorectomy in transmen).
¶Those who were too old (≥18 years) after the diagnostic phase for PS could begin directly with HT.
#Only those people who underwent gonadectomy.

Table 2. Description of adult study population for every 5-year cohort

	1st visit, n	Started HT*, %	Age (y) at start of HT, median (IQR)	Previous HT, %	Underwent gonadectomy†, %
Transwomen (≥18 y)					
1972–1979	119	89.9	33 (26–40)	16.8	79.4
1980–1984	189	88.4	33 (25–40)	12.6	71.9
1985–1989	319	75.9	31 (25–39)	15.3	76.5
1990–1994	392	65.8	30 (25–41)	20.5	76.7
1995–1999	522	65.5	34 (27–41)	26.6	78.7
2000–2004	605	56.0	38 (30–45)	29.2	67.3
2005–2009	476	61.6	39 (29–47)	22.9	68.6
2010–2014	926 (138‡)	60.9‡	32 (23–42)‡	29.8‡	NA
Transmen (≥18 y)					
1972–1979	30	96.7	24 (21–30)	10.3	72.4
1980–1984	69	84.1	24 (21–32)	3.5	82.8
1985–1989	105	84.8	24 (21–30)	1.1	79.8
1990–1994	142	69.0	27 (21–33)	7.1	88.8
1995–1999	177	65.0	29 (24–37)	7.0	88.7
2000–2004	207	63.3	32 (26–39)	5.3	87.0
2005–2009	185	63.8	29 (23–37)	3.4	81.4
2010–2014	518 (70‡)	71.4‡	24 (21–37)‡	0‡	NA

HT = gender-affirming hormonal therapy; IQR = interquartile range; NA = not applicable.
*People who started HT within 5 years after the 1st visit.
†People who had this procedure within 5 years after the start of HT.
‡Only in people who had their 1st visit 5 years before December 31, 2015 (n = 138 transwomen; n = 70 transmen).

transwomen applied for treatment in 2015. This change in sex ratio was mainly due to the increase in adolescent transgender boys, because the ratio of transwomen to transmen in adults remained stable over time.

Prevalence and Treatment

At the end of 2015, 3,838 transgender people at least 16 years old had received medical treatment and were not deceased. Because the total population of people at least 16 years old in the Netherlands in 2015 was 13,870,426, the prevalence was 27.7 per 100,000 people (95% CI = 26.8–28.6), or 1:3,600. Stratification for transwomen and transmen showed a prevalence of 36.4 (95% CI = 35.0–37.8) per 100,000 people (or 1:2,800) for men (transwomen) and 19.3 (95% CI = 18.3–20.3) per 100,000 people (or 1:5,200) for women (transmen). The calculation of prevalence numbers of people at least 12 years old and specific age groups are presented in Table 3.

The percentage of adult people who started HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable (Figure 2). Of the total study population at least 18 years old treated with HT for at least 1.5 years, 75.6% of transwomen (n = 1,742) and 82.4% of transmen (n = 885) underwent gonadectomy. The median time from the 1st visit to the start of HT for adults was 327 days (IQR = 36–570 days) and from the 1st visit to gonadectomy was 1,029 days (IQR = 679–1,465 days). The median follow-up time for people treated with HT was 6.4 years (range = 0.4–41.6 years).

Of adolescents, 41.0% started PS, whereas only 1.9% of these adolescents stopped PS and did not start HT (Table 1). 32.2% of adolescents started directly with HT, because they were too old (≥18 years) to start with PS after the diagnostic phase.

Regret

Regret was identified in 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy. The characteristics of these people are presented in Table 4. Their ages at start of HT ranged from 25 to 54 years, and they expressed their regrets 46 to 271 months after initiation of HT. Reasons for regret were divided into social regret, true regret, or feeling non-binary. Transwomen who were classified as having social regret still identified as women, but reported reasons such as "ignored by surroundings" or "the loss of relatives is a large sacrifice" for returning to the male role. People who were classified as having true regret reported that they thought gender-affirming treatment would be a "solution" for, for example, homosexuality or personal acceptance, but, in retrospect, regretted the diagnosis and treatment.

DISCUSSION

The aim of this study was to generate a dataset of all individuals who presented to our clinic for gender-affirming care from 1972 to 2015. We found that the number of people with

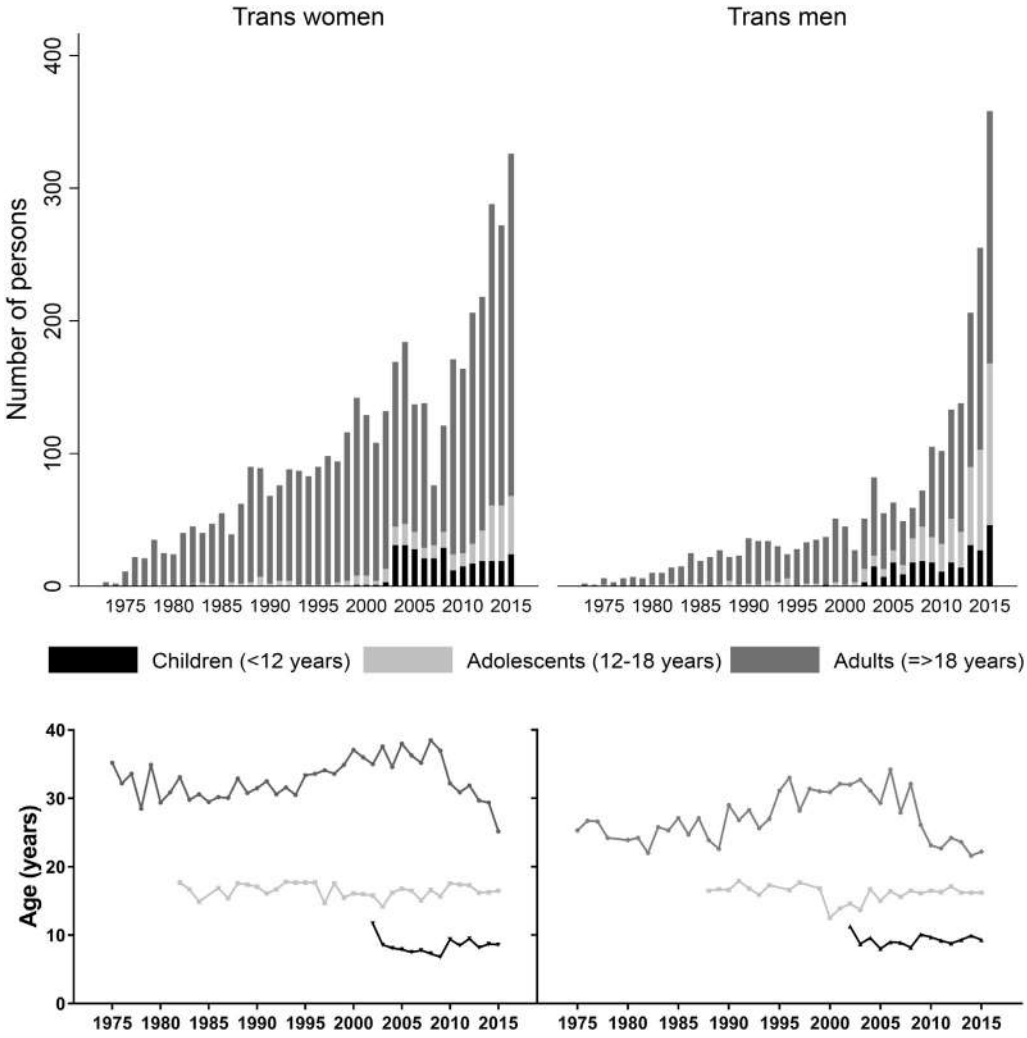

Figure 1. Number of people and median age for each year, stratified for transwomen and transmen and for children (<12 years), adolescents (12–18 years), and adults (≥18 years). Age is defined as age at the 1st visit to the VU University Medical Center, Amsterdam. From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.

gender identity issues who sought professional help increased dramatically in recent decades and that the median age of adults at presentation decreased. The ratio of transwomen to transmen remained stable over the years for adults, whereas in adolescents the population of transgender boys increased compared with the population of transgender girls. Currently, more transgender boys than transgender girls are seen. This phenomenon also has been described by Aitken et al.[17] The age at the 1st visit was

Table 3. Prevalence numbers, specified for different age groups*

	Total population		Male sex assigned at birth (transwomen)		Female sex assigned at birth (transmen)	
Age (y)	Per 100,000	1 per	Per 100,000	1 per	Per 100,000	1 per
≥12	26.9 (26.1–27.8)	3,700	34.8 (33.5–36.2)	2,900	19.3 (18.3–20.3)	5,200
≥16	27.7 (26.8–28.6)	3,600	36.4 (35.0–37.8)	2,800	19.3 (18.3–20.3)	5,200
12–18	16.0 (13.9–18.4)	6,300	11.1 (8.8–14.1)	9,000	21.0 (17.7–25.1)	4,800
18–30	35.7 (33.5–38.2)	2,800	30.3 (27.4–33.4)	3,300	41.4 (37.9–45.1)	2,400
30–50	30.5 (29.0–32.2)	3,300	40.1 (37.6–42.8)	2,500	21.0 (19.2–23.0)	4,800
≥50	23.0 (21.9–24.2)	4,300	37.6 (35.5–39.8)	2,700	9.7 (8.7–10.8)	10,300

*Data are presented as number (95% CI).

Table 4. Characteristics of people with regret

Case	Type	Year started HT	Age (y) at start of HT	Year of gonadectomy	Time after HT (mo)	Time after gonadectomy (mo)	Reversal surgery	Reason for regret
1	M-F-M	1978	31	1979	±153	±130	None	Social acceptance
2	M-F-M	1982	25	1984	±54	±27	Mastectomy	Social acceptance
3	M-F-M	1986	47	1988	±216	±197	Mastectomy	Social acceptance
4	M-F-M	1988	33	1990	±186	±167	None	True regret
5	M-F-M	1988	38	1990	±70	±44	Mastectomy	Social acceptance
6	M-F-M	1991	41	1993	±67	±49	Mastectomy, vaginectomy, phalloplasty	Social acceptance
7	M-F-M	1991	38	1995	±271	±225	Mastectomy	True regret
8	M-F-M	1993	30	1994	±79	±61	None	Feels non-binary
9	M-F-M	1996	33	1997	±90	±73	Mastectomy, phalloplasty	True regret
10	M-F-M	1997	43	1999	±46	±27	Mastectomy	True regret
11	M-F-M	2004	54	2007	±130	±92	Mastectomy, vaginectomy	True regret
12	F-M-F	1987	25	1990	±91	±50	Breast augmentation, remove testicular implants	True regret
13	F-M-F	1990	34	1993	±102	±74	Remove testicular implants	Feels non-binary
14	F-M-F	1993	31	1997	±258	±212	None	True regret

F-M-F = female to male to female; HT = hormonal treatment; M-F-M = male to female to male.

older for adult transwomen than for transmen. The percentage of adult people starting HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable. Of the total population treated with HT, 77.8% underwent a gonadectomy. Only a very small percentage of people who underwent gonadectomy regretted their decision, expressed as the start of HT in line with their sex assigned at birth.

An explanation for the increase in referrals could be the increased attention in society and media, which contributes not only to awareness of the existence of GD and possibilities for medical treatment but also to greater social acceptance. In addition, information about transgender identities has become much more accessible through the internet within the past decade, which could lead to an earlier recognition of gender identity issues. Also, transgender and gender non-binary individuals might be more willing to access care and more access to care has become available.

The increase in the prevalence of people with GD who sought medical treatment in the Netherlands (1:11,900 transwomen and 1:30,400 transmen in 1990[8] vs 1:2,800 transwomen and 1:5,200 transmen currently) suggests that the transgender population is dramatically increasing. The highest prevalence for transwomen was found for the 30- to 50-year age group (1:2,500), whereas that for transmen was found in the 18- to 30-year age group (1:2,400). Transgender people in the Netherlands seem to experience a reasonable degree of acceptance owing to a tolerant social climate in contrast to many other countries.[20] For example, medical costs are reimbursed by medical insurance companies, and it is possible to change the legal sex status (even without gonadectomy). These points can lead to a lower threshold to seek help, making this study population useful for an adequate estimation of the current prevalence of people with GD who seek medical treatment. More than 95% of transgender people are treated in our gender identity clinic. However, not all transgender people seek medical help. Some use self-medication or go abroad for treatment. Therefore, these numbers might still be an underestimation of the real prevalence. Our data represent a population that actively sought help in a medical setting. In 2012, a Dutch study of non-clinical people reported that 0.6% (1:167) of those with male sex assigned at birth and 0.2% (1:500) of those with female sex assigned at birth reported an incongruent gender identity with a wish for hormones or surgery.[21] However, that was a population-based study with a response rate of 20.9%, which could lead to non-response bias. In addition, the existence of incongruent gender identities was based on self-report and no detailed assessment of GD was performed, which could have led to higher prevalence rates.

An interesting finding is the percentage of children who were referred in childhood (before 12 years of age) and who started PS when the GD persisted and the eligibility criteria were fulfilled. This 40% of children who started PS is almost identical to the 39% of persistence of childhood GD reported in a previous

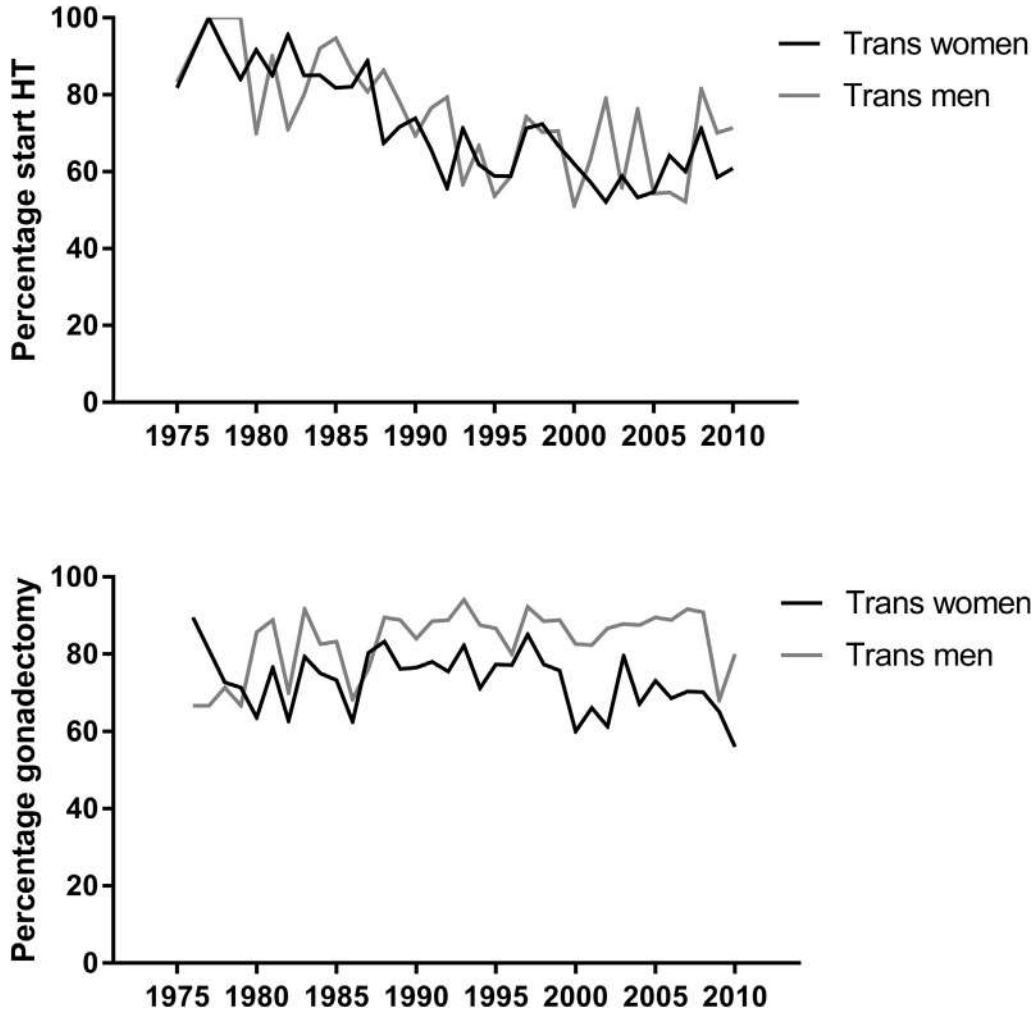

Figure 2. Top panel shows percentage of transgender adults beginning gender-affirming HT within 5 years after the 1st visit, stratified for transwomen and transmen. Bottom panel shows percentage of transgender adults with occurrence of gonadectomy within 5 years after starting HT for each year, stratified for transwomen and transmen. Year is defined as the year of the 1st visit. HT = gender-affirming hormonal treatment.

Dutch study (using a smaller cohort of children).[22] In addition, the finding that the persistence is higher in natal girls (49.1%) compared with natal boys (33.6%) is in line with observations in previous follow-up studies on the persistence of GD in children (for an overview, see Ristori and Steensma[23]).

Remarkably, we found a decrease over time in the percentage of referred adult people who actually started HT. This finding might be explained by the fact that in the past it was harder to find information about GD and its treatment, and only people with extreme types of GD managed to visit our gender identity clinic for treatment. Currently, owing to media attention and the internet, it is easier to access information about our gender identity clinic, making the threshold lower to search for help. This could have led to referrals of people with milder forms of GD and people who were not sure of their feelings and just wanted to explore these with a psychologist. Such people eventually might not pursue HT. Another explanation might be that not all transgender people want to undergo HT, such as transmen or people with a non-binary identity who only want a mastectomy.[24]

By contrast, we noticed that the percentage of people who underwent gonadectomy within 5 years after the start of HT remained stable over time. At the start of the clinic in 1972, knowledge about transgender care was limited and only people who wished for a classic treatment, consisting of a diagnostic phase, HT plus social transitioning, and surgery (in this order), were treated. There was no room for partial treatments. Since the publication of the Standards of Care Version 6 in 2001, other types of treatment are offered.[25] In addition, in 2014, a change in Dutch law allowed transgender people without a wish to undergo gonadectomy to alter the sex on their birth certificate with a statement of an expert who declared that the individual was diagnosed with GD (Dutch civil law, article 1:28). Although these changes in clinical guidelines and the law might have led to a decrease in the number of transgender people choosing gonadectomy, the current results do not show this. However, the follow-up time of this study might be too short to notice such changes.

In the HT group, 22% of people who were eligible for surgery had not undergone gonadectomy. These numbers are

comparable with a study from Sweden[26] but larger than in a study from Belgium,[27] in which approximately 15% of transwomen and transmen did not undergo gonadectomy. A possible wish to carry a child could change these numbers in the future, because fertility has become a more important issue.

Despite the large increase in treated transgender people, the percentage of people who underwent gonadectomy but regretted their decision was still very small (0.5%). In a review by Pfäfflin[28] in 1992, regret was reported by less than 1% of transmen and 1% to 1.5% by transwomen after gonadectomy. More recent studies have reported regret percentages of 0%[29,30] to 2%[7] and 6%[31] after gonadectomy. 13 of the 14 people who regretted gonadectomy had started HT from 1978 through 1997 and 1 started in 2004. At best, this indicates that the diagnostic and eligibility criteria for treatment have improved over the past decade. Another explanation might be the altered treatment protocol, which also allowed people to receive HT without gonadectomy. Our findings could be an underestimation of people with regret after gonadectomy, because some might choose to go elsewhere for reversal therapy or might experience regret without pursuing reversal surgery or HT. Regret might not always result in a desire for reversal therapy, as it may be hidden from others. In addition, in our population the average time to regret was 130 months, so it might be too early to examine regret rates in people who started with HT in the past 10 years.

The Center of Expertise on Gender Dysphoria of the VUmc Amsterdam is the largest gender identity clinic in the Netherlands, where people of all ages, including children and adolescents, are treated. Life-time follow-up is recommended, making it a useful study population for collection of epidemiologic data and future long-term studies of treatment effects. However, there are some limitations. Because this is a retrospective chart review study, some data could be lacking. (i) Some people who once visited our clinic might not be reported in our database. However, we used several search strategies to identify the total study population, thereby decreasing the possibility of missing people. (ii) A large number of transgender people who had initially received treatment in our center were lost to follow-up. Although transgender people receive lifelong care, a large group (36%) did not return to our clinic after several years of treatment. Therefore, we could have missed some information on, for example, gonadectomies performed at other centers or people with regret.

CONCLUSIONS

We found that the prevalence of treated transgender people increased exponentially. Because of this growing population, it is necessary that health care providers outside university clinics also have knowledge about GD and its treatment, because HT can influence the course of several diseases[32,33] and interact with several types of medication.[34] We also found that of all transgender people treated with HT, approximately 22% kept their gonads in situ. These people require special attention, because the long-term effects of HT on the testes, ovaries, and uterus are not established. These topics and other possible complications, such as cancer risks, are subjects for further research.

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STATEMENT OF AUTHORSHIP

Category 1

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

2. Wylie K, Knudson G, Khan SI, et al. Serving transgender people: clinical care considerations and service delivery models in transgender health. **Lancet 2016;388:401-411.**
3. Arcelus J, Bouman WP, Van Den Noortgate W, et al. Systematic review and meta-analysis of prevalence studies in transsexualism. **Eur Psychiatry 2015;30:807-815.**
4. De Cuypere G, Van Hemelrijck M, Michel A, et al. Prevalence and demography of transsexualism in Belgium. **Eur Psychiatry 2007;22:137-141.**
5. Esteva de Antonio I, Gomez-Gil E, Almaraz MC, et al. [Organization of healthcare for transsexual persons in the Spanish national health system]. **Gac Sanit 2012;26:203-209 [in Spanish].**
6. Caldarera A, Pfäfflin F. Transsexualism and sex reassignment surgery in Italy. **Int J Transgend 2011;13:26-36.**
7. Dhejne C, Oberg K, Arver S, et al. An analysis of all applications for sex reassignment surgery in Sweden, 1960–2010: prevalence, incidence, and regrets. **Arch Sex Behav 2014;43:1535-1545.**
8. Bakker A, van Kesteren P, Gooren L, et al. The prevalence of transsexualism in the Netherlands. **Acta Psychiatr Scand 1993;87:237-238.**
9. Van Kesteren P, Asscheman H, Megens J, et al. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. **Clin Endocrinol 1997;47:337-342.**
10. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: changing insights. **J Sex Med 2008;5:1892-1897.**
11. Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. **Nat Rev Endocrinol 2011;7:466-472.**
12. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993.
13. Asscheman H, Giltay EJ, Megens JA, et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. **Eur J Endocrinol 2011;164:635-642.**
14. Asscheman H, Gooren LJG, Eklund PLE. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. **Metabolism 1989;38:869-873.**
15. Dekker MJ, Wierckx K, Van Caenegem E, et al. A European network for the investigation of gender incongruence: endocrine part. **J Sex Med 2016;13:994-999.**
16. Kreukels BP, Haraldsen IR, De Cuypere G, et al. A European network for the investigation of gender incongruence: the ENIGI initiative. **Eur Psychiatry 2012;27:445-450.**
17. Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. **J Sex Med 2015;12:756-763.**
18. de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. **J Homosex 2012;59:301-320.**
19. Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. **Public Health Rep 2009;124:471-474.**
20. Kuyper L. Transgenders in Nederland: prevalentie en attitudes. **Tijdschr Seksuol 2012;36:129-135 [in Dutch].**
21. Kuyper L, Wijsen C. Gender identities and gender dysphoria in the Netherlands. **Arch Sex Behav 2014;43:377-385.**
22. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. **J Am Acad Child Adolesc Psychiatry 2008;47:1413-1423.**
23. Ristori J, Steensma TD. Gender dysphoria in childhood. **Int Rev Psychiatry 2016;28:13-20.**
24. Beek TF, Kreukels BP, Cohen-Kettenis PT, et al. Partial treatment requests and underlying motives of applicants for gender affirming interventions. **J Sex Med 2015;12:2201-2205.**
25. De Cuypere G, Gijs L. Care for adults with gender dysphoria. In: Kreukels BPC, Steensma TD, de Vries ALC, eds. Gender dysphoria and disorders of sex development: progress in care and knowledge. New York: Springer Science + Business Media; 2014. p. 231-254.
26. Johansson A, Sundbom E, Hojerback T, et al. A five-year follow-up study of Swedish adults with gender identity disorder. **Arch Sex Behav 2010;39:1429-1437.**
27. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. **Eur J Endocrinol 2013;169:471-478.**
28. Pfäfflin F. Regrets after sex reassignment surgery. **J Psychol Hum Sex 1993;5:69-85.**
29. Vujovic S, Popovic S, Sbutega-Milosevic G, et al. Transsexualism in Serbia: a twenty-year follow-up study. **J Sex Med 2009;6:1018-1023.**
30. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. **Arch Sex Behav 2003;32:299-315.**
31. Imbimbo C, Verze P, Palmieri A, et al. A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. **J Sex Med 2009;6:2736-2745.**
32. Johnson EL, Kaplan PW. Caring for transgender patients with epilepsy. **Epilepsia 2017;58:1667-1672.**
33. Tauboll E, Sveberg L, Svalheim S. Interactions between hormones and epilepsy. **Seizure 2015;28:3-11.**
34. Polderman KH, Gooren LJG, Asscheman H, et al. Induction of insulin resistance by androgens and estrogens. **J Clin Endocrinol Metab 1994;79:265-271.**

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Original article

Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers

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A B S T R A C T

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.

IMPLICATIONS AND CONTRIBUTION

This study found increased behavioral and emotional problems among adolescents referred to a specialized gender identity clinic compared with their cisgender peers from the general population. After the start of gender-affirming treatment, the transgender adolescents showed similar or better psychological functioning compared with their cisgender peers from the general population.

In recent years, a sharp increase has been seen in media attention, clinical referrals, and number of publications on adolescents with gender dysphoria (GD), the DSM-5 term used to describe the incongruence between one's birth-assigned gender and the experienced gender [1,2]. A number of these studies report on psychological functioning and show that feelings of GD are frequently associated with psychological difficulties [3].

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Adolescents referred to specialized gender identity clinics have prevalence rates of depression ranging from 12% to 58% and for anxiety 16% to 24% [3–8]. In these studies, histories of suicidal thoughts and self-harming behaviors were reported by 34%–51% and 12%–39% of youth, respectively, in the various studies [3–8]. In addition, comparison studies of transgender youth with lesbian, gay, and bisexual adolescents revealed comparable rates of psychological difficulties [9]. Several studies have used the standardized self-report and parental measures of the Youth Self-Report (YSR) and the Child Behavior Checklist [10,11] and found more behavioral and emotional problems in transgender youth compared with the normative samples of these measures [12,13]. In general, comparisons made with normative samples drawn from the general population show similar findings, with a predominance of internalizing problems over externalizing problems (for an overview, see [14]). Summarizing the YSR and Child Behavior Checklist results, transgender adolescents show psychological problems comparable to clinical norm populations, with some cross-national variation in levels of psychological problems between North America and Europe [15,16].

A framework for understanding GD and the associated mental health disparities is offered by the minority stress model that posits that sexual minorities experience chronic stressors related to the stigmatization of their identities [17,18]. Psychological functioning is better when there is more acceptance of GD by the youth and their environment, including better peer relations [12,16]. In addition, other more general risk factors might be related, and other models of explanations have been proposed [14]. In addition, the onset of puberty and the developing body might endorse an intensification of psychological distress [19].

Transgender care for adolescents with GD is often offered in a step-wise model. During the first phase, the nature of the adolescent's gender identity and general psychosocial functioning are explored, and medical interventions are not yet provided [19]. During the second phase, adolescents with GD receive puberty suppression by means of reversible gonadotropin-releasing hormone analogs to “create time” to enable further exploration of the decision for gender-affirming treatments without the accompanying distress caused by the physical changes of puberty [19]. Thereafter, gender-affirming hormones (GAHs) can be provided, androgens in assigned girls at birth and estrogens in assigned boys at birth to induce the development of secondary sex characteristics of the experienced gender [19–21]. The present article will refer to assigned boys or girls when assigned gender at birth is boy or girl, respectively, which may be incongruent from the experienced gender in the group of adolescents with GD.

The first follow-up studies evaluating the use of puberty suppression in relation to psychological well-being in adolescents with GD come from the Netherlands and showed that behavioral and emotional problems and depressive symptoms decreased and general functioning significantly improved during treatment [22,23]. A study from the United Kingdom showed that psychological support and puberty suppression were associated with an improved global psychosocial functioning in adolescents with GD with a combination of psychological support and puberty suppression, attributing to a greater improvement than psychological support only [24]. These psychological evaluation studies were performed using self-reported psychosocial functioning (internalizing and externalizing problems, suicidality, and peer relations) in comparison with normative standardization samples. The YSR normative sample was recruited over 20 years ago, and a more recent recruited sample from the general population is lacking [11]. The present study is the first to compare transgender adolescents receiving gender-affirmative treatment by means of puberty suppression with recently collected nonclinical cisgender peers from the general population, exploring psychological functioning and the role of specialized transgender care.

Methods

Participants and procedure

The samples in this study 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, and a control group of cisgender adolescents recruited in 2015 in the general population. During this period, 504 adolescents were seen in our gender identity service. Fifty-three participants did not complete the assessment process and did, therefore, 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.

Therefore, in this cross-sectional study, the three groups that were compared consisted of (1) adolescents who just started the assessment process (n = 272; mean age = 14.5 years; 116 assigned boys at birth and 156 assigned girls at birth), (2) adolescents diagnosed with GD who were on puberty suppression and about to start GAH treatment (n = 178; mean age = 16.8 years; 68 assigned boys at birth and 110 assigned girls at birth), and (3) cisgender adolescents recruited from the general population (n = 651; mean age = 15.4 years; 346 assigned boys at birth and 305 assigned girls at birth). 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 [20].

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.

Measures

Key demographic variables that were collected included the adolescents' birth-assigned gender, age, ethnicity, level of education, and parent's marital status. The demographic characteristics of the three groups are shown in Table 1.

The Dutch version of the YSR was used to assess internalizing and externalizing problem behavior, self-harm/suicidality, and poor peer relations [11]. The YSR consists of a total of 118 items, rated on a 0- to 2-point scale: “never,” “sometimes,” or “often,” asking adolescents about their emotional and behavioral problems during the previous 6 months. The YSR is well established with regard to reliability and validity and has acceptable reliability and adequate criterion and construct validity [11]. The YSR has one item specifically pertaining to GD: “wish to be of the opposite sex” (Item 110). In line with previous studies, this item was scored as 0 to avoid increased associations with psychological challenges and GD [25]. For internalizing and

Table 1
General characteristics for transgender adolescents and the general population sample

Variable	General population (n = 651)	Transgender at referral (n = 272)	Transgender using puberty suppression (n = 178)
Age (in years)			
Mean (SD)	15.39 (1.36)	14.47 (2.18)	16.75 (1.24)
Ethnicity, n (%)			
Dutch	580 (89.1)	185 (68)	131 (73.6)
Non-Dutch	67 (10.3)	30 (11)	16 (9)
Unknown	4 (.6)	57 (21)	31 (17.4)
Level of education, n (%)			
VMBO	99 (15.2)	203 (74.3)	126 (70.6)
HAVO	274 (42.1)	29 (10.8)	29 (16.4)
VWO	278 (42.7)	40 (14.9)	23 (13)
Parent's marital status, n (%)			
Both parents	520 (79.9)	153 (56.3)	103 (57.9)
Other	129 (19.8)	116 (42.6)	74 (41.6)
Unknown	2 (.3)	3 (1.1)	1 (.6)

HAVO = higher general continued education; SD = standard deviation; VMBO = prevocational education; VWO = preparatory scholarly education.

externalizing problems, mean scale scores and clinical range percentages (>90th percentile in nonreferred samples) were calculated. To assess peer relations, and following the procedure as done in previous studies [25], a 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). Self-harm/suicidality was examined by two YSR items, namely, "I deliberately try to hurt or kill myself" (Item 18) and "I think about killing myself" (Item 91) as metrics of suicidality.

Analyses

First, multivariate general linear modeling (GLM) analysis was used to analyze between-group differences for internalizing, externalizing, suicidality, and peer relations together. Second, 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. These analyses were followed by univariate GLM analyses with Bonferroni correction to correct for multiple comparisons. Third, multivariate GLM analyses with group and assigned gender at birth as predictors and age, ethnicity, level of education, and parent's marital status as covariates were performed. Fourth, Cohen's *d* was used to measure the effect sizes between the groups [26]. Finally, clinical range percentages were calculated for internalizing and externalizing.

Results

Mean scores for internalizing, externalizing, suicidality, and peer relations

Table 2 shows the mean scores for internalizing, externalizing, suicidality, and peer relations per sample. On average, the scores of the transgender adolescents who have just been referred on internalizing, suicidality, and peer relations were higher than the scores of the transgender adolescents using puberty suppression and the cisgender comparison group, respectively. A multivariate GLM analysis with group as a fixed factor and the internalizing, externalizing, suicidality, and poor peer relations as the dependent measures showed an overall difference using Pillai's trace ($F = 707.61$, $df = 4$; $p < .001$). Subsequent analyses for the internalizing, externalizing, suicidality, and poor peer relations indicated that groups differed from each other on internalizing, suicidality, and poor peer relations (all three univariate p values $< .001$) but not on externalizing ($p = .709$).

Post hoc analyses

Post hoc analyses showed that transgender adolescents who just have been referred had significantly higher scores on internalizing, suicidality, and peer relations compared with the cisgender comparison group and transgender adolescents using puberty suppression. In addition, the transgender adolescents using puberty suppression scored significantly lower on internalizing problems but higher on peer relations compared with the comparison group. No differences were found between adolescents using puberty suppression and the comparison group on self-harm/suicidality (Table 2 provides all effect sizes).

Gender differences

When we added assigned gender at birth as a predictor, we confirmed the main effect of group ($F = 686.47$, $df = 4$; $p < .001$), and the previously mentioned univariate group effects for internalizing, suicidality, and peer relations were also confirmed (all $p < .001$). In addition, we found a main effect for gender ($F = 14.22$, $df = 4$; $p < .001$) and a group by gender interaction effect ($F = 9.52$, $df = 8$; $p < .001$). Subsequent univariate analysis found an effect for gender and an interaction effect on internalizing and peer relations. Within-group post hoc t tests revealed that the interaction arose on internalizing because in the cisgender comparison group, assigned girls at birth had higher mean scores than assigned boys at birth, whereas in both the transgender groups, no differences were found in internalizing scores between assigned girls and assigned boys at birth. On the peer relations, the interaction arose because in both transgender groups, assigned boys at birth had higher scores, whereas in the cisgender comparison group, assigned girls at birth had higher scores. Table 3 provides mean scores by assigned gender at birth. In addition, as for the demographic variables age, ethnicity, level of education, and parent's marital status statistical group differences were found, all analyses were repeated with these variables as covariates and showed similar findings.

Table 2
Mean scores on the Youth Self-Report for internalizing, externalizing, peer relations, and suicidality problems for transgender adolescents and the general population sample

Measures[c]	General population (n = 651)		Transgender at referral (n = 272)		Transgender using puberty suppression (n = 178)		Statistical analysis[a]		Effect sizes Cohen's *d*[b]		
	Mean	SD	Mean	SD	Mean	SD	F[d]	*p* values	GP versus T0[e]	GP versus T1[e]	T0 versus T1[e]
Internalizing	9.71	7.73	11.67	8.38	7.76	6.68	14.16	**<.001**	−.24	.30	.52
Externalizing	10.25	6.10	10.19	6.33	9.82	5.79	.34	.709	.01	.07	.06
Peer relations	.41	.81	1.08	1.31	.70	1.06	12.58	**<.001**	−.62	−.31	.32
Suicidality	.19	.60	.41	.78	.17	.52	44.26	**<.001**	−.32	.04	.36

SD = standard deviation.
[a] Additional post hoc analyses comparing the transgender group at referral, the transgender group using puberty blockers, and the general population sample, demonstrated that on internalizing, peer relations, and suicidality, the adolescents at referral had significantly higher scores than the adolescents using suppression and the adolescents from the general population. In addition, the adolescents using puberty suppression scored significantly lower on internalizing but significantly higher on peer relations compared with the general population sample.
[b] 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 [26].
[c] Internalizing problems = disturbances of emotions (e.g., depression, anxiety; absolute range: 0–62); externalizing problems = behavioral excess or disturbances of conduct (e.g., aggression, hyperactivity; absolute range: 0–64); peer relations = problems with relations with peers (absolute range: 0–6); suicidality = thinking about or attempting suicide (absolute range: 0–4) [11].
[d] $df = 2$.
[e] GP = sample of cisgender adolescents from the general population; T0 = sample of transgender adolescents referred to transgender affirmative care who did not receive any medical treatment; T1 = transgender adolescents receiving affirmative care consisting of puberty suppression.

Finally, four (internalizing, externalizing, poor peer relations, and self-harm/suicidality) between-group analyses for each assigned gender at birth were performed using Bonferroni correction. These analyses showed that of the four between group comparisons for assigned boys at birth at referral with cisgender boys, significant higher scores were found for internalizing ($d = -.66$), peer relations ($d = -.92$), and self-harm/suicidality ($d = -.63$) for the assigned boys who just started the assessment. Assigned girls at birth who just started the assessment only scored significantly higher than the cisgender girls on peer relations ($d = -.36$). The three other scales were not significantly different.

In the transgender adolescent sample using puberty suppression, the assigned boys at birth scored only higher on peer relations ($d = -.53$) but not on the three other scales compared with the cisgender boys. For the assigned girls at birth using puberty suppression compared with the cisgender girls, the scores on internalizing were found to be significantly lower ($d = .63$). No other significant differences were found.

Of the four scale comparisons for assigned boys at birth at referral with the assigned boys at birth using puberty suppression, significant lower scores were found for those using puberty suppression on internalizing ($d = .54$), peer relations ($d = .41$), and self-harm/suicidality ($d = .37$). For the comparisons between the assigned girls at referral with the assigned girls using puberty suppression, significant lower scores were found for those using puberty suppression on internalizing ($d = .50$) and self-harm/suicidality ($d = .35$).

Clinical range percentages

Of the transgender adolescents just referred to the clinic, 31.3% had clinical range scores for internalizing problems (assigned boys at birth: 35.3% and assigned girls at birth: 28.2%), and 17.3% (assigned boys at birth: 6.0% and assigned girls at birth: 25.6%) had those for externalizing compared with 22.9% (assigned boys at birth: 13.0% and assigned girls at birth: 34.1%) and 13.8% (assigned boys at birth: 11.3% and assigned girls at birth: 16.7%) of the cisgender comparison sample. For the transgender adolescents using puberty suppression, the percentages were 16.3% for internalizing (assigned boys at birth: 16.2% and assigned girls at birth: 16.4%) and 14.0% for externalizing (assigned boys at birth: 8.8% and assigned girls at birth:17.3%).

Table 3
Mean scores on the Youth Self-Report by gender assigned at birth for internalizing, externalizing, peer relations, and suicidality for transgender adolescents and the general population sample

Measures[a]	General population					Transgender at referral					Transgender using puberty suppression				
	Assigned boys (n = 346)		Assigned girls (n = 305)		Effect sizes Cohen's *d*[b]	Assigned boys (n = 116)		Assigned girls (n = 156)		Effect sizes Cohen's *d*[b]	Assigned boys (n = 68)		Assigned girls (n = 110)		Effect sizes Cohen's *d*[b]
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Internalizing	7.21	5.89	12.54	8.55	−.73	11.74	7.74	11.62	8.84	.01	7.79	6.76	7.74	6.66	.01
Externalizing	10.90	5.91	9.50	6.24	.23	9.69	5.52	10.56	6.86	−.14	10.32	6.26	9.51	5.31	.14
Peer relations	.38	.77	.45	.85	−.09	1.45	1.46	.81	1.11	.49	.91	1.18	.57	.95	.32
Suicidality	.12	.44	.27	.73	−.25	.39	.73	.42	.81	−.04	.16	.48	.18	.54	−.04

SD = standard deviation.
[a] Internalizing problems = disturbances of emotions (e.g., depression, anxiety; absolute range: 0–62); externalizing problems = behavioral excess or disturbances of conduct (e.g., aggression, hyperactivity; absolute range: 0–64); peer relations = problems with relations with peers (absolute range: 0–6); suicidality = thinking about or attempting suicide (absolute range: 0–4) [11].
[b] Within group effect size differences; Cohen's *d*: .80 or higher is a large effect size, .50–.79 a medium effect size, .20–.49 small, and <.20 is negligible [26].

Endorsement of self-harm/suicidality

In the sample of transgender adolescents at referral, 74 (27.2%) endorsed the metric of suicidality. In the sample of transgender adolescents using puberty suppression, this was n = 22 (12.4%). In the cisgender comparison group, the percentage was 11.9% (n = 77).

Discussion

Our study revealed that adolescents referred for gender-affirmative care have increased behavioral and emotional problems, especially internalizing problems, reported increased self-harm/suicidality, and poorer peer relations compared with cisgender adolescents from the general population. This finding, including the clinical range percentage for internalizing problems, is in line with the current literature that in general, transgender adolescents are at risk for mental health problems [3–8]. However, our study also showed that transgender adolescents receiving gender-affirmative care involving puberty suppressing treatment not only have less emotional and behavior problems than transgender adolescents who have just been referred to gender-affirmative care but also reported similar rates of mental health problems as their nonclinical cisgender peers on internalizing problems (with a lower clinical range percentage) and self-harm/suicidality but not on peer relation problems. This second finding of less internalizing problems and self-harm/suicidality is also in line with previous follow-up studies on transgender adolescents [22,23], providing further evidence that transgender adolescents could benefit from gender-affirmative care.

With regard to gender differences, we found that in both the transgender samples, assigned boys at birth scored higher on internalizing than assigned girls at birth, which is contrary to general population adolescents' mean scores but in line with previous findings [12]. For externalizing, and also in contrast with general population mean scores, assigned girls at birth who have just been referred but not assigned girls at birth on puberty suppression scored somewhat higher than assigned boys at birth with GD. These findings are partly in line with the hypothesis that the sex-typical pattern of more internalizing problems in girls and more externalizing problems in boys in the cisgender population might be inversed in transgender people [12]. This hypothesis deserves more research.

A clinical implication of these findings is the need for worldwide availability of gender-affirmative care, including puberty suppression for transgender adolescents to alleviate mental health problems of transgender adolescents. It should be acknowledged that the care provided in the present study also involved the offering of appropriate mental health care. Thus, transgender care providers need to actively screen for mental health problems and offer this care. In addition, clinicians should receive special training to provide this care, for example, to become more experienced in disentangling psychological problems stemming from bullying related to GD or having other origins. Our study found that transgender adolescents using puberty suppression consider their peer relations better than adolescents at referral but still reported more challenges with peers than the cisgender adolescents. As it has been established in different studies that stigmatization and peer victimization seem to be common for transgender people [27], and psychological problems are correlated with peer support [28], clinicians should also take the importance of peer support during the transition into account.

Although the treatment with puberty suppression for adolescents with GD is now available in an increasing number of countries, the small amount of scientific evidence of the medical safety and efficacy and the psychological efficacy comes from a limited number of studies, mostly performed in the Netherlands [22]. It should, therefore, additionally be stressed that the gender-affirmative treatment described in the Dutch protocol is a highly protocolled treatment with regard to eligibility criteria and psychological support, including affirmative psychoeducation of GD for youth and parents or caregivers and the continued discussion of psychosexual development with themes such as school and friendships but also dating and romantic relationships [29]. This does imply that the findings of our study might not apply to all transgender adolescents, as, for example, in other health care systems, psychological support is incomparable to the psychological support received following the Dutch protocol [29]. More research is needed to see whether our findings of effective affirmative care involving puberty suppression improving the mental health of transgender adolescents is generalizable to other countries.

In addition, the results of this study should be seen in the light of three limitations. First, this study did not make use of a random nonclinical national probability sample. However, although the mean scores in this study of the general population comparison sample were consistent with the findings of the YSR standardization sample used in other studies in the Dutch population [11,22], the generalizability of our findings might not be corroborated. Second, although the YSR is a well-validated questionnaire for behavioral and emotional challenges [11], it cannot be equated with a diagnosis of any mental health condition made by clinical assessment. Third and most important, although those individuals with and without a GD diagnosis after assessment did not differ in internalizing, externalizing, peer relations, and suicidality scores at baseline in the group that has just been referred to the clinic, the cross-sectional design of this study with different participants in the groups before and after puberty suppression may potentially limit the results with participants being different on characteristics not measured and controlled for. The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-term mental health outcomes. Conclusions about long-term benefits of puberty suppression should thus be made with extreme caution needing prospective long-term follow-up studies with a repeated measure design with individuals being followed over time to confirm the current findings.

Future studies should, therefore, not only investigate the benefit of gender-affirmative care in other health care settings together with a matched nonclinical general population sample but should also make comparisons to transgender adolescents receiving GAH treatment and gender-affirming surgery to investigate the impact of these treatments on long-term mental health. As this study did not ask specifically for the increasingly recognized nonbinary identities [30], future studies should also cover if nonbinary transgender adolescents might equally benefit from this type of gender-affirmative care. Despite the previously mentioned limitations, this first study comparing a group of transgender adolescents just referred for gender-affirmative care, a group of transgender adolescents receiving treatment with puberty suppression, and a group of cisgender adolescents

from the general population showed that when affirmative care involving puberty suppression is provided, transgender adolescents may have comparable mental health levels to their cisgender peers. This type of gender-affirmative care seems thus extremely important for this group.

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References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edition. Washington, DC: Author; 2013.
[2] Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. J Sex Med 2015;12:756–63.
[3] Connolly MD, Zervos MJ, Barone CJ, et al. The mental health of transgender youth: Advances in understanding. J Adolesc Health 2016;59:489–95.
[4] de Vries ALC, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. J Child Psychol Psychiatry 2011;52:1195–202.
[5] Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: Demographics and associated difficulties. Clin Child Psychol Psychiatry 2016;21:108–18.
[6] Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr 2014;164:906–11.
[7] Olson J, Schrager SM, Belzer M, et al. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. J Adolesc Health 2015;57:374–80.
[8] Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics 2012;29:418–25.
[9] Mustanski B, Garofalo R, Emerson E. Mental health disorders, psychological distress, and suicidality in a diverse sample of lesbian, gay, bisexual, and transgender youth. Am J Public Health 2010;100:2426–32.
[10] Achenbach TM, Edelbrock CS. Manual for the child behavior checklist and revised child behavior profile. Burlington: Department of Psychiatry, University of Vermont; 1983.
[11] Achenbach TM. Manual for the youth self-report and 1991 profile. Burlington: Department of Psychiatry, University of Vermont; 1991.
[12] de Vries ALC, Steensma TD, Cohen-Kettenis PT, et al. 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;25:579.
[13] 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;38:151–89.
[14] Zucker KJ, Wood H, VanderLaan DP. Models of psychopathology in children and adolescents with gender dysphoria. In: Kreukels BPC, Steensma TD, de Vries ALC, eds. Gender dysphoria and disorders of sex development. New York: Springer; 2014:171–92.
[15] de Graaf NM, Cohen-Kettenis PT, Carmichel P, et al. Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: A clinical comparison study between four clinics. Eur Child Adolesc Psychiatry 2018;27:909–19.
[16] Steensma TD, Zucker KJ, Kreukels BPC, et al. Behavioral and emotional problems on the teacher's report form: A cross-national, cross-clinic comparative analysis of gender dysphoric children and adolescents. J Abnorm Child Psychol 2014;42:635–47.
[17] Meyer IH. Minority stress and mental health in gay men. J Health Soc Behav 1995;36:38–56.
[18] Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: Conceptual issues and research evidence. Psychol Bull 2003;129:674–97.
[19] de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: The Dutch approach. J Homosex 2012;59:301–20.
[20] Cohen-Kettenis PT, Steensma TD, de Vries ALC. Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am 2011;20:689–700.
[21] Cohen-Kettenis PT, Klink D. Adolescents with gender dysphoria. Best Pract Res Clin Endocrinol Metab 2015;29:485–95.
[22] de Vries ALC, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. J Sex Med 2011;8:2276–83.
[23] de Vries ALC, McGuire JK, Steensma TD, et al. Adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696–704.
[24] Costa R, Dunsford M, Skagerberg E, et al. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. J Sex Med 2015;12:2206–14.
[25] Zucker KJ, Bradley SJ, Sanikhani M. Sex differences in referral rates of children with gender identity disorder: Some hypotheses. J Abnorm Child Psychol 1997;25:217–27.
[26] Cohen J. Statistical power analysis for the behavioral sciences. 2nd edition. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
[27] Baams L, Beek T, Hille H, et al. Gender nonconformity, perceived stigmatization, and psychological well-being in Dutch sexual minority youth and young adults: A mediation analysis. Arch Sex Behav 2013;42:765–73.
[28] McConnell EA, Birkett MA, Mustanski B. Typologies of social support and associations with mental health outcomes among LGBT youth. LGBT Health 2015;2:55–61.
[29] Steensma TD, Wensing-Kruger A, Klink DT. How should physicians help gender-transitioning adolescents consider potential iatrogenic harms of hormone therapy? AMA J Ethics 2017;19:762–70.
[30] Richards C, Bouman WP, Seal L, et al. Non-binary or genderqueer genders. Int Rev Psychiatry 2016;28:95–102.

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Original Articles

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Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood

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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.

Keywords: gender-affirming treatment, gender incongruence, mental health, self-esteem, self-perception, transgender

Introduction

Over the past decade, the number of adolescents referred to transgender clinics and the absolute number of adolescents treated with gender-affirming medical interventions have increased sharply.[1,2] Although gender diversity is observed more often among adolescents than earlier, they remain a vulnerable minority group and various studies have shown relatively high prevalence rates of mood and anxiety complaints among transgender adolescents.[3–6] Another major point of concern is self-injurious behavior and suicidality.[6–9] The state of mental health in part of the young transgender population is concerning and it is important to identify the factors that affect their mental health. As

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low self-esteem seems to be related to emotional and behavioral problems, one factor that could possibly play a role is self-perception.[10]

Self-perception is the awareness of the characteristics that define one's self.[11] This is a cognitive dimension of one's self. Self-esteem, on the other hand, is the emotional dimension of self-awareness, is evaluative, and involves a value judgment.[12] During childhood and adolescence, various factors influence the development of self-esteem. How competent on different domains individuals perceive themselves (self-perception) and how supportive one's social environment is, largely determine the self-esteem of a child or adolescent.[13] Global self-esteem can be seen as an overall evaluation of one's value as a person.[14]

As one of the key characteristics of transgender adolescents is discomfort with the incongruence between their experienced gender and their assigned gender at birth and because they still experience stigmatization,[15] one can imagine that their development of positive self-perception and with that possibly a healthy self-esteem is at stake. A previous study by Alberse et al. found that the majority of transgender adolescents reported lower self-perception at the time of intake at a transgender clinic compared with their peers and compared with referred prepubescent transgender children. Further, they found that trans boys were more self-satisfied than trans girls.[16] Considering that poor self-esteem is seen as a risk factor for mental health problems, positive self-esteem could be seen as a protective factor that contributes to better mental health.[17] This principle is supported by a study from 2011, which showed that higher self-esteem among transgender adolescents predicted positive mental health outcomes.[18] For this reason, helping transgender youth develop positive self-perception that can contribute to healthy self-esteem seems very important. One factor that could possibly contribute to the development of positive self-perception is gender-affirming treatment.

Early gender-affirming medical interventions for adolescents may consist of puberty suppression followed by gender-affirming hormones and surgery/ies.[19] Puberty suppression pauses the physical maturation of the body so that trans boys do not (further) feminize and trans girls do not (further) masculinize. The effect of puberty suppression is considered reversible, as opposed to the effect of hormone treatment, which is (partly) irreversible. Hormone treatment (testosterone/estrogens) ensures that the physical appearance of the adolescents aligns better with their experienced gender.[19] Medical treatment should relieve the discomfort that transgender adolescents feel with their physical appearance and therefore should contribute to healthy psychological development, including the development of positive self-perception.[20] Although not all studies have found that gender-affirming treatment contributes to improved psychological functioning,[21] the results of a number of studies do indicate this.[22–25] However, at present, there are no longitudinal studies that have examined whether gender-affirming treatment consisting of hormone treatment and surgeries meets this expectation with regard to changes in self-perception over the course of treatment. Therefore, the aim of this study was to measure, in a clinic-referred transgender adolescent sample, (1) whether different aspects of self-perception changed after irreversible gender-affirming treatment and (2) whether this is different for trans men compared with trans women.

Methods

Participants and procedure

This longitudinal study was performed at the Center of Expertise on Gender Dysphoria (CEGD) of Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands and was part of a larger evaluation study that aims to assess longer-term outcomes of early gender-affirming medical interventions for transgender adolescents.[24,26] Adolescents who were referred between 2000 and 2013, who met the criteria for a ''Gender Identity Disorder'' diagnosis according to the DSM-IV-TR[27] (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. The complete set of administered questionnaires in the larger evaluation study that measures mental health and well-being outcomes of early medical intervention for transgender adolescents is described in de Vries et al.[24]

Participants were assessed twice, pretreatment and post-treatment. The pretreatment assessment took place before the start of treatment with puberty suppression or before the start of gender-affirming hormone treatment (Table 1). The reason for this is that the questionnaire to measure self-perception, the Self-Perception Profile for Adolescents (SPPA), only became part of the standard assessment from December 2004 onward. Therefore, adolescents who had been referred before December 2004 completed the SPPA at a later time, when they had already started with puberty suppression. The post-treatment assessment took place when the adolescents were at least 6 months post gender-affirming surgery. Post-treatment assessments were conducted between 2009 and 2016. Regarding the different gender-affirming surgeries: Until July 2014, transgender people had to be sterilized according to Dutch law to have their gender confirmed on their birth certificate[28]; therefore, for this group, the participants were invited for assessment at least 6 months after hysterectomy for trans men and vaginoplasty for trans women. After July 2014, trans men were assessed at least 6 months after their first gender-affirming operation. For most trans men, this was a mastectomy; some of them opted for a metoidioplasty or a phalloplasty afterward.

Thirty participants in the current study were also included in another study that focused on psychological outcomes in young adulthood after gender-affirming treatment, including puberty suppression, and were also part of the larger evaluation study.[24] Informed consent was signed by all adolescents and their parents at the pretreatment assessment and by the participants at the post-treatment assessment. The VU University Medical Center medical ethics committee approved the study.

Table 1. Demographic Variables

N (%)	
Gender	
Trans men	49 (70.0%)
Trans women	21 (30.0%)
M (SD)	
Age at assessment in years	
Pre-irreversible gender-affirming treatment (pretreatment assessment)[a]	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
N (%)	
Living situation of the adolescent at the pretreatment assessment	
Living with both biological parents	43 (61.4%)
Other	27 (38.6%)
M (SD)	
Full-scale IQ	99.63 (14.23), range 72–135

[a]At the time of the pre-irreversible gender-affirming treatment assessment, 18 adolescents were already using puberty suppression whereas 52 adolescents were not.

M, mean; SD, standard deviation; IQ, intelligence quotient.

Measures

Key demographic variables collected at the pretreatment and post-treatment assessment included the adolescents' birth-assigned gender, living situation at the pretreatment assessment, full-scale intelligence quotient (IQ), age at pretreatment and post-treatment assessment, and age at gender-affirming surgery. During data collection, people were not specifically asked whether they identified outside the gender binary. The Dutch version of the SPPA was used to measure pretreatment and post-treatment self-perception.[29–31] The SPPA was developed by Harter to measure self-perception on eight specific domains (scholastic competence, social acceptance, athletic competence, physical appearance, job competence, romantic appeal, behavioral conduct, and close friendship) and an overall sense of self-worth (global self-worth).[29,30] The first Dutch version of the SPPA was developed in 1991. Factor analyses in a Dutch sample showed that the factor structure of the eight specific domains did not correspond to the eight-factor model found by Harter. Because the domains of job competence and romantic appeal were not found in any of the analyses, it was decided to omit them. A confirmatory factor analysis confirmed a good fit of the six-factor model in a Dutch sample.[30]

The test–retest reliabilities of the Dutch version of the SPPA tested with the average test–retest Pearson correlation vary from moderate to good (0.67–0.87) and are significant ($p < 0.001$).[30] The construct validity is considered sufficient. The reason for this is that a validation study found that the SPPA domains were negatively associated with depression, physical complaints, and anxiety, and with referral to an outpatient clinic for child and adolescent psychiatry.[30]

Each of the seven domains of the Dutch version of the SPPA contains five pairs of statements. For the scholastic competence domain, these are statements such as ''Some teenagers feel that they are just as smart as others their age BUT Other teenagers aren't so sure and wonder if they are as smart.'' and for the domain of social acceptance such as ''Some teenagers find it hard to make friends BUT Other teenagers find it pretty easy to make friends.'' An example of a statement in the athletic competence domain is: ''Some teenagers do very well at all kinds of sports BUT Other teenagers don't feel that they are very good when it comes to sports.'' An example of a statement in the physical appearance domain is: ''Some teenagers are not happy with the way they look BUT Other teenagers are happy with the way they look.'' For the behavioral conduct domain, the statements are such as: ''Some teenagers usually do the right thing BUT Other teenagers often don't do what they know is right.'' For the close friendship domain, they are such as: ''Some teenagers are able to make really close friends BUT Other teenagers find it hard to make really close friends.'' The statements for the domain global self-worth are such as: ''Some teenagers are often disappointed with themselves BUT Other teenagers are pretty pleased with themselves.''

The adolescents have to choose which statement describes them best. The adolescents are then given two response options to indicate the extent to which that statement describes them (''Sort of true'' or ''Really true''). Each item is scored on a four-point scale from 1 to 4. A higher score reflects a higher level of competence. Scores on each domain are summed and range from a minimum of 5 to a maximum of 20 points.[29] For the means, standard deviations, and effect sizes (Cohen's d[32]) of Dutch adolescents referred for mental health care and non-referred Dutch adolescents, see Table 2.

Data analyses

All data analyses were performed by using SPSS version 24.0 (IBM Corp., Armonk, NY). A significance level of $p < 0.05$ was used for all analyses. At first, the frequencies, means, and standard deviations (SDs) of the demographic characteristics were analyzed. Second, the means and 95% confidence intervals (CIs) of the pretreatment and post-treatment self-perception scores on the different domains were computed. Third, multilevel modeling (random intercepts model) was conducted to determine the effect of time for all domains of self-perception. Subsequently, possible confounders (gender, age at pretreatment and post-treatment assessment, use of puberty suppression at pretreatment assessment, but also full-scale IQ and living situation of the

Table 2. Self-Perception Profile for Adolescents' Norm Scores for Referred and Non-Referred Dutch Adolescents

Domains[a]	*Referred adolescents*	*Non-referred adolescents*	*Effect sizes, Cohen's d*[b]
Scholastic competence			
Vocational educated[c]	12.5 (2.10)	13.4 (2.65)	0.38
Higher vocational educated	11.3 (1.87)	14.4 (2.60)	1.37
Social acceptance	12.0 (1.83)	15.1 (2.87)	1.29
Athletic competence	12.3 (1.64)	14.3 (3.57)	0.72
Physical appearance	12.3 (1.63)	13.9 (3.51)	0.58
Behavioral conduct			
Vocational educated[c]	12.0 (1.18)	13.9 (2.87)	0.87
Higher vocational educated	10.9 (1.41)	15.3 (3.18)	1.79
Close friendship			
Boys	12.0 (2.82)	16.3 (3.12)	1.45
Girls	11.6 (2.45)	17.9 (2.52)	2.53
Global self-worth	12.3 (1.63)	15.6 (3.22)	1.29

[a]When interaction effects with education or gender were found, self-perception scores are reported separately.
[b]Effect sizes Cohen's *d:* 0.80 or higher is a large effect size, 0.50–0.79 a medium effect size, 0.20–0.49 small, and effect sizes <0.20 are negligible.[32]
[c]The average educational level of our study sample is in between "Vocational educated" and "Higher vocational educated."

adolescent, since these variables could influence navigating the gender-affirming treatment process[33]) were added to the models. Gender was also examined as an effect modifier. The crude models as well as the adjusted models are reported.

Results

Participants

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, among whom 107 participated. A variety of reasons existed for nonparticipation: Some individuals could not be contacted due to lack of proper contact information; some agreed to participate but did not complete the questionnaires despite repeated reminders; and some did not want to participate. 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%.

Of the 72 nonparticipating individuals, pretreatment data on self-perception were available for 62 of them. To check for representativeness, the 70 included participants were compared on demographic characteristics and pretreatment self-perception scores with the 62 individuals who did not participate in the study. Independent-sample *t*-tests and chi-square tests showed that the mean age at the pretreatment assessment, the mean age at gender-affirming surgery, the sex ratio, and the living situation of the adolescents were similar between the two groups. However, the included participants had a significantly higher mean full-scale IQ than the nonparticipants [$t(110) = 2.407, p = 0.018$]. Regarding pretreatment self-perception, participants scored significantly higher on only one of the seven subdomains (the domain of "behavioral conduct" [$t(130) = 2.029, p = 0.044$]).

Of the 70 participants, most adolescents ($N = 52$) had not yet started treatment with puberty suppression at the time of the pretreatment assessment, whereas some ($N = 18$) had. Independent-sample *t*-tests were used to examine whether the mean pretreatment self-perception was comparable for the adolescents who had not yet started puberty suppression and the adolescents who had. Apart from the fact that adolescents who had not yet started treatment with puberty suppression scored significantly lower [$t(68) = 2.173, p = 0.033$] on the domain of physical appearance, the groups were similar. The use of puberty suppression at the pretreatment assessment was included as a confounder in further analyses.

The total study sample included 70 adolescents (49 trans men and 21 trans women) who had received gender-affirming treatment consisting of puberty suppression, affirming hormones (testosterone/estrogens), and gender-affirming surgeries. The mean age of these adolescents at the pretreatment assessment was 14.65 (SD = 2.08, range 11.23–19.74) years, and their mean age at the post-treatment assessment was 20.70 (SD = 1.49, range 18.97–26.28) years. They were, on average, 1.47 years (SD = 0.67, range 0.69–4.79) after their gender-affirming surgery/ies at the time of the post-treatment assessment. The time between pretreatment and post-treatment assessment was 6.05 years (SD = 1.82, range 2.77–10.63). The sex ratio of our sample was 2.33:1 favoring trans men. This is consistent with samples in other studies with transgender adolescents.[34] All key demographic variables that were collected at the pre- and post-treatment assessment are shown in Table 1.

Self-perception of transgender adolescents before and after irreversible gender-affirming treatment

The mean scores and 95% CIs of self-perception on the seven separate domains at the pretreatment and post-treatment assessment are shown in Table 3 for the total sample and in Table 4 and Table 5 for trans men and trans women. Multilevel modeling revealed that the domains of physical appearance ($p < 0.001$) and global self-worth ($p < 0.001$) improved significantly over time. For the domains of scholastic competence, social acceptance, athletic competence, and close

Table 3. Self-Perception Descriptive Scores for the Total Sample Before and After Gender-Affirming Treatment

Domains	*Pre-irreversible gender-affirming treatment Mean (95% CI)*	*Post-irreversible gender-affirming treatment Mean (95% CI)*
Scholastic competence $N=70$	14.26 (13.54–14.98)	14.96 (14.22–15.69)
Social acceptance $N=70$	14.81 (14.05–15.58)	15.23 (14.48–15.98)
Athletic competence $N=69$	12.86 (11.87–13.84)	12.54 (11.62–13.46)
Physical appearance $N=69$	10.16 (9.37–10.95)	12.81 (11.92–13.70)
Behavioral conduct $N=70$	15.81 (15.17–16.46)	16.83 (16.23–17.43)
Close friendship $N=70$	16.87 (16.18–17.57)	17.30 (16.57–18.03)
Global self-worth $N=68$	12.01 (11.13–12.90)	14.19 (13.32–15.06)

The absolute range is 5–20.
CI, confidence interval.

friendship, no significant change over time was found (no significant increase nor decrease, all $p>0.05$). Only for the domain of behavioral conduct, an interaction effect for gender was found; a significant improvement was only observed for trans men ($p=0.003$). The estimates of multilevel model fixed effect and random effects variances (± SE) without and with adjustment for possible confounders are provided in Table 6.

Discussion

This single-arm retrospective study on the changes of self-perception among transgender adolescents over the course of irreversible medical gender-affirming treatment found an improvement on two different domains of self-perception. Therefore, this study suggests that the self-perception domains of physical appearance and global self-worth improved over the course of irreversible gender-affirming treatment among transgender adolescents. The improvement in these two different domains did not differ significantly between trans men and trans women. In the domain of behavioral conduct, a significant improvement was also seen over the course of irreversible gender-affirming treatment; however, this was only observed among trans men.

Regarding the physical appearance domain, positive development could be understood from the perspective of gender diversity. At the time of the pretreatment assessment, adolescents experienced that their physical appearance was not in line with how they identified. After medical gender-affirming treatment, their physical appearance was in better alignment with their gender identity and, for this reason, the adolescents were more content with it and felt more

Table 4. Self-Perception Descriptive Scores Before and After Gender-Affirming Treatment in Trans Men

Domains	*Pre-irreversible gender-affirming treatment Mean (95% CI)*	*Post-irreversible gender-affirming treatment Mean (95% CI)*
Scholastic competence $N=49$	14.25 (13.33–15.16)	14.53 (13.65–15.41)
Social acceptance $N=49$	14.78 (13.80–15.75)	15.02 (14.03–16.01)
Athletic competence $N=48$	13.27 (12.01–14.53)	13.13 (12.06–14.19)
Physical appearance $N=48$	9.23 (8.44–10.02)	11.88 (10.85–12.90)
Behavioral conduct $N=49$	15.37 (14.53–16.20)	16.88 (16.11–17.64)
Close friendship $N=49$	16.61 (15.71–17.51)	17.14 (16.32–17.97)
Global self-worth $N=47$	11.32 (10.39–12.24)	13.68 (12.58–14.78)

The absolute range is 5–20.

Table 5. Self-Perception Descriptive Scores Before and After Gender-Affirming Treatment in Trans Women

Domains	*Pre-irreversible gender-affirming treatment Mean (95% CI)*	*Post-irreversible gender-affirming treatment Mean (95% CI)*
Scholastic competence $N=21$	14.29 (13.06–15.51)	15.95 (14.61–17.29)
Social acceptance $N=21$	14.91 (13.66–16.15)	15.71 (14.64–16.79)
Athletic competence $N=21$	11.91 (10.32–13.49)	11.19 (9.41–12.97)
Physical appearance $N=21$	12.29 (10.65–13.92)	14.95 (13.48–16.42)
Behavioral conduct $N=21$	16.86 (16.04–17.68)	16.71 (15.71–17.72)
Close friendship $N=21$	17.48 (16.46–18.49)	17.67 (16.07–19.27)
Global self-worth $N=21$	13.57 (11.63–15.51)	15.33 (13.99–16.68)

The absolute range is 5–20.

confident about it. Individuals who are more comfortable with their physical appearance could also feel better in other areas of their lives.[20] This may have contributed to adolescents also being better able to be well behaved, which may have resulted in them scoring higher on the behavioral domain after treatment. However, this does not explain why this improvement was only seen among trans men. It is important to keep in mind that interpreting the change of self-perception scores over time on the domain of behavioral conduct requires some caution, because the participants in this study had significantly higher mean pretreatment scores in this domain of self-perception than the nonparticipants.

Table 6. Estimates of Multilevel Model Fixed Effect and Random Effects Variances (±Standard Error) Without and With Adjustment for Possible Confounders

	Unadjusted model (estimates)	*Adjusted model (estimates)*
Fixed effect estimates		
Scholastic competence		
Intercept	13.56 (0.64)*	7.14 (5.26)
Time	0.70 (0.38)	0.71 (0.39)
Social acceptance		
Intercept	14.40 (0.76)*	22.34 (5.10)*
Time	0.41 (0.46)	0.43 (0.48)
Athletic competence		
Intercept	13.16 (0.73)*	12.98 (7.54)
Time	−0.31 (0.39)	−0.25 (0.40)
Physical appearance		
Intercept	7.48 (0.72)*	21.57 (5.20)*
Time	2.66 (0.42)*	2.65 (0.42)*
Behavioral conduct		
Intercept trans men	13.86 (0.80)*	6.16 (5.06)
Time trans men	1.51 (0.49)*	1.51 (0.49)*
Intercept trans women	17.00 (0.85)*	17.51 (7.99)*
Time trans women	−0.14 (0.52)	−0.05 (0.57)
Close friendship		
Intercept	16.44 (0.66)*	21.30 (4.97)*
Time	0.43 (0.40)	0.49 (0.41)
Global self-worth		
Intercept	9.71 (0.87)*	14.24 (5.53)*
Time	2.23 (0.54)*	2.27 (0.55)*

*$p<0.05$.

The domain of global self-worth, which refers to a general perception of the self, also improved. By starting medical treatment, adolescents felt more supported and affirmed. In addition, people in their social environment may have approached them more often in their experienced gender because their outward appearance was more in line with how they identified. We postulate that these aspects contributed to the adolescents generally feeling better about themselves.

Although some self-perception domains improved after irreversible gender-affirming treatment, others remained stable over time. One reason for this could be that the adolescents' self-perception domains were already relatively high when they were referred to our clinic, possibly because they grew up in a supportive social environment while trusting that medical affirming treatment would be offered. However, this hypothesis does not completely align with the study by Alberse et al., which found that adolescents referred to a gender clinic had lower self-perception scores compared with referred children.[16] Nonetheless, some transgender adolescents included in this study, especially the trans boys, had significantly higher self-perception scores on two of the seven domains (scholastic competence and athletic competence) than the standardization sample.[16] This may, indeed, suggest that some self-perception domains were already relatively high pretreatment in our sample and, therefore, were slightly less likely to increase over time. Future studies should focus on baseline self-perception and potential moderating factors (e.g., supportive social environment/family support).

Another possible explanation for some domains remaining stable over time might be that self-perception and thereby

self-esteem decreases during adolescence in general. Robins et al. studied the development of self-esteem across the lifespan by using cross-sectional data from 326,641 individuals. They concluded that self-esteem was high in childhood, decreased during adolescence, and then steadily increased throughout adulthood.[35] It is possible that irreversible gender-affirming treatment prevents a (further) decline in self-perception and thereby self-esteem during adolescence. This could mean that a positive effect of treatment is reflected in the absence of a decrease in self-perception scores, rather than an increase.

Early gender-affirming medical interventions possibly contributed to developing a more positive self-perception and with it a healthy self-esteem. This may have contributed to better psychological functioning, as healthy self-esteem can be a protective factor for psychological problems.[17] In-depth studies on relations between different gender identity components and psychosocial adjustment concluded that perceiving one's self as gender-typical and being satisfied with one's gender were associated with better well-being.[36,37]

However, social factors should not be underestimated. It is possible that making a social transition also plays a role in the well-being of adolescents. Although the association of social transition with psychological functioning and self-perception has not yet been investigated in adolescents, there are such studies in pre-pubertal gender diverse children that may hint at this. Durwood et al. found that a convenience sample of non-referred children who had socially transitioned reported similar self-worth and depression as their cisgender matched peers.[38] This was in contrast with other research on clinic-referred transgender children who had not (yet) socially transitioned, where high rates of anxiety and depression were found.[39,40] However, the results of this study should be interpreted with caution due to the absence of baseline data before a social transition and the study's convenience sample that may not be comparable to our clinical adolescent sample.[38] In addition, other studies did not find an association between social transition and psychological well-being.[41,42]

The effect of self-esteem on psychological functioning may also work the other way around: An improvement in psychological functioning will also be beneficial for an improvement in self-perception and self-esteem. It is conceivable that an improvement in self-perception and self-esteem and an improvement in psychological functioning reinforce each other in a positive way. For clinical purposes, it is relevant in further studies to investigate the association between improvement in self-perception and self-esteem and (improvement in) psychological functioning; should clinicians, for example, focus on improving an adolescents' self-perception and will that improve emotional difficulties, or should the primary focus be on depression, for example, and will an improved mood lead to better self-perception?

Limitations

Our study results should be interpreted in light of several limitations. The small sample size and the imbalance between the number of trans men and trans women were limiting factors in this study. Another limitation is the fact that the adolescents included in this study had a higher mean full-scale IQ than adolescents who did not participate. For this reason, it is difficult to determine the extent to which these results are generalizable, and they should therefore be interpreted with caution. In addition, a minority of the participants had already started puberty suppression at the time of the first assessment, whereas most had not. Although we included the use of puberty suppression at the pretreatment assessment as a confounder in all analyses, this probably deflated the results, as some improvement of self-perception could already be expected while participants were on puberty suppression.

This finding is especially relevant in the development of self-perception in the domain of physical appearance, because the adolescents who had already started with puberty suppression scored significantly higher on this domain at the pretreatment assessment.

Further, our study lacked control groups, which made it more difficult to assess the role of gender-affirming treatment in the development of self-perception. In addition, we cannot conclude from this study when changes in self-perception started because we only measured self-perception before and after irreversible gender-affirming treatment and not in the interim. Finally, this study is a historical cohort study. This means that changes over time can be identified but that, although possible confounders have been taken into account in the analyses, no definitive conclusion can be drawn about the cause–effect relationship. This is especially relevant, as transgender adolescents have become increasingly visible in society in the past decade. Future research should, therefore, focus on more recent referred adolescents as well as social/cultural factors relating to self-perception.

Conclusion

This long-term follow-up study suggests that early gender-affirming medical interventions for transgender adolescents may be important for developing positive self-perception by showing that physical appearance and global self-worth improved after irreversible gender-affirming treatment. These improvements were the same for trans men and trans women. However, because this study was conducted within a small and heterogeneous sample, it is important that further studies with larger samples examine whether the findings of the study could be confirmed and whether positive development in self-perception may contribute to the improvement of psychological functioning among transgender adolescents. Findings from such studies may help clinicians and counselors in tailoring their approach to and support for transgender adolescents.

Authors' Contributions

M.A., A.I.R.M., W.S.E., A.E.A., A.P., T.D.S., A.L.C.V. contributed to the design of the study, analyses of the data, interpreting the results, and writing of the article. All authors approved the final article as submitted and agreed to be accountable for all aspects of the work.

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References

1. Kaltiala R, Bergman H, Carmichael P, et al.: Time trends in referrals to child and adolescent gender identity services: A study in four Nordic countries and in the UK. Nord J Psychiatry 2020;74:40–44.
2. Arnoldussen M, Steensma TD, Popma A, et al.: Re-evaluation of the Dutch approach: Are recently referred transgender youth different compared to earlier referrals? Eur Child Adolesc Psychiatry 2020;29:803–811.
3. Chen M, Fuqua J, Eugster EA: Characteristics of referrals for gender dysphoria over a 13-year period. J Adolesc Health 2016;58:369–371.
4. Nahata L, Quinn GP, Caltabellotta NM, Tishelman AC: Mental health concerns and insurance denials among transgender adolescents. LGBT Health 2017;4:188–193.
5. Becerra-Culqui TA, Liu Y, Nash R, et al.: Mental health of transgender and gender nonconforming youth compared with their peers. Pediatrics 2018;141:e20173845.
6. Conolly MD, Zervos MJ, Barone CJ 2nd, et al.: The mental health of transgender youth: Advances in understanding. J Adolesc Health 2016;59:489–495.
7. de Graaf NM, Steensma TD, Carmichael P, et al.: Suicidality in clinic-referred transgender adolescents. Eur Child Adolesc Psychiatry 2022;31:67–83.
8. 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;55:93–99.
9. Institute of Medicine Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities: *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding*. Washington, DC: National Academies Press (US), 2011.
10. Leary MR, Schreindorfer LS, Haupt AL: The role of low self-esteem in emotional and behavioral problems: Why is low self-esteem dysfunctional? J Soc Clin Psychol 1995; 14:297–314.
11. Brown JD: Self-esteem and self-evaluation: Feeling is believing. In: *Psychological Perspectives on the Self: The Self in Social Perspective*. Edited by Suls J. Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc., 1993, pp 27–58.
12. Wells LE, Marwell G: *Self-esteem: Its Conceptualization and Measurement*. Beverly Hills, CA: Sage Publications, 1976.
13. Harter S: *The Construction of the Self: A Developmental Perspective*. New York, NY: The Guilford Press, 1999.
14. Harter S: The development of self-representations during childhood and adolescence. In: *Handbook of Self and Identity*. Edited by Leary MR, Tagney JP. New York, NY: The Guilford Press, 2003, pp 610–642.
15. Kuehn B: Transgender youth victimization. JAMA 2019; 321:931.
16. Alberse A, de Vries ALC, Elzinga WS, Steensma TD: Self-perception of transgender clinic referred gender diverse children and adolescents. Clin Child Psychol Psychiatry 2019;24:388–401.
17. Mann M, Hosman CMH, Schaalma HP, de Vries NK: Self-esteem in a broad-spectrum approach for mental health promotion. Health Educ Res 2004;19:357–372.
18. Grossman AH, D'Augelli AR, Frank AR: Aspects of psychological resilience among transgender youth. J LGBT Youth 2011;8:103–115.
19. Cohen-Kettenis PT, Steensma TD, de Vries ALC: Treatment of adolescents with gender dysphoria in The Netherlands. Child Adolesc Psychiatr Clin N Am 2011;20: 689–700.
20. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG: The treatment of adolescent transsexuals: Changing insights. J Sex Med 2008;5:1892–1897.
21. 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:e0243894.
22. Allen LR, Waston LB, Egan AM, Moser CN: Well-being and suicidality among transgender youth after gender-affirming hormones. Clin Pract Pediatr Psychol 2019;7: 302–311.
23. 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;2020:8.
24. de Vries ALC, McGuire JK, Steensma TD, et al.: Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696–704.
25. Costa R, Dunsford M, Skagerberg E, et al.: Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. J Sex Med 2015;12: 2206–2214.
26. Bungener SL, Steensma TD, Cohen-Kettenis PT, de Vries ALC: Sexual and romantic experiences of transgender youth before gender-affirmative treatment. Pediatrics 2017;139:e20162283.
27. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2000.
28. Jansen I: Legal status of transgender people [Rechtspositie transgenders]. FJR 2014;17:3.
29. Harter S: *Self-perception Profile for Adolescents: Manual and Questionnaires*. Denver: University of Denver, 2012.
30. Treffers DA, Goedhart AW, Veerman JW, et al.: *Self-perception Profile for Adolescents (SPPA)*. [*Competentiebelevingsschaal voor adolescenten (CBSA)*]. Amsterdam, The Netherlands: Pearson Assessment and Information BV, 2002.
31. Treffers DA, Goedhart AW, Veerman JW, et al.: *Self-perception Profile for Adolescents (SPPA) Manual*. [*Handleiding competentiebelevingsschaal voor adolescenten (CBSA)*.] Lisse, The Netherlands: Swets & Zeitlinger, 2012.
32. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, *2nd ed*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
33. Strang JF, Chen D, Nelson E, et al.: Transgender youth executive functioning: Relationships with anxiety symptoms, autism spectrum disorder, and gender-affirming medical treatment status. Child Psychiatry Hum Dev 2021 [Epub ahead of print]; DOI: 10.1007/s10578-021-01195-6.
34. Aitken M, Steensma TD, Blanchard R, et al.: Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. J Sex Med 2015;12:756–763.
35. Robins RB, Trzesniewski KH, Tracy JL, et al.: Global self-esteem across the life span. Psychol Aging 2002;17:423–434.

36. Egan SK, Perry DG: Gender identity: A multidimensional analysis with implications for psychosocial adjustment. Dev Psychol 2001;37:451–463.
37. Yunger JL, Carver PR, Perry DG: Does gender identity influence children's psychological well-being? Dev Psychol 2004;40:572–582.
38. Durwood L, McLaughlin KA, Olson KR: Mental health and self-worth in socially transitioned transgender youth. J Am Acad Child Adolesc Psychiatry 2017;56:116–123.
39. Cohen-Kettenis PT, Owen A, Kaijser VG, et al.: Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. J Abnorm Child Psychol 2003;31:41–53.
40. Wallien MS, van Goozen SH, Cohen-Kettenis PT: Physiological correlates of anxiety in children with gender identity disorder. Eur Child Adolesc Psychiatry 2007;16: 309–315.
41. Wong WI, van der Miesen AIR, Li TGF, et al.: Childhood social gender transition and psychosocial well-being: A comparison to cisgender gender-variant children. Clin Pract Pediatr Psychol 2019;7:241–253.
42. Sievert ED, Schweizer K, Barkmann C, et al.: Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with gender dysphoria. Clin Child Psychol Psychiatry 2021;26:79–95.

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Original Investigation | Pediatrics

Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents

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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.

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Key Points

Question Is there an association between use of gonadotropin-releasing hormone analogue and subsequent use of gender-affirming hormones among transgender and gender-diverse adolescents?

Findings In this cohort study of 434 adolescents, there was no significant association between gonadotropin-releasing hormone use and subsequent initiation of gender-affirming hormones.

Meaning These findings suggest that clinicians can offer gonadotropin-releasing hormone analogues to transgender and gender-diverse adolescents during pubertal development for mental health and cosmetic benefits without an increased likelihood of subsequent use of gender-affirming hormones.

+ Invited Commentary

Author affiliations and article information are listed at the end of this article.

Introduction

In the US, 1.8% of high school students identify as transgender, with an increasing number of children and adolescents seeking gender identity–specific health care in recent years.[1-4] Transgender and gender-diverse (TGD) youth are at high risk for depression, anxiety, self-harm, and suicidality.[1,5-7] This is likely related to gender dysphoria, family rejection, and increased exposure to bullying, discrimination, harassment, violence, and social isolation.[1,6]

Multiple medical societies and evidence-based treatment guidelines support the use of gonadotropin-releasing hormone analogues (GnRHa) to reversibly suppress further pubertal development in peripubertal youth with gender dysphoria.[8-11] This treatment is associated with improvements in global functioning, depression, suicidal ideation, and overall behavioral and emotional problems among youth with gender dysphoria.[12-16] Treatment with GnRHa can improve gender dysphoria by reversibly halting development of secondary sex characteristics that are not consistent with the patient's experienced gender. Relieving the pressure associated with additional pubertal development can also give young adolescents more time to fully confirm their gender identities before making a decision about initiating further gender-affirming treatment with irreversible effects.[8,9,17] Pubertal suppression may also affect cosmetic outcomes if the patient elects to progress to gender-affirming hormones, decreasing the need for certain future interventions, such as mastectomies in people with trans-masculine gender identities and facial feminization in people with trans-feminine gender identities.[18] However, the use of GnRHa for pubertal suppression is associated with short-term physical symptoms, such as headaches, hot flashes, and fatigue, and long-term risks such as decreased bone mineral density and changes in body composition. Use of GnRHa in early puberty followed by treatment with estrogen can also impair fertility and complicate future vaginoplasty.[19-22] The benefits of GnRHa treatment in postpubertal youth are not as clear. Assisting patients and families with assessment of the risks and benefits of treatment and managing adverse effects that occur is an important part of caring for transgender youth.

In prior studies[4,20,23] of gender-affirming medical care for TGD adolescents, 96.5% to 98.1% of individuals who started GnRHa subsequently used gender-affirming hormones. This high rate has led some clinicians, judges, and legislators to express concerns that initiation of GnRHa treatment in young adolescents does not serve as a pause in pubertal development, but instead inappropriately advances the decision to start gender-affirming hormones to a younger age when the adolescent has not yet completed the cognitive development required to assent to this treatment.[8,24-27] Guidelines for gender-affirming care suggest that most adolescents do not reach cognitive maturity until age 15 to 16 years, after most have completed puberty and can no longer obtain maximum benefit from GnRHa treatment.[8]

In the United Kingdom, a court ruled that GnRHa treatment could not be administered to transgender patients younger than 16 years without a court order because they assert that this treatment inevitably leads to use of gender-affirming hormones. This ruling also suggested that gender-affirming care for patients aged 16 and 17 years old should be restricted as well.[26] In the US, 3 states have outlawed all gender-affirming medical care for minors, 1 state government has taken administrative action to classify gender-affirming medical care for minors as child abuse, and 16 state public medical insurance programs for those with limited income or resources (Medicaid) do not pay for gender-affirming medical care. An additional 19 state legislatures are considering laws to make some or all aspects of gender-affirming medical care for minors illegal.[28,29]

It is unknown whether GnRHa treatment among TGD youth leads to an increase in subsequent use of gender-affirming hormones or whether the high continuation rate seen in previous studies reflects the natural history of gender dysphoria among adolescents or the rigorous screening process used before administration of GnRHa in previous studies. The purpose of our study is to compare the rates of gender-affirming hormone initiation between patients who are treated with GnRHa and those who are not treated with GnRHa. We hypothesized that TGD youth who were treated with

GnRHa would not have a higher rate of future gender-affirming hormone use compared with TGD youth who were not treated with GnRHa.

Methods

This is a retrospective cohort study examining the association between GnRHa use and subsequent use of gender-affirming hormones among TGD youth enrolled in the US Military Health System (MHS) between October 2009 and April 2018 and using their TRICARE health plan benefit. TRICARE Prime is the medical health plan benefit for almost 4.8 million people stationed around the world, including active-duty service members in the US Army, Air Force, Marines, and Navy; military retirees; and their families. Data for this study were extracted from the Military Health System Data Repository (MDR) by a member of the research team (A.S.) in 2019. The MDR includes insurance billing records for inpatient care, outpatient care, and outpatient prescriptions that were paid for by TRICARE. This study was approved by the authors' local institutional review boards as a secondary analysis of deidentified, preexisting data. Consent was not needed because the data were deidentified, in accordance with 45 CFR, subpart A, §46.104, exempt research, exception 4. This manuscript was prepared in accordance with the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement.

In a previous study,[7] using the same data source as this study, the investigators identified 3754 youth, younger than 18 years, who had at least 1 health care encounter with a transgender-related diagnosis. For this study, we further refined our sample population using the inclusion criteria outlined here. Patients were required to have at least 2 distinct encounters associated with 1 or more of the following codes: *International Classification of Diseases, Ninth Revision* codes 302.6, 302.85, 302.50, 302.51, 302.52, and 302.53; and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F64.0, F64.1, F64.2, F64.8, and Z87.890. The initial TGD-related visit had to occur between ages 10 and 17 years, and the patient needed to have at least 1 medical encounter, for any reason, occurring after their 14th birthday. On the basis of current guidelines, patients are required to have the cognitive capacity to provide meaningful informed consent or assent to treatments with permanent effects before starting gender-affirming hormones. Some adolescents have developed this level of cognitive capacity as early as age 14 years, and most have developed it by age 16 years.[8] Therefore, age 14 years is generally the earliest a clinician will consider prescribing a patient gender-affirming hormones. Requiring a patient to have at least 1 clinical encounter after turning 14 years old provided all subjects an opportunity to start hormone therapy during our study period.

Pharmacy records were accessed to identify all prescriptions for GnRHa and initial prescriptions for gender-affirming hormones occurring between 30 days before their first clinic visit addressing gender dysphoria and 90 days after their final clinic visit addressing gender dysphoria. Discontinuation of GnRHa treatment was defined as no GnRHa prescriptions for a period 3 times as long as their most recent prescription length. Initiation of gender-affirming hormones was defined as first use of sex hormones inconsistent with their sex assigned at birth. We used sex indicated by the earliest gender marker recorded in the MDR as a proxy for sex assigned at birth. We excluded patients if their first prescription for gender-affirming hormones occurred before or at the same time as starting GnRHa.

Demand for gender-affirming medical care for pediatric age patients increased during our study period. Demand peaked in 2016 when TRICARE officially authorized payment for gender-affirming medical care, on September 1, 2016.[30,31] We created a measure of time by dividing our sample of patients into 3 roughly equal-sized groups according to the date of their initial TGD-related encounter. Our periods included the period of lower demand for gender-affirming care before official approval of payment for gender-affirming care by TRICARE (October 2009 to December 2014), the period of increased demand for gender-affirming care before official authorization of care (January 2015 to August 2016), and the period after insurance approval (September 2016 to April 2018). We

also collected insurance sponsor's rank (officer vs enlisted) as a proxy for socioeconomic status on the basis of the assumption that an enlisted insurance sponsor would have a lower income than an officer while on active duty, and most officers have a college education whereas many enlisted sponsors do not.[32]

Statistical Analysis

The analysis for this study was completed in August 2022. We used Kaplan-Meier survival analyses to estimate the time from the patient's first encounter for a TGD-related diagnosis to initiation of gender-affirming hormones. We also assessed the association of time to initiation of gender-affirming hormones with GnRHa use and demographic factors. Patients were censored if they reached their final billable clinical encounter in the MHS before the end of the study period. We used the Breslow (generalized Wilcoxon) χ^2 test to assess the bivariate association of demographic factors, TRICARE transgender coverage status (officially approved vs unapproved), and date of initial transgender-related encounter with time to starting hormones. We used bivariable and multivariable Cox proportional hazard analyses to assess the independent association of our variables on the hazard of starting gender-affirming hormones. We used visual inspection of the log-log survival curve to ensure that the proportional hazard assumption was not violated. Our threshold for statistical significance in this study was $P < .05$ for 2-sided tests.

We conducted a subanalysis of the association between GnRHa use and time to initiation of gender-affirming hormones among patients who were aged 10 to 13 years at the time of their initial TGD-related medical encounter. Previous research has suggested that age 10 to 13 years is a key period in the development of gender identity and persistence or desistence of gender dysphoria.[33] Many patients are also experiencing pubertal development during this period and would obtain the most benefit from GnRHa treatment. SPSS statistical software version 28.0.1.0 (IBM) was used for statistical analysis.

Results

We identified 434 TGD youth who met our inclusion criteria: 143 with an initial encounter in October 2009 to December 2014, 133 in January 2015 to August 2016, and 158 in September 2016 to April 2018. Most patients were assigned female at birth (312 patients [71.9%]) and had an enlisted

Table 1. Transgender Individuals Aged 10 to 17 Years Seeking Gender-Affirming Medical Care in the Military Heath System by Year of First Transgender-Related Encounter, 2009-2018

Characteristic	Participants, No. (%)			
	TRICARE did not officially cover gender-affirming medical care		TRICARE officially covered gender-affirming medical care, September 2016 to April 2018 (n = 158)[c]	Total sample, October 2009 to April 2018 (N = 434)
	October 2009 to December 2014 (n = 143)[a]	January 2015 to August 2016 (n = 133)[b]		
Age at first transgender-related encounter, mean (SD), y	15.2 (1.8)	15.4 (1.6)	15.6 (1.2)	15.4 (1.6)
Age group at first transgender-related encounter, y				
10-13	22 (15.4)	22 (16.5)	12 (7.4)	56 (12.9)
14-17	121 (84.6)	111 (83.5)	146 (92.6)	378 (87.1)
Sex assigned at birth				
Male	47 (32.9)	35 (26.3)	40 (25.2)	122 (28.1)
Female	96 (67.1)	98 (73.7)	118 (74.8)	312 (71.9)
Parent enlisted or an officer[d]				
Enlisted	99 (69.2)	93 (69.9)	108 (68.1)	300 (69.1)
Officer	44 (30.8)	40 (30.1)	50 (31.9)	134 (30.9)
Prescribed gonadotropin-releasing hormone analogue	19 (13.3)	27 (20.0)	24 (15.2)	70 (16.1)

[a] There were 20 new patients in October 2009 to December 2010, 15 new patients in 2011, 20 new patients in 2012, 34 new patients in 2013, and 54 new patients in 2014.

[b] There were 92 new patients in 2015 and 41 new patients in 2016.

[c] There were 64 new patients September 2016 to December 2016 and 94 new patients January 2017 to April 2018.

[d] Denotes current rank or rank before retirement from the military.

insurance sponsor (300 patients [69.1%]). The mean (SD) age at the first TGD-related encounter was 15.4 (1.6) years. The number of patients presenting for gender-affirming medical care increased over time. The mean age at the first TGD-related encounter and the ratio of those assigned male to female did not change over time (**Table 1**).

The median interval between the first TGD-related encounter and starting gender-affirming hormones was 1.1 years (95% CI, 0.9-1.3 years). Within 1 year of the initial TGD-related encounter, an estimated 46.4% of TGD adolescents aged 10 to 17 years (95% CI, 41.7%-51.1%) had started gender-affirming hormones. Within 4 years of the initial encounter, 88.3% of TGD adolescents (95% CI, 84.8%-91.8%) had started gender-affirming hormones.

The median interval between the first TGD-related encounter and starting hormones 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. Hormone use at 18 months after diagnosis increased with recency of first diagnosis date: 36.6% of adolescents (95% CI, 28.8%-44.4%) in October 2009 to December 2014, 65.4% (95% CI, 58.0%-72.8%) in January 2015 to August 2016, and 95.3% (95% CI, 87.3%-100%) in September 2016 to April 2018. TGD youth who

Table 2. Gonadotropin-Releasing Hormone Analogue Use

Demographics	Patients started using a gonadotropin-releasing hormone analogue, No. (%) (N = 434)	
	No (n = 364)	Yes (n = 70)
Sex assigned at birth[a]		
Male	94 (77.0)	28 (23.0)
Female	270 (86.5)	42 (13.5)
Age at first transgender diagnosis, y[a]		
10-13	24 (42.9)	32 (57.1)
14-17	340 (88.9)	38 (10.1)
Insurance sponsor rank		
Enlisted	251 (83.7)	49 (16.3)
Officer	113 (84.3)	21 (15.7)

[a] Differences between groups were statistically significant at $P < .05$.

Table 3. Association of Patient Factors With Initiation of Gender-Affirming Hormones

Factor	Time from initial encounter to initiation of gender-affirming hormones (KM estimate), median (95% CI), y	HR (95% CI)[a]	
		Hazard of starting hormones (bivariable analyses)	Independent hazard of starting hormones (multivariable analyses)
Total sample	1.1 (0.9-1.3)	NA	NA
Date of initial diagnosis			
October 2009 to December 2014	2.3 (1.7-2.8)	1 [Reference]	1 [Reference]
January 2015 to August 2016	1.1 (0.9-1.3)	2.25 (1.71-2.97)	2.43 (1.84-3.21)
September 2016 to April 2018[b]	0.6 (0.5-0.6)	4.92 (3.59-6.74)	5.12 (3.72-7.04)
Prescribed gonadotropin-releasing hormone analogue			
No	1.0 (0.8-1.2)	1 [Reference]	1 [Reference]
Yes	1.8 (1.1-2.4)	0.52 (0.37-0.71)	0.54 (0.38-0.77)
Age at initial diagnosis, y			
10-13	2.1 (1.5-2.8)	1 [Reference]	1 [Reference]
14-17	1.0 (0.9-1.2)	2.03 (1.46-2.84)	1.42 (0.98-2.07
Sponsor's rank[c]			
Enlisted	1.1 (0.9-1.3)	1 [Reference]	NA[d]
Officer	1.0 (0.7-1.3)	1.06 (0.85-1.33)	
Sex assigned at birth			
Male	1.3 (1.0-1.5)	1 [Reference]	NA[d]
Female	1.1 (0.9-1.2)	1.25 (0.99-1.58)	

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; NA, not applicable.

[a] HRs and 95% CIs were determined by Cox proportional hazards analyses.

[b] On September 1, 2016, TRICARE adjusted the list of covered conditions to include gender-affirming medical rendered to military retirees and family members of active duty and retired service members.

[c] Enlisted service members are required to complete high school, whereas officers are required to complete college before joining the US military. Officers also have higher pay while in the military and military pension after retirement. We are using this factor as a proxy for family income.

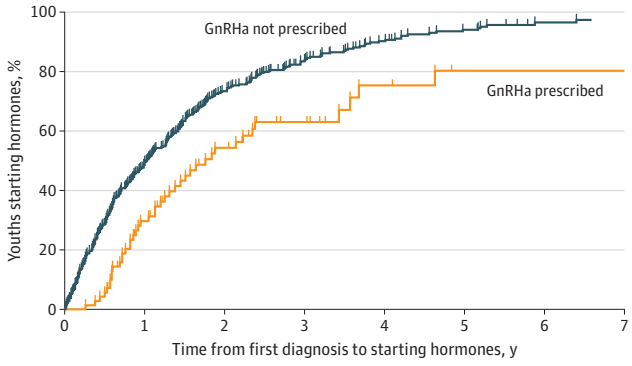
[d] Not included in multivariable model.

were initially seen after September 2016 had an almost 5 times higher hazard of starting gender-affirming hormones (hazard ratio, 4.92; 95% CI, 3.59-6.74) than patients who had an initial transgender-related encounter between 2009 and 2014.

Patients who were 10 to 13 years old at the initial TGD-related encounter were more likely than patients who were 14 to 17 years old to be prescribed GnRHa (32 patients [57.1%] vs 38 patients [10.1%]) and had a larger interval between the initial TGD-related appointment and starting gender-affirming hormones (**Tables 2** and **3**). Compared with patients without GnRHa use, GnRHa use was associated with a longer median gap between the initial appointment and starting gender-affirming hormones (1.8 years [95% CI, 1.1-2.4 years] vs 1.0 years [95% CI, 0.8-1.2 years]) and a lower hazard of starting gender-affirming hormones (hazard ratio, 0.52; 95% CI, 0.37-0.71) (**Figure 1**). This association was consistent across time periods. We saw this same association when we restricted our analyses to 54 patients who were aged 10 to 13 years at the time of their first TGD-related encounter (**Figure 2**). Most patients (63 of 70 patients [90%]) who started GnRHa continued treatment until they started gender-affirming hormones or were censored from further analysis. Of the 7 patients in our study who started and then stopped GnRHa treatment while continuing to seek medical care using their TRICARE benefit, 3 went on to start testosterone.

GnRHa use was more common among patients who were assigned male at birth than those who were assigned female (28 patients [23.0%] vs 42 patients [13.5%]) but GAH use was not (Table 3).

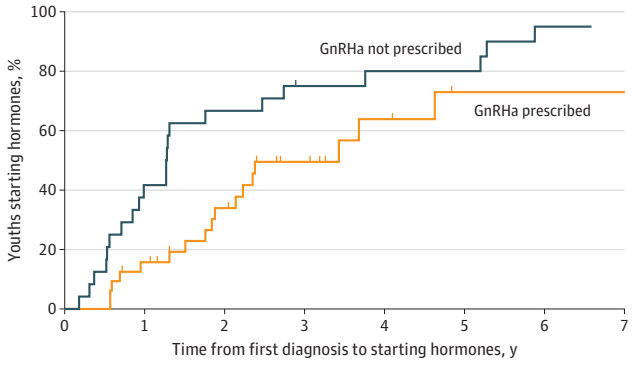
Figure 1. Use of Gonadotropin-Releasing Hormone Analogues (GnRHa) and Gender-Affirming Hormones Among Transgender Youth Aged 10 to 17 Years



No. at risk

GnRHa not prescribed	364	83	23	4
GnRHa prescribed	70	24	6	3

Figure 2. Use of Gonadotropin-Releasing Hormone Analogues (GnRHa) and Gender-Affirming Hormones Among Transgender Youth Aged 10 to 13 Years



No. at risk

GnRHa not prescribed	23	8	4	1
GnRHa prescribed	31	18	6	2

Sponsor's military rank (a proxy for socioeconomic status) was not associated with initiation of GnRHa or gender-affirming hormones (Table 3). In multivariable analysis including GnRHa use, time of the initial transgender-related encounter, and patient age at the time of the first encounter, only GnRHa use and time of the initial encounter had an independent association with the hazard of initiating gender-affirming hormones.

Discussion

The findings of this cohort study suggest that GnRHa treatment is not associated with increased progression to gender-affirming hormones among treatment-seeking TGD adolescents in a population receiving low or no-cost medical care in the MHS. We also found that number of patients per year presenting for gender-affirming medical care increased during our study period, whereas the time between the initial TGD-related encounter and initiation of gender-affirming hormones decreased, but the median age at presentation remained the same. Patients who were older at the time of the initial TGD-related encounter had a shorter median time between the first medical encounter and initiation of gender-affirming hormones and were more likely to start gender-affirming hormones in general. We also found that assigned male patients were significantly more likely than assigned female patients to start GnRHa, but not gender-affirming hormones. In a medical system with low or no-cost medical care, the sponsor's military rank (a proxy for socioeconomic status) was not associated with differences in use of gender-affirming hormones by TGD adolescents.

Across the MHS, we saw lower rates of progression from GnRHa treatment to gender-affirming hormones among TGD adolescents than were seen in studies of specialized gender clinics in Europe (92%-98%).[4,20,23] Some of the national centers in Europe examined in prior studies had more stringent criteria for initiation of gender-affirming treatment than patients seen in the MHS, such as requiring patients to have at least 6 months of involvement with child psychology or psychiatry before starting GnRHa treatment,[4,21] requiring patients to have persistent gender dysphoria since childhood that increased with puberty,[13,17,21] or requiring patients to start GnRHa treatment before obtaining access to gender-affirming hormones.[23] These additional criteria may influence patterns of GnRHa use and account for some of the difference observed in progression from GnRHa use to gender-affirming hormone use. We also included younger children in our study compared with previous studies, and clinicians in the MHS initiated GnRHa at younger ages than in previous studies.[4,5] In our study, younger patients were less likely to initiate gender-affirming hormones; therefore, inclusion of these patients might also account for the lower rate of gender-affirming hormone use seen in our study. This lower rate of starting gender-affirming hormone therapy among younger patients is consistent with previous studies finding that age 10 to 13 years is a key period for confirmation of gender identity and determining whether gender dysphoria will persist or resolve.[33] TGD patients first presenting at an older age may have passed through this period of identity consolidation and are more likely to have persistent gender dysphoria. However, consistent with other studies, few TGD patients discontinued treatment.

Use of GnRHa treatment in younger adolescents is reversible and associated with improvements in mental health and cosmetic outcomes if gender dysphoria persists.[8,9,12-18] In our study, we found that use of GnRHa treatment among adolescents did not collectively increase future use of gender-affirming hormones. This suggests that clinicians can offer GnRHa treatment to young TGD adolescents without an increased likelihood of future use of gender-affirming hormones.

Limitations

This study has limitations that should be addressed. It is a retrospective cohort analysis of administrative data from patients enrolled in the US military health plan program, TRICARE. The children of active duty or retired service members identified in our study are different from the general population in several ways. Compared with the general population in the US, children of active duty and retired service members have families with a higher average socioeconomic standing,

higher levels of parental education, medical care coverage with lower out-of-pocket expenses and more comprehensive health care coverage, and higher geographic mobility. These factors limit the generalizability of our findings. As this is a study of health plan administrative data, we do not have information on care obtained by the family without using their TRICARE benefit. In the US, medical expenses can be covered by employer-funded private medical insurance, government insurance programs for the economically disadvantaged and elderly adults, individually purchased private insurance obtained with or without cost subsidies from the government, and paying out of pocket at the time of service. Individuals can have multiple types of insurance at the same time, such as a military retiree with TRICARE and commercial insurance through their employer, and can select which program they use to pay for health care services. It is possible that patients elected to obtain gender-affirming medications without using their TRICARE benefit, while still obtaining other medical care in the MHS. However, the difference in cost between commercial insurance programs and TRICARE make this less likely. The average out-of-pocket medication costs would be $500 per year using commercial insurance vs $0 to $36 per year using TRICARE for a transgender woman and $230 per year vs $0 to $72 per year for a transgender man.[34] We also did not capture information on individual patient, parent, and clinician factors that may influence decisions about starting or stopping gender-affirming medical treatments, or to seek out these treatments at all. Future studies examining the individual patient, family, clinician, and governmental factors influencing initiation and discontinuation of gender-affirming medications, conducted with more generalizable samples, would be helpful to clinicians when counseling patients and families on the risks and benefits of gender-affirming medications and monitoring treatment.

Conclusions

In this cohort study of transgender adolescents, GnRHa use was not associated with an increased hazard of subsequent gender-affirming hormone use. These data suggest that clinicians can offer the benefits of GnRHa treatment to TGD youth with gender dysphoria without concern for unduly or inappropriately increasing rates of subsequent gender-affirming hormone use.

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Author Contributions: Dr Roberts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Nos, Klein, Adirim, Schvey, Hisle-Gorman, Roberts.

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Supervision: Klein, Adirim, Roberts.

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REFERENCES

1. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students: 19 states and large urban school districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(3):67-71. doi:10.15585/mmwr.mm6803a3

2. Klein DA, Roberts TA, Adirim TA, et al. Transgender children and adolescents receiving care in the US military health care system. *JAMA Pediatr*. 2019;173(5):491-492. doi:10.1001/jamapediatrics.2019.0105

3. 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

4. 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

5. 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

6. Strauss P, Cook A, Winter S, Watson V, Wright Toussaint D, Lin A. Associations between negative life experiences and the mental health of trans and gender diverse young people in Australia: findings from Trans Pathways. *Psychol Med*. 2020;50(5):808-817. doi:10.1017/S0033291719000643

7. 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

8. 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

9. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people, 7th version. 2012. Accessed September 26, 2022. https://www.wpath.org/publications/soc

10. Department of Family and Community Medicine, University of California San Francisco. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people, 2nd edition. June 17, 2016. Accessed September 26, 2022. https://transcare.ucsf.edu/guidelines

11. Rafferty J; Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*. 2018;142(4):e20182162. doi:10.1542/peds.2018-2162

12. 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;2020:8. doi:10.1186/s13633-020-00078-2

13. 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

14. 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

15. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics*. 2020;145(2):e20191725. doi:10.1542/peds.2019-1725

16. 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):e20193006. doi:10.1542/peds.2019-3006

17. Cohen-Kettenis PT, Steensma TD, de Vries AL. Treatment of adolescents with gender dysphoria in the Netherlands. *Child Adolesc Psychiatr Clin N Am*. 2011;20(4):689-700. doi:10.1016/j.chc.2011.08.001

18. 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):e20193653. doi:10.1542/peds.2019-3653

19. 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

20. 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

21. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol*. 2006;155:S131-S137. doi:10.1530/eje.1.02231

22. 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

23. Brik T, Vrouenraets LJJJ, 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

24. Kremen J, Williams C, Barrera EP, et al; Gender Multispecialty Service (GeMS) Team. Addressing legislation that restricts access to care for transgender youth. *Pediatrics*. 2021;147(5):e2021049940. doi:10.1542/peds.2021-049940

25. National Center for Transgender Equality. 2021 State action center. Accessed September 11, 2021. https://transequality.org/2021-state-action-center

26. 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

27. Laidlaw MK, Van Meter QL, Hruz PW, Van Mol A, Malone WJ. Letter to the editor: "Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline". *J Clin Endocrinol Metab*. 2019;104(3):686-687. doi:10.1210/jc.2018-01925

28. Movement Advancement Project. Equality maps: healthcare laws and policies. Accessed March 8, 2022. https://www.lgbtmap.org/equality-maps/healthcare_laws_and_policies

29. Zaliznyak M, Jung EE, Bresee C, Garcia MM. Which U.S. states' Medicaid programs provide coverage for gender-affirming hormone therapy and gender-affirming genital surgery for transgender patients?: a state-by-state review, and a study detailing the patient experience to confirm coverage of services. *J Sex Med*. 2021;18(2):410-422. doi:10.1016/j.jsxm.2020.11.016

30. Military Health System. TRICARE Policy Manual 6010.60-M. Gender Dysphoria, Chapter 7, Section 1.2. September 6, 2016. Accessed September 26, 2022. https://manuals.health.mil/pages/DisplayManualHtmlFile/2021-03-23/AsOf/tp15/c7s1_2.html

31. 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

32. Military One Source. *Demographics Profile of the Military Community: Department of Defense (DoD)*. Office of the Deputy Assistant Secretary of Defense for Military Community and Family Policy; 2020.

33. 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

34. Koch JM, McLachlan CT, Victor CJ, Westcott J, Yager C. The cost of being transgender: where socio-economic status, global health care systems, and gender identity intersect. *Psychol Sex*. 2020;11(1-2):103-119. doi:10.1080/19419899.2019.1660705

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Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents

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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.

Keywords

Gender dysphoria, gender incongruence, transgender adolescents, puberty suppression, gender-affirming medical treatment, intelligence, educational achievement

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Introduction

Gender dysphoria (GD) refers to incongruence between a person's assigned sex based on their biological sex characteristics and their experienced gender, resulting in psychological distress (de Vries et al., 2014; Hembree et al., 2017; Mahfouda et al., 2017).

Puberty suppression (PS) in the form of GnRH analogues may be prescribed in adolescents with GD to delay the development of secondary sex characteristics, providing time for exploring gender identity and relieve the distress of physical pubertal development before any decisions regarding more irreversible steps in gender affirmative treatment are made (de Vries et al., 2014; Mahfouda et al., 2017). PS can be prescribed to transgender adolescents who have shown persistent, long lasting GD, have no interfering psychological difficulties, are socially supported and understand the pros and cons of this treatment (de Vries et al., 2014; Hembree et al., 2017; Mahfouda et al., 2017). The adolescents should have entered puberty Tanner stage G2/B2 to ascertain that they have experienced at least some physical pubertal development. After puberty suppression, transgender adolescents may continue with gender-affirming hormone therapy (GAHT) (Hembree et al., 2017). A study evaluating psychological outcomes in young adulthood of this approach showed improved psychological functioning and general wellbeing comparable to same age peers (de Vries et al., 2014).

Specific information about the impact of PS and GAHT on the maturation of the brain, including their effects on cognitive development, is still limited (Hembree et al., 2017; Richards et al., 2019). Concerns have been raised regarding the risks of PS on neurodevelopment (Chen et al., 2020; Costa et al., 2016; Laidlaw et al., 2019). A study on long-term effects of PS on brain development of sheep who received PS found that long-term spatial memory performance remained reduced after discontinuation of PS (Hough et al., 2017). Another study showed that PS treatment after puberty onset exerts sex-specific effects on social and affective behaviour, stress regulation, and neural activity in mice (Anacker et al., 2021). It is important to emphasize that these results are from research with animal models. The few studies that have been conducted on the effect of PS on cognitive performance in human yielded mixed results. A study in adopted children ($N = 30$) with precocious puberty who were treated with GnRH analogues, either alone or with growth hormone, showed that their IQ levels had decreased about 7 points after this treatment (Mul et al., 2001). However, yet another study found no differences in cognitive performance between 15 GnRHa treated girls with precocious puberty and their age-matched controls (Wojniusz et al., 2016).

Assessing the effect of PS on cognitive development is very challenging. A randomized controlled trial in which some of the adolescents receive PS and others do not, would provide the most accurate estimate of the effect. However, since such studies are not at all desirable from an ethical perspective, other methods will have to be explored to gain a better insight. To what extent IQ at young age and final educational attainment in adulthood are correlated could possibly shed more light on this effect. Numerous studies have shown that cognitive ability, as measured by IQ scores, is positively correlated with educational achievement in the general population (Sternberg et al., 2001). For example, a 5-year prospective longitudinal study in England of over 70.000 children examined the association between intelligence at age eleven and educational achievements at age sixteen and found a strong correlation: 0.81 (Deary et al., 2007). For this reason, we hypothesized that the association between IQ pre-treatment and educational achievement post-treatment in transgender adolescents provides a proxy of the effects that PS followed by GAHT may have on cognitive development.

There are several factors that could potentially affect the association between IQ and educational achievement. Psychological distress as well as behavioural problems are negatively associated with educational achievement (Loe & Feldman, 2007; Rothon et al., 2009). Furthermore,

Israel et al. (2001) found that for high school students, the social support of their family is a key factor affecting educational achievement.

This study focused on the association between pre-treatment intelligence (before gender-affirming treatment starting with PS followed by GAHT and affirming surgeries) and post-treatment educational achievement in young adulthood (after gender-affirming treatment) of transgender adolescents. Apart from age and gender, emotional and behavioural problems of the adolescents as well as the family situation and family functioning were examined as covariates in this study.

Methods

Participants

This study was performed at the Center of Expertise on Gender Dysphoria (CEGD) of Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands and was part of a larger research project to measure the outcome of early medical intervention in transgender adolescents (de Vries et al., 2014). Adolescents who were referred before 2010, met the criteria for the diagnosis of gender dysphoria (according to the DSM-IV-TR) (American Psychiatric Association, 2000), started with PS before the age of 17 years followed by gender-affirming hormonal treatment and gender-affirming surgery (vaginoplasty, hysterectomy or mastectomy), could be included in this study. There were no exclusion criteria.

Of the 119 adolescents who were eligible for this study, 72 participated. There were several reasons for non-participation; some could not be contacted because correct address information was lacking, some agreed to participate but did not fill out the questionnaires despite repetitive reminders, and some declined to participate. The 72 included subjects were compared on demographic characteristics with the 47 individuals who did not participate in the study. Chi-square tests showed that the sex-ratio was not significantly different between the two groups, but that the included adolescents were significantly more likely to live with their biological parents than the adolescents who did not participate. Independent sample *t*-tests revealed that the included group was significantly younger when they started with puberty suppression. The total IQ and the time between the start with PS and the start with GAHT was comparable between the two groups.

Of the 72 participants, 45 were trans men and 27 were trans women. During data collection, people were not specifically asked if they identified outside the gender binary. The participants received on average 2.40 years (SD 1.08, range 0.52–5.06 years) of PS before starting with GAHT. Demographic characteristics are shown in Table 1.

Procedure

The adolescents followed the usual diagnostic process (de Vries et al., 2014). The participants were assessed two times: pre-treatment (before the start of PS or GAHT, mean age 12.78 years) and post-treatment (after gender-affirming hormones and surgery, mean age 20.40 years). Pre-treatment, sex assigned at birth and the living situation of the adolescent were collected from the medical chart. Depending on age, the IQ was measured using the Wechsler Intelligence Scale for Children (WISC) (Wechsler et al., 2002) or Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997), and emotional- and behavioural problems were examined using the total internalizing and externalizing problems scale of the Child Behaviour Checklist (CBCL) (Verhulst et al., 1996), and Youth Self Report (YSR) (Verhulst et al., 1997). Besides, the age at which PS and GAHT were started were collected from the medical charts. Post-treatment assessment took place between 2009 and 2016 and was defined as at least 1 month after affirming surgeries (mastectomy, hysterectomy or

Table 1. Sociodemographic characteristics of the study sample.

Gender, N (%)		
- Trans men	45 (62.5%)	
- Trans women	27 (37.5%)	
Living situation of the adolescent before treatment, N (%)		
- Living with both biological parents	52 (72.2%)	
- Other	19 (26.4%)	
- Unknown	1 (1.4%)	
Age in years	M (SD)	Range
- Clinical entry/baseline	12.78 (1.48)	10.73–16.94
- Start puberty suppression	13.77 (1.46)	11.47–16.99
- Start gender-affirming hormonal treatment	16.22 (0.82)	13.93–18.98
- Gender-affirming surgery	18.70 (0.77)	17.56–21.87
- Evaluation educational achievement	20.40 (1.03)	18.64–23.78
Years between start puberty suppression and start of gender-affirming hormonal treatment	M (SD)	Range
	2.40 (1.08)	0.52–5.06

Note. M = mean, SD = standard deviation.

vaginoplasty). Participants were invited for research evaluation at the CEDG. Part of this evaluation was a survey about current or finished educational achievement. In the Netherlands, school systems can be divided in pre-vocational, higher pre-vocational and pre-university education (van den Bos et al., 2012). In this study, educational achievement was dichotomized into 'vocational educated' and 'higher vocational educated/academic educated'. 'Vocational educated' included pre-vocational education (VMBO in Dutch) and vocational education (MBO in Dutch), depending on the age of the adolescent at the moment of the research evaluation. 'Higher vocational educated' included higher pre-vocational education (HAVO in Dutch), pre-university education (VWO in Dutch), higher vocational education (HBO in Dutch) and academic education (university). In the Netherlands, vocational education traditionally focuses on preparing students to work in a trade or craft, while higher vocational and academic education concentrates on higher learning and professional training. Furthermore, family functioning was evaluated post-treatment using the general functioning scale of the Family Assessment Device (FAD) (Epstein et al., 1983).

Informed consent was signed by all adolescents and their parents at the baseline-assessment and by the participants at follow-up. The VU University Medical Center medical ethics committee approved the study.

Statistics

All data analyses were performed using SPSS statistics 26. To determine the correlation between total IQ and educational achievement, the square root of the Nagelkerke R square was obtained. Furthermore, binary logistic regression analyses were performed. The independent, continuous variables were total, verbal and performance IQ, the dependent binary variable was educational achievement. Gender was examined as a possible effect modifier. Independent *t*-tests and Chi-square tests identified if the variables internalizing problems, externalizing problems, living situation of the adolescent, family functioning, age at which the adolescent started PS/GAHT and age at which the educational achievement was evaluated, were associated with the outcome variable. Since externalizing problems and the age at which the adolescent started GAHT were significantly associated with the outcome variable, these were included and reported as control variable in the logistics regression analyses.

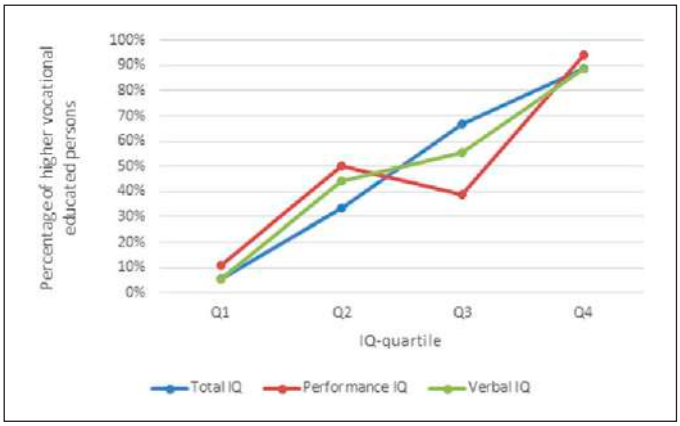

Figure 1. Percentage of higher vocational educated persons per IQ quartile. Quartiles: TIQ: Q1 = 71–89. Q2 = 90–98. Q3 = 98–110. Q4 = 110–136. PIQ: Q1 = 65–89. Q2 = 90–99. Q3 = 100–110. Q4 = 110–135. VIQ: Q1 = 72–88. Q2 = 88–97. Q3 = 97–107. Q4 = 108–136. TIQ = total IQ, PIQ = performance IQ, VIQ = verbal IQ.

Results

The mean total IQ of the participants was 100.29 (SD = 15.07). For verbal IQ, the mean was 99.53 (SD = 15.01), for performance IQ the mean was 100.72 (SD = 14.26). Of the 72 adolescents, 37 were vocational educated (51.4%) and 35 were higher vocational educated (48.6%). The IQ scores and educational achievement were not significantly different between trans men and trans women. All variables were normally distributed. As shown in Figure 1, the associations between total IQ, verbal IQ and educational achievement were linear and therefore suitable for logistic regression. Performance IQ was not entirely linear but sufficient for logistic regression.

The correlation coefficient (Nagelkerke R) between total IQ and educational achievement was 0.71. The binary logistic regression analyses found that for each increase of one point in total IQ score, the chance of being higher educated increased with 1.170 odds (β 0.157 $p < 0.001$, 95% CI: 1.074–1.275) when controlled for externalizing problems and age at which the adolescent started GAHT. For each increase of one point in verbal and performance IQ score, the chance of being higher educated was 1.164 odds (β 0.152, p 0.001, 95% CI: 1.068–1.268) and 1.127 odds (β 0.120, $p < 0.001$, 95% CI: 1.054–1.206) respectively when controlled for externalizing problems and age at which the adolescent started GAHT. Gender was not found to be an effect modifier in the association between total, verbal, performance IQ and educational achievement.

Discussion

The current study on the association between pre-treatment IQ and educational achievement after gender-affirming treatment in transgender adolescents found a strong correlation (Nagelkerke R = 0.71) between pre-treatment IQ and post-treatment (PS, GAHT and gender-affirming surgery) educational achievement after a mean duration of 7.6 years. The association was linear, for each increase of one point in total IQ, the chance of being higher educated increased with 1.170 odds.

The positive correlation between pre-treatment IQ (mean age 12.78 years) and post-treatment educational achievement (mean age 20.40 years) that was found in our sample seems similar to the correlation between IQ at young age and educational achievement later in life in the general

population. A meta-analysis that included results from 20 studies with 26,504 participants with an average age of less than 19 years at testing intelligence and an age of over 29 years at the measurement of education, found a correlation of 0.49 (Strenze, 2007). The correlation found in the aforementioned study on the relationship between IQ measured at the age of 11 years and educational achievement measured at the age of 16 years in more than 70,000 English children was even higher: 0.81 (Deary et al., 2007). The comparability of the correlation of IQ and educational achievement between transgender young adults who had received medical affirmative treatment including PS followed by GAHT and the general population thus may suggest that the treatment with PS followed by GAHT in transgender adolescents has not (conspicuously) affected the relation between their IQ and their educational achievement.

Another finding from this study that may suggest that treatment with PS followed by GAHT in transgender adolescents did not noticeably influence the relationship between their cognitive ability and their educational achievement is the fact that the mean of respectively total IQ, verbal IQ and performance IQ of the participating adolescents is almost similar to the general Dutch population according to Statistics Netherlands (Centraal Bureau voor de Statistiek, 2019) whereas their educational achievement was on average higher. In our study, 51.4% of the participants was higher educated compared to 35.5% in the general Dutch population of the age of 15–25 years (Centraal Bureau voor de Statistiek, 2019). One explanation could be that the transgender adolescents in this study were positively stimulated by the psychological counselling they received, so they ended up with more intrinsic motivation to achieve their (educational) goals than cisgender adolescents. After all, these adolescents received psychological support as part of their gender-affirming treatment trajectory for years and their psychosocial and school development was regularly evaluated and when necessary support was organized.

Limitations in this study were the lack of a control group, the small sample size ($N = 72$) and the heterogeneous study population (e.g. age, treatment duration). In addition, since the demographic characteristics of our sample and the methods used to examine IQ and educational achievement were not similar to the studies that have examined this association in the general population, the comparison of the results of these studies should be interpreted with caution. Furthermore, the fact that the adolescents included in this study were on average younger (mean age 13.77 years) when they started PS than adolescents who did not participate (mean age 14.43 years), raises the question of whether these results also apply to adolescents who begin this treatment at an older age (e.g. above the age of 14 or 15 years). In addition, this study had only two measurement points and could therefore not differentiate effects from either PS or GAHT alone. Furthermore, all participants in this study had gender-affirming surgery so the results may not be representative for people who chose not to have gender-affirming surgery. Finally, neurocognitive skills that develop specifically during adolescence like social-emotional processing, executive functioning, risk and reward processing, were not measured in the current study (Chen et al., 2020).

Future studies should use a greater sample size, make use of an age-matched control group and take a longer follow-up including more frequent measurements of IQ and examining effects on executive and neurocognitive functioning (Chen et al., 2020). To investigate which effects are related to which part of treatment, studies focussing specifically on PS, similar studies focussing on only GAHT and studies focussing on the combination of both should be conducted. Future studies should therefore use more time points (at least three) and use measures that better capture neurodevelopmental effects of PS and GAHT on neurocognitive development during adolescence, for example, regarding social-emotional processing, executive functioning, risk and reward processing, possibly including MRI studies (Chen et al., 2020).

Conclusion

In transgender young adults starting early treatment in adolescence with PS and subsequent GAHT and affirming surgeries, the correlation between pre-treatment IQ at young age and post-treatment educational achievement in young adulthood found in this study seems to be comparable to the general population. Although further research is indicated to clarify the exact effects of treatment with PS and GAHT on neurodevelopment, these results are reassuring in the sense that gender-affirming medical treatment including PS does not seem to negatively affect the association between IQ and educational achievement.

Abbreviations

TIQ = total IQ, PIQ = performance IQ, VIQ = verbal IQ.

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Contributors' Statement Page

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References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). American Psychiatric Publishing, text rev.

Anacker, C., Sydnor, E., Chen, B. K., LaGamma, C. C., McGowan, J. C., Mastrodonato, A., Hunsberger, H. C., Shores, R., Dixon, R. S., McEwen, B. S., Byne, W., Meyer-Bahlburg, H., Bockting, W., Ehrhardt, A. A., & Denny, C. A. (2021). Behavioral and neurobiological effects of GnRH agonist treatment in mice-potential implications for puberty suppression in transgender individuals. *Neuropsychopharmacology*, *46*(5), 882–890. https://doi.org/10.1038/s41386-020-00826-1

Centraal Bureau voor de Statistiek. (2019). Bevolking; onderwijsniveau; geslacht, leeftijd en migratieachtergrond. Centraal Bureau voor de Statistiek. https://statline.cbs.nl/StatWeb/publication/?VW = T&DM = SLnl&PA = 82275NE D&LA = nl. (Accessed 20 April 2019).

Chen, D., Strang, J. F., Kolbuck, V. D., Rosenthal, S. M., Wallen, K., Waber, D. P., Steinberg, L., Sisk, C. L., Ross, J., Paus, T., Mueller, S. C., McCarthy, M. M., Micevych, P. E., Martin, C. L., Kreukels, B., Kenworthy, L., Herting, M. M., Herlitz, A., Haraldsen, I., Dahl, R., & Garofalo, R. (2020). Consensus Parameter: Research methodologies to evaluate neurodevelopmental effects of pubertal suppression in transgender youth. *Transgender health*, *5*(4), 246–257. https://doi.org/10.1089/trgh.2020.0006

Costa, R., Carmichael, P., & Colizzi, M. (2016). To treat or not to treat: Puberty suppression in childhood-onset gender dysphoria. *Nature Reviews Urology*, *13*(8), 456–462. https://doi. org/10.1038/nrurol.2016.128

de Vries, A. L. C., McGuire, J. K, Steensma, T. D., Wagenaar, E. C. F., Doreleijers, T. A. H., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*, *134*(4), 696- 704. https://doi.org/10.1542/peds.2013-2958

Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence*, *35*(1), 13-21. https://doi.org/10.1016/j.intell.2006.02.001

Epstein, N. B., Baldwin, L. M., & Bishop, D. S. (1983). The McMaster family assessment device. *Journal of Marital and Family Therapy*, *9*(2), 171-180. https://doi.org/10.1111/j.1752-0606.1983.tb01497.x

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *102*(11), 3869-3903. https://doi.org/10.1210/jc.2017-01658

Hough, D., Bellingham, M., Haraldsen, I. R., McLaughlin, M., Robinson, J. E., Solbakk, A. K., & Evans, N. P. (2017). A reduction in long-term spatial memory persists after discontinuation of peripubertal GnRH agonist treatment in sheep. *Psychoneuroendocrinology*, *77*, 1–8. https://doi.org/10.1016/j.psyneuen.2016.11.029

Israel, G. D., Beaulieu, L. J., & Hartless, G. (2001). The influence of family and community social capital on educational achievement. *Rural Sociology*, *66*(1), 43–68. https://doi.org/10.1.1.66.7676

Laidlaw, M. K., Van Meter, Q. L., Hruz, P. W., Van Mol, A., & Malone, W. J. (2019). Letter to the Editor: "Endocrine treatment of gender-dysphoric/gender- incongruent persons: An endocrine society clinical practice guideline". *The Journal of Clinical Endocrinology & Metabolism*, *104*(3), 686–687. https://doi.org/10.1210/jc.2018-01925

Loe, I. M., & Feldman, H. M. (2007). Academic and educational outcomes of children with ADHD. *Ambulatory Pediatrics*, *7*(1 Suppl), 82–90. https://doi.org/10.1016/j.ambp.2006.05.005

Mahfouda, S., Moore, J. K., Siafarikas, A., Zepf, F. D., & Lin, A. (2017). Puberty suppression in transgender children and adolescents. *Lancet Diabetes Endocrinology*, *5*(10), 816-826. https://doi.org/10.1016/S22138587(17)30099-2

Mul, D., Versluis-den Bieman, H. J., Slijper, F. M., Oostdijk, W., Waelkens, J. J., & Drop, S. L. (2001). Psychological assessments before and after treatment of early puberty in adopted children. *Acta Paediatrica*, *90*(9), 965–971. https://doi.org/10.1080/080352501316978011

Richards, C., Maxwell, J., & McCune, N. (2019). Use of puberty blockers for gender dysphoria: A momentous step in the dark. *Archives of Disease in Childhood*, *104*(6), 611-612. http://doi.org/10.1136/archdischild-2018-315881

Rothon, C., Head, J., Clark, C., Klineberg, E., Cattell, V., & Stansfeld, S. (2009). The impact of psychological distress on the educational achievement of adolescents at the end of compulsory education. *Social Psychiatry and Psychiatric Epidemiology*, *44*(5), 421–427. https://doi.org/10.1007/s00127-008-0452-8

Sternberg, R. J., Grigorenko, E. L., & Bundy, D. A. (2001). The predictive value of IQ. *Merrill-Palmer Q*, *47*(1), 1–41. https://doi.org/10.1353/mpq.2001.0005

Strenze, T. (2007). Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence*, *35*(5), 401–426. https://doi.org/10.1016/j.intell.2006.09.004

van den Bos, W., Crone, E. A., & Güroğlu, B. (2012). Brain function during probabilistic learning in relation to IQ and level of education. *Developmental Cognitive Neuroscience*, *2*(Suppl 1), S78–S89. https://doi.org/10.1016/j.dcn.2011.09.007

Verhulst, F. C., Van Der Ende, J., & Koot, H. M. (1996). Handleiding voor de CBCL/4-18. Rotterdam: Afdeling Kinder- en jeugdpsychiatrie, Sophia Kinderziekenhuis/Academisch Ziekenhuis Rotterdam/Erasmus Universiteit Rotterdam.

Verhulst, F. C., Van Der Ende, J., & Koot, H. M. (1997). Handleiding voor de Youth self-report (YSR). Rotterdam: Afdeling Kinder- en jeugdpsychiatrie, Sophia Kinderziekenhuis/Academisch Ziekenhuis Rotterdam/Erasmus Universiteit Rotterdam.

Wechsler, D. (1997). Wechsler adult intelligence scale (WAIS-III) (3rd ed.). Dutch version. Swets and Zetlinger.

Wechsler, D., Kort, W., Compaan, E. L., Bleichrodt, N., Resing, W. C. M., & Schittkatte, M. (2002). Wechsler intelligence scale for children (WISC-III). 3rd ed. : Swets and Zetlinger.

Wojniusz, S., Callens, N., Sütterlin, S., Andersson, S., De Schepper, J., Gies, I., Vanbesien, J., De Waele, K., Van Aken, S., Craen, M., Vögele, C., Cools, M., & Haraldsen, I. R. (2016). Cognitive, emotional, and psychosocial functioning of girls treated with pharmacological puberty blockage for idiopathic central precocious puberty. *Frontiers in Psychology*, *7*, 1053. https://doi.org/10.3389/fpsyg.2016.01053

Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation

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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.

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Dr Turban conceptualized and designed the study, drafted the initial manuscript, and incorporated all revisions and comments; Ms King conducted statistical analyses and reviewed and revised the manuscript for important intellectual content, with a focus on statistical aspects of the manuscript; Dr Carswell assisted in the design of the study and in interpretation of the data analyses and critically reviewed and revised the manuscript for important intellectual content, with a focus on relevant clinical endocrinology; Dr Keuroghlian supervised and contributed to the conceptualization and design of the study and the design of the statistical analyses and reviewed and revised the manuscript for important intellectual content as it relates to mental health considerations for transgender people; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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WHAT'S KNOWN ON THIS SUBJECT: Gonadotropin-releasing hormone analogues are commonly used to suppress endogenous puberty for transgender adolescents. Small studies have revealed that pubertal suppression results in favorable mental health outcomes. No studies to date have examined associations between pubertal suppression and suicidality.

WHAT THIS STUDY ADDS: In this study, using the largest survey of transgender adults to date, we show that access to pubertal suppression during adolescence is associated with lower odds of lifetime suicidal ideation among transgender young adults.

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According to the Centers for Disease Control and Prevention's Youth Risk Behavior Surveillance System, ~1.8% of adolescents in the United States identify as transgender.[1] These youth suffer mental health disparities that include higher rates of internalizing psychopathology (ie, anxiety and depression) and suicidality, theorized to be due to a combination of dysphoria toward their bodies and minority stress.[2–5] In a large study of transgender adults in the United States, 40% endorsed a lifetime suicide attempt.[6]

Over the past 2 decades, protocols have been developed to provide transgender adolescents with gender-affirming medical interventions that align their bodies with their gender identities. Most prominent among these are the Endocrine Society guidelines[7] and the World Professional Association for Transgender Health (WPATH) Standards of Care.[8] Both sets of guidelines recommend that transgender adolescents be offered gonadotropin-releasing hormone analogues (GnRHas), colloquially referred to as "puberty blockers," once they reach Tanner 2 of puberty. These medications are provided as subcutaneous implants or are administered as either 1- or 3-month depot injections. GnRHa therapy effectively halts the production of gonadal sex steroids (testosterone and estrogen) by persistently activating and thereby desensitizing the gonadotropin-releasing hormone receptor, which in turn leads to suppression of luteinizing hormone and follicle-stimulating hormone release from the anterior pituitary gland.[9] This process inhibits endogenous puberty for the duration of GnRHa use. Once further pubertal development is delayed, youth are able to explore gender identities without the pressure of dysphoria associated with gender-incongruent physical development.[10] GnRHa therapy is unique among gender-affirming medical interventions in that the resultant pubertal suppression is fully reversible, with the resumption of endogenous puberty after their discontinuation.[7,8]

Since the publication of the WPATH Standards of Care and the Endocrine Society guidelines, the use of pubertal suppression for transgender youth has become more common in the United States[9] There are limited data, however, regarding the mental health outcomes of pubertal suppression. To date, there have been 2 published studies in which the effects of this treatment on the mental health of transgender youth were examined. In the first study, the authors assessed changes in mental health among 55 Dutch adolescents who received pubertal suppression.[11] This study, which notably lacked a control group, revealed that internalizing psychopathology improved after treatment with pubertal suppression. In the second study, researchers followed a group of 201 adolescents with gender dysphoria and found that those who received pubertal suppression in addition to psychological support (n = 101) had superior global functioning, measured by the Children's Global Assessment Scale, when compared with those who received psychological support alone (n = 100).[12]

In the current study, we use the largest survey of transgender people to date, a community-recruited sample of transgender adults in the United States, to conduct the first-ever investigation into associations between pubertal suppression and suicidality.

Transgender youth present to clinicians with a range of concerns. Some have minimal body dysphoria and do not desire pubertal suppression, whereas others report significant dysphoria around the physical changes related to puberty. Because not all transgender and gender-diverse youth desire medical interventions, we examined only those youth who desired pubertal suppression because these are the young people who would present to care and for whom clinicians would need to decide about whether to initiate pubertal suppression. We specifically examined measures of past-year suicidality, lifetime suicidality, past-month severe psychological distress, past-month binge drinking, and lifetime illicit drug use. We hypothesized that among those who wanted pubertal suppression, those who received it would have superior mental health outcomes when compared with those who wanted but did not receive it.

METHODS

Study Design and Data Source

The 2015 US Transgender Survey (USTS) was conducted over a 1-month period in 2015 by the National Center for Transgender Equality (NCTE). It is, to our knowledge, the largest existing data set of transgender adults and includes data regarding demographics, past gender-affirming medical treatment, family support, and mental health outcomes. Participants were recruited through community outreach in collaboration with >400 lesbian, gay, bisexual, and transgender organizations and were provided with a Web address to complete the survey online. Details regarding outreach efforts are further described in the NCTE report on the survey.[6] The USTS protocol was approved by the University of California, Los Angeles Institutional Review Board. For the purposes of the current study, data were obtained via a data-sharing agreement with the NCTE, and the current protocol was reviewed by The Fenway Institute

Institutional Review Board and determined to not comprise human subjects research.

Study Population

The USTS data set contains responses from 27 715 US transgender adults, with respondents from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. Given that pubertal suppression for transgender youth was not available in the United States until 1998,[4] only participants who were 17 or younger in 1998 would have had health care access to GnRHa for pubertal suppression. We thus restricted the analysis to participants who were 36 or younger at the time of the survey, resulting in a sample of 20 619 participants. Data were further restricted to those who selected "puberty blocking hormones (usually used by youth ages 9–16)" in response to the question "Have you ever wanted any of the health care listed below for your gender identity or gender transition? (Mark all that apply)." Response options for this question were "counseling/therapy," "hormone treatment/HRT," "puberty blocking hormones (usually used by youth ages 9–16)," or "none of the above." This resulted in a sample of 3494 individuals between the ages of 18 and 36 who ever wanted pubertal suppression as part of their gender-affirming medical care.

Exposures

Exposure to pubertal suppression was defined as selecting "puberty blocking hormones (usually used by youth ages 9–16)" in response to the question "Have you ever had any of the health care listed below for your gender identity or gender transition? (Mark all that apply)." Response options for this question were "counseling/therapy," "hormone treatment/HRT," "puberty blocking hormones (usually used by youth ages 9–16)," and "none of the above." Participants who reported having pubertal suppression were also asked, "At what age did you begin taking Puberty Blocking Hormones?" Those who reported beginning treatment after age 17 were excluded to only include participants who likely had pubertal suppression during active endogenous puberty. The vast majority of adolescents would have reached Tanner 5, the final stage of puberty, by age 17.[13,14]

Outcomes

Comparing those who received pubertal suppression with those who did not, we examined past-month severe psychological distress (defined as a score of ≥13 on the Kessler Psychological Distress Scale [K6], a cutoff previously validated among US adults[15]), past-month binge drinking (operationalized as drinking ≥5 standard alcoholic beverages during 1 occasion; the rationale for this threshold when studying alcohol use among transgender people has been discussed previously[16]), lifetime illicit drug use (not including marijuana), past-year suicidal ideation, past-year suicidal ideation with a plan, past-year suicide attempts, past-year suicide attempts resulting in inpatient care, lifetime suicidal ideation, and lifetime suicide attempts.

Control Variables

Demographic variables collected included age, age of social transition, age of initiation of gender-affirming hormone therapy, current gender identity, sex assigned at birth, sexual orientation, race, education level, employment status, relationship status, total household income at the time of data collection in 2015, family support for gender identity, and current hormone treatment.

Statistical Analysis

Data were analyzed by using SPSS software version 25 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Descriptive statistics were conducted and are presented as frequency (percentage) or mean (SD). Analysis of variance and χ^2 tests were used to assess significance by age, gender identity, sex assigned at birth, race, education level, employment status, relationship status, total household income, family support for gender identity, and current hormone treatment between those who received pubertal suppression and those who did not. We used univariate logistic regression to examine associations between receiving pubertal suppression and each mental health outcome, as well as between age and both ever wanting and receiving pubertal suppression. $P < .05$ defined statistical significance. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with level of family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide attempts were associated with gender identity, and this model was therefore additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and therefore models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts; therefore models were therefore additionally adjusted for race.

RESULTS

Of the 20 619 survey respondents 18 to 36 years of age, 3494 (16.9%) reported that they had ever wanted pubertal suppression. Of those who wanted pubertal suppression, only 89 (2.5%) had

received this treatment. The following variables were found to be associated with those who wanted and received pubertal suppression compared with those who wanted pubertal suppression but did not receive it: younger age, age of social transition, age of initiation of hormone therapy, feminine gender identity, male sex assigned at birth, heterosexual sexual orientation, higher total household income, and greater family support of gender identity (Table 1).

In univariate analyses, when comparing those who received pubertal suppression with those who did not, receiving pubertal suppression was associated with decreased odds of past-year suicidal ideation, lifetime suicidal ideation, and past-month severe psychological distress (Table 2). After controlling for demographic variables from Table 1, pubertal suppression was associated with decreased odds of lifetime suicidal ideation. Raw

TABLE 1 Sample Demographics

		Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?			
	All (N = 3494)	Yes (n = 89; 2.5%)	No (n = 3405; 97.5%)	F	P
n (%) n (%) n (%)					
Age	23.4 (5.0)	21.7 (4.7)	23.4 (5.0)	10.3	.001*
Age of social transition	20.0 (5.5)	15.2 (4.5)	20.1 (5.5)	67.5	<.001*
Age began hormone therapy	22.1 (4.5)	15.7 (2.4)	22.5 (4.3)	217.4	<.001*
Gender identity				25.5[a]	<.001*
Woman		23 (25.8)	617 (18.2)		
Man		19 (21.3)	383 (11.3)		
Transgender woman		25 (28.1)	720 (21.3)		
Transgender man		16 (18.0)	795 (23.5)		
Nonbinary or genderqueer		6 (6.7)	866 (25.6)		
Sex assigned at birth				4.4[a]	.04*
Female		39 (43.8)	1874 (55.0)		
Male		50 (56.2)	1531 (45.0)		
Sexual orientation				36.5[a]	<.001*
Heterosexual or straight		27 (30.3)	350 (10.3)		
Asexual		9 (10.1)	437 (12.8)		
Pansexual or queer		36 (40.4)	1784 (52.4)		
Gay or lesbian		12 (13.5)	539 (15.8)		
Not listed		5 (5.6)	295 (8.7)		
Race, n (%)				3.5[a]	.06
Racial minority		28 (31.5)	782 (23.0)		
Not racial minority (white or European American)		61 (68.5)	2623 (77.0)		
Education level				2.9[a]	.41
Less than high school		9 (10.1)	220 (6.5)		
High school graduate or GED		20 (22.5)	683 (20.1)		
Some college or associate degree		39 (43.8)	1729 (50.8)		
Bachelor's degree or higher		21 (23.6)	773 (22.7)		
Employment status				0.6[a]	.45
Employed		51 (79.7)	1976 (75.6)		
Unemployed		13 (20.3)	638 (24.4)		
Relationship status				0.5[a]	.47
Partnered		35 (40.2)	1447 (44.1)		
Unpartnered		52 (59.8)	1834 (55.9)		
Total household income, $				21.9[a]	<.001*
<25 000		21 (26.3)	1153 (38.3)		
25 000–49 999		13 (16.3)	652 (21.7)		
50 000–99 000		14 (17.5)	630 (20.9)		
>100 000		32 (40.0)	574 (19.1)		
Family support for gender identity					
Supportive		71 (81.6)	1551 (55.8)	24.3[a]	<.001*
Neutral		11 (12.6)	573 (20.6)		
Unsupportive		5 (5.7)	658 (23.7)		
Current hormone treatment		87 (97.8)	1617 (96.3)	0.5[a]	.48

Descriptive statistics for transgender adults in the United States who ever wanted pubertal suppression for their gender identity or gender transition when comparing those who received this treatment with those who did not receive this treatment (total N = 3494). Percentages were calculated from the total of nonmissing values.

*Indicates statistical significance.

[a] χ^2.

TABLE 2 Mental Health Outcomes Among Those Who Received Pubertal Suppression

	Univariate Analyses		Multivariable Analyses	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Suicidality, past 12 mo				
Ideation	0.6 (0.4–0.8)	.006*	0.6 (0.3–1.1)	0.09
Ideation with plan	0.9 (0.5–1.6)	.73		
Ideation with plan and attempt	1.2 (0.6–2.3)	.64		
Attempt resulting in inpatient care	2.8 (0.8–9.4)	.09		
Suicidality, lifetime				
Ideation	0.3 (0.2–0.5)	<.001*	0.3 (0.2–0.6)	0.001*
Attempts	0.7 (0.4–1.0)	.08		
Mental health and substance use				
Past-month severe psychological distress, K6 ≥13	0.5 (0.3–0.8)	.001*	0.8 (0.4–1.4)	0.38
Past-month binge drinking	1.3 (0.8–2.0)	.29		
Lifetime illicit drug use	1.1 (0.7–1.8)	.67		

Univariate and multivariable analyses of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression when comparing those who received this treatment with those who did not. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide attempts were associated with gender identity, and this model was additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and thus these models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts, and thus these models were additionally adjusted for race. Models for psychological distress and past-year suicidal ideation were also adjusted for age, gender identity, and relationship status. aOR, adjusted odds ratio.

[a] Indicates statistical significance.

frequency outcomes are presented in Table 3.

To examine associations between age, ever wanting, and ever receiving pubertal suppression, we divided participants into 2 age groups with the cutoff point at the median, 18 to 22 and 23 to 36, in light of the skewed distribution of age.[17] The younger age group had increased odds both of ever wanting pubertal suppression (odds ratio [OR] = 1.4, $P < .001$, 95% confidence interval [CI]: 1.3–3.5) and of receiving pubertal suppression (OR = 2.1, $P = .001$, 95% CI: 1.4–3.4).

Among those who had ever received pubertal suppression, 60% reported traveling <25 miles for gender-affirming health care, 29% traveled between 25 and 100 miles, and 11% traveled >100 miles.

TABLE 3 Raw Frequencies of Outcome Variables

	Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?	
	Yes (*n* = 89; 2.5%)	No (*n* = 3405; 97.5%)
	n (%)	*n* (%)
Suicidality (past 12 mo)		
Ideation	45 (50.6)	2204 (64.8)
Ideation with plan	25 (55.6)	1281 (58.2)
Ideation with plan and attempt	11 (24.4)	473 (21.5)
Attempt resulting in inpatient care	5 (45.5)	108 (22.8)
Suicidality (lifetime)		
Ideation	67 (75.3)	3062 (90.2)
Attempts	37 (41.6)	1738 (51.2)
Mental health and substance use		
Past-month severe psychological distress (K6 ≥13)	32 (37.2)	1847 (55.1)
Past-month binge drinking	26 (29.2)	825 (24.3)
Lifetime illicit drug use	24 (27.3)	850 (25.3)

Raw frequencies of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression. Percentages were calculated from the total of nonmissing values.

DISCUSSION

This study is the first in which the association between access to pubertal suppression and measures of suicidality is examined. Treatment with pubertal suppression among those who wanted it was associated with lower odds of lifetime suicidal ideation when compared with those who wanted pubertal suppression but did not receive it. Suicidality is of particular concern for this population because the estimated lifetime prevalence of suicide attempts among transgender people is as high as 40%.[6] Approximately 9 of 10 transgender adults who wanted pubertal suppression but did not receive it endorsed lifetime suicidal ideation in the current study (Table 3). Access to pubertal suppression was associated with male sex assignment at birth, heterosexual sexual orientation, higher total household income, and higher level of family support for gender identity.

Results from this study suggest that the majority of transgender adults in the United States who have wanted pubertal suppression did not receive it. Of surveyed transgender adults in

the current study, 16.9% reported ever desiring pubertal suppression as part of their gender-related care; however, only 2.5% of these respondents indicated they had in fact received this wanted treatment. This was the case even for the youngest survey respondents, who were 18 years old at the time of data collection in 2015. Only 4.7% of 18-year-olds who wanted the treatment reported receiving it.

Although rates both of desiring and of receiving pubertal suppression were higher among younger respondents, results from the current study indicate that still only 29.2% of the youngest participants in the study (ie, those who were 18 years of age in the year 2015) reported ever desiring pubertal suppression as part of gender-related care. No individuals <18 years of age were captured by this data set; future research should investigate the rate of desiring pubertal suppression among younger populations. Some respondents may have simply never been aware of the possibility of puberty suppression while still within the range of developmentally suitable candidates for receiving this treatment, or they may have believed that they were not suitable candidates. This finding may also reflect the diversity of experience among transgender and gender-diverse people, highlighting that not all will want every type of gender-affirming intervention.[7,8] Future research is needed to understand why younger participants reported desiring pubertal suppression at higher rates; we hypothesize that this is likely due in part to recent increased public awareness about and access to gender-affirming interventions.[5]

Access to pubertal suppression was associated with a greater total household income. Without insurance, the annual cost of GnRHa therapy ranges from $4000 to $25 000.[18] Among adolescents treated with pubertal suppression at the Boston Children's Hospital Gender Management Service before 2012, <20% obtained insurance coverage.[19] More recently, insurance coverage for these medications has increased: a study from 2 academic medical centers in 2015 revealed that insurance covered the cost of GnRHa therapy in 72% of cases.[18] This is 1 potential explanation for why younger age was found to be associated with accessing pubertal suppression in the current study (Table 1). It is also plausible that those who receive pubertal suppression experience more improvement in mental health, which in turn may contribute to greater socioeconomic advancement.[20] This study's cross-sectional design limits further interpretation.

Participants who endorsed a heterosexual sexual orientation were more likely to have received pubertal suppression. This is in line with past research revealing that nonheterosexual transgender people are less likely to access gender-affirming surgical interventions.[21] Some clinicians may be biased against administering pubertal suppression to patients whose sexual orientation identities do not align with society's heteronormative assumptions.[21] In the current study, nonbinary and genderqueer respondents were also less likely to have accessed pubertal suppression, suggesting that clinicians may additionally be uncomfortable with delivering this treatment to patients whose gender identities defy more traditional binary categorization. Of note, because research on gender-affirming hormonal interventions for adolescents has been focused on transgender youth with binary gender identities,[11] some clinicians have reservations about prescribing pubertal suppression interventions to nonbinary youth in the event of a potentially prolonged state of low sex-steroid milieu.

Family support was also associated with receiving pubertal suppression among those who wanted this treatment. This finding is unsurprising given that most states require parental consent for adolescents to receive pubertal suppression.[22] Past studies have revealed that family support of gender identity is associated with favorable mental health outcomes.[6] Of note, treatment with pubertal suppression in the current study was associated with lower odds of lifetime suicidal ideation, even after adjustment for family support (Table 2).

We did not detect a difference in the odds of lifetime or past-year suicide attempts or attempts resulting in hospitalization. It is possible that we were underpowered to detect these differences given that suicide attempt items were less frequently endorsed than suicidal ideation items (Table 3). Given this study's retrospective self-report survey design, we were unable to capture information regarding completed suicides, which may have also reduced the number of suicide attempts we were able to account for. Given that suicidal ideation alone is a known predictor of future suicide attempts and deaths from suicide, the current results warrant particular concern.[23]

This study adds to the existing literature[11,12] on the relationship of pubertal suppression to favorable mental health outcomes. The theoretical basis for these improved mental health outcomes is that pubertal suppression prevents irreversible, gender-noncongruent changes that result from endogenous puberty (eg, bone structure, voice changes, breast development, and body hair growth) and that may cause significant distress among transgender youth. Pubertal suppression allows these adolescents more time to decide if they wish to either induce exogenous gender-congruent puberty or allow

endogenous puberty to progress.[7,8] Some have also theorized that gender-affirming medical care may have mental health benefits that are separate from its physical effects because it provides implied affirmation of gender identity from clinicians, which may in turn buffer against minority stress.[24]

Strengths of this study include its large sample size and representation of a broad geographic area of the United States. It is the first study in which associations between pubertal suppression for transgender youth and suicidality are examined. Limitations include the study's cross-sectional design, which does not allow for determination of causation. Longitudinal clinical trials are needed to better understand the efficacy of pubertal suppression. Because the 2015 USTS data do not contain the relevant variables, we were unable to examine associations between access to pubertal suppression and degree of body dysphoria in this study. Notably, past studies have revealed that body image difficulties persist through pubertal suppression and remit only after administration of gender-affirming hormone therapy with estrogen or testosterone.[11] It is also limited by its nonprobability sample design. Future researchers should work toward the collection of population-based survey data that include variables related to gender-affirming medical interventions. Of note, because pubertal suppression for transgender youth is a relatively recent intervention, some participants might not have known that these interventions existed and thus would not have reported ever wanting them. Had these individuals known about pubertal suppression, it is possible that they might have desired it. Because we do not have data on whether individuals who did not desire pubertal suppression would have wanted it had they known about it, we restricted our analysis to those who reported ever desiring pubertal suppression. Reverse causation cannot be ruled out: it is plausible that those without suicidal ideation had better mental health when seeking care and thus were more likely to be considered eligible for pubertal suppression. The Endocrine Society guidelines for pubertal suppression eligibility recommend that other mental health concerns be "reasonably well controlled."[7] Because this study includes only adults who identify as transgender, it does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender. Notably, however, a recent study from the Netherlands of 812 adolescents with gender dysphoria revealed that only 1.9% of adolescents who initiated pubertal suppression discontinued this treatment without proceeding to gender-affirming hormone therapy with estrogen or testosterone.[25]

CONCLUSIONS

Among transgender adults in the United States who have wanted pubertal suppression, access to this treatment is associated with lower odds of lifetime suicidal ideation. This study strengthens recommendations by the Endocrine Society and WPATH for this treatment to be made available for transgender adolescents who want it.

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ABBREVIATIONS

CI: confidence interval
GnRHa: gonadotropin-releasing hormone analogue
K6: Kessler Psychological Distress Scale
NCTE: National Center for Transgender Equality
OR: odds ratio
USTS: US Transgender Survey
WPATH: World Professional Association for Transgender Health

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REFERENCES

1. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students - 19 states and large urban school districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(3):67–71
2. 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
3. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender Dysphoria. *J Adolesc Health*. 2015;57(4):374–380
4. 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
5. Turban JL, Ehrensaft D. Research Review: gender identity in youth: treatment paradigms and controversies. *J Child Psychol Psychiatry*. 2018;59(12):1228–1243
6. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anafi M. *The Report of the 2015 U.S. Transgender Survey*. Washington, DC: National Center for Transgender Equality; 2016
7. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline [published corrections appear in *J Clin Endocrinol Metab*. 2018;103(2):699 and in *J Clin Endocrinol Metab*. 2018;103(7):2758–2759]. *J Clin Endocrinol Metab*. 2017;102(11):3869–3903
8. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgend*. 2012;13(4):165–232
9. 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
10. 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
11. 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
12. 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
13. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–512
14. Herman-Giddens ME, Steffes J, Harris D, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. *Pediatrics*. 2012;130(5). Available at: www.pediatrics.org/cgi/content/full/130/5/e1058
15. 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):4–22
16. Gilbert PA, Pass LE, Keuroghlian AS, Greenfield TK, Reisner SL. Alcohol research with transgender populations: a systematic review and recommendations to strengthen future studies. *Drug Alcohol Depend*. 2018;186:138–146
17. Maxwell SE, Delaney HD. Bivariate median splits and spurious statistical significance. *Psychol Bull*. 1993;113(1):181–190
18. Stevens J, Gomez-Lobo V, Pine-Twaddell E. Insurance coverage of puberty blocker therapies for transgender youth. *Pediatrics*. 2015;136(6):1029–1031
19. Hartocollis A. The new girl in school: transgender surgery at 18. *The New York Times*. June 16, 2015. Available at: https://www.nytimes.com/2015/06/17/nyregion/transgender-minors-gender-reassignment-surgery.html. Accessed December 18, 2019
20. Meyer IH, Brown TN, Herman JL, Reisner SL, Bockting WO. Demographic characteristics and health status of transgender adults in select US regions: Behavioral Risk Factor Surveillance System, 2014. *Am J Public Health*. 2017;107(4):582–589
21. Beckwith N, Reisner SL, Zaslow S, Mayer KH, Keuroghlian AS. Factors associated with gender-affirming surgery and age of hormone therapy initiation among transgender adults. *Transgend Health*. 2017;2(1):156–164
22. Puckett JA, Cleary P, Rossman K, Newcomb ME, Mustanski B. Barriers to gender-affirming care for transgender and gender nonconforming individuals. *Sex Res Social Policy*. 2018;15(1):48–59
23. Rossom RC, Coleman KJ, Ahmedani BK, et al. Suicidal ideation reported on the PHQ9 and risk of suicidal behavior across age groups. *J Affect Disord*. 2017;215:77–84
24. Cai X, Hughto JMW, Reisner SL, Pachankis JE, Levy BR. Benefit of gender-affirming medical treatment for transgender elders: later-life alignment of mind and body. *LGBT Health*. 2019;6(1):34–39
25. 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

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Review Article

A systematic review of patient regret after surgery- A common phenomenon in many specialties but rare within gender-affirmation surgery

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A B S T R A C T

Regret after gender-affirming surgery (GAS) is a complex issue. Comparing regret after GAS to regret after plastic surgery operations and other major life decisions is a novel approach that can provide insight into the magnitude of this issue.

A systematic review of three databases was conducted to investigate regret after common plastic surgery operations. Three separate literature reviews on regret after GAS, regret after elective operations, and regret after major life decisions were performed.

A total of 55 articles examining regret after plastic surgery were included. The percentage of patients reporting regret ranged from 0 to 47.1 % in breast reconstruction, 5.1–9.1 % in breast augmentation, and 10.82–33.3 % in body contouring. In other surgical subspecialties, 30 % of patients experience regret following prostatectomy and up to 19.5 % following bariatric surgery. Rate of regret after GAS is approximately 1 %. Other life decisions, such as having children and getting a tattoo have regret rates of 7 % and 16.2 %, respectively.

When comparing regret after GAS to regret after other surgeries and major life decisions, the percentage of patients experiencing regret is extremely low.

1. Introduction

In the United States, approximately 1.3 million adults self-identify as transgender or gender non-conforming.[1] This represents over 0.5 % of the general population and has increased over time due to more widespread social acceptance and access to gender affirming health care. Gender-affirming surgery (GAS) has been shown to improve quality of life and alleviate gender dysphoria for appropriately selected patients.[2] From 2015 to 2019, the popularity of gender-affirming surgery has exponentially increased by approximately 400 % with improvements in access to care and insurance coverage.[3] While many individuals report satisfaction and improved measures of mental health after undergoing gender affirming surgery, there is a small but vocal minority who experience regret after their procedures.[4] Regret after gender affirming surgery is complex, with significant impact from postoperative complications, unsatisfactory surgical results, unrealistic expectations, continued social stigma and discrimination, and inadequate social support.[5]

Regret is a negative emotion that can be described as "the feeling that the outcome would have been better had one made a different choice."[6] It can be a powerful motivator to either act or not act in medical and non-medical settings. Regret is difficult to assess, as there is not a universally applied tool to measure it. Additionally, most research on regret is retrospective and is therefore impacted by recall bias.[6]

Extensive research has been conducted to explore rates of regret and types of regret after gender affirming surgery. However, there is paucity in comparing the rates of regret after GAS to the rates of regret within plastic surgery, other surgical specialties, and other major life decisions. Importantly, this systematic review does not seek to equate the decision to undergo gender affirming surgery to other elective surgeries or decisions, but instead aims to provide a framework to understand feelings of regret through a broader life experience.

2. Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines, a comprehensive research of several databases from each database's inception to July 12, 2023, was conducted. The databases included PubMed, Scopus, and Web of Science. Search terms were "regret" in addition to the following operations: breast reconstruction, breast reduction, breast augmentation, mastopexy, facelift, neck lift, abdominoplasty, blepharoplasty, brow lift, rhinoplasty, liposuction, thighplasty, and buttock lift. The study selection was performed in a 2-stage screening process (Fig. 1). The first step was conducted by 2 screeners (SMT and AE), who reviewed titles and abstracts and selected those of relevance to the research question. Then, 1 screener

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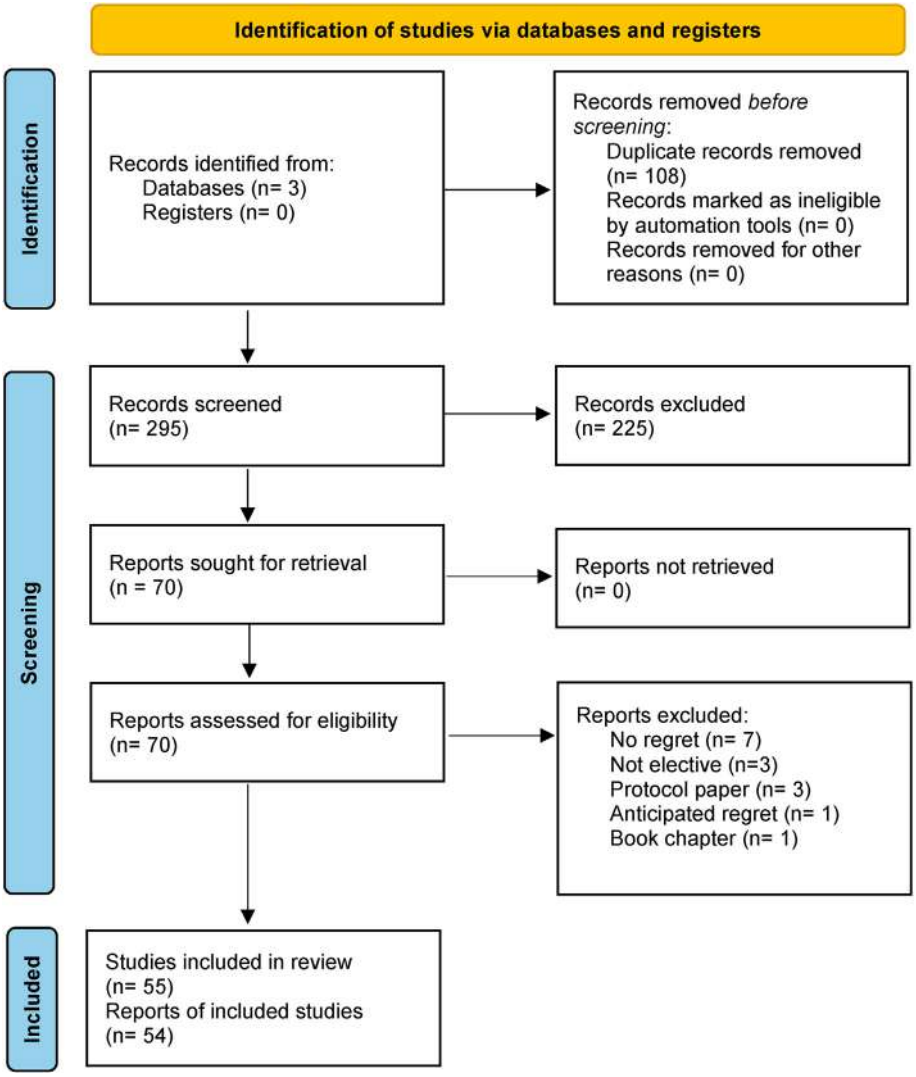

Fig. 1. PRISMA flow diagram for systematic reviews.

(SMT) reviewed full text of the remaining articles and selected those eligible according to the inclusion and exclusion criteria (Fig. 1). Inclusion criteria were all articles that included elective plastic surgery-related operations and patient-reported regret in the English language. Exclusion criteria for studies regarding regret after plastic surgery procedures included articles that did not investigate regret, non-English language articles, systematic reviews, literature reviews, meta-analyses, letters to the editor, and book chapters.

After selecting the articles, we identified which operation was assessed, what scale was used to determine regret, and what patients scored on the scale (mean and standard deviation).

Next, we performed a literature review regarding regret after gender-affirming surgery using the PubMed database with the search terms "regret" and "gender-affirming surgery." Subsequent search terms combined "regret" with terms such as, "surgery", "elective surgery", "sterilization", "weight loss surgery", and "bariatric." Finally, "regret" was combined with various life decisions, including "children", "parenthood", "car", "house", "sex", and "tattoo."

Non-surgical decisional regret proved to be less extensively researched. Our search terms were chosen either due to the large magnitude of the decision itself (e.g., getting married) or the rumored high frequency of regret (e.g., getting a tattoo).

3. Results

3.1. Regret after plastic surgery-related operations

A total of 295 articles were identified in the search. After the first-step screening process, 70 articles were relevant based on the information provided in their titles and abstracts. After the second-step process, a total of 55 articles were included in the systematic review (Fig. 1). Of the included studies investigating post-operative regret, 43 focused on breast reconstruction, four on mastectomy, three on breast augmentation, two on brachioplasty, one on nipple reconstruction, one on breast reduction, two on rhytidectomy, one on adjuvant radiotherapy, one on body contouring, and one on septoplasty (Fig. 2, Fig. 3).

Of the included articles, regret was either reported as a percentage of total respondents reporting regret, a numerical score on the Decision Regret Scale, or was qualitatively assessed.

Percentage of regret after plastic surgery procedure ranged from 0 % to 47.1 % (Supplemental Table 1). The procedures with the lowest percentage of regret were brachioplasty, breast reconstruction, breast augmentation, prophylactic mastectomy, and facelift, with 0 % of patients reporting regret.[7–15] While breast reconstruction was reported to have one of the lowest rates of regret in multiple papers, other research

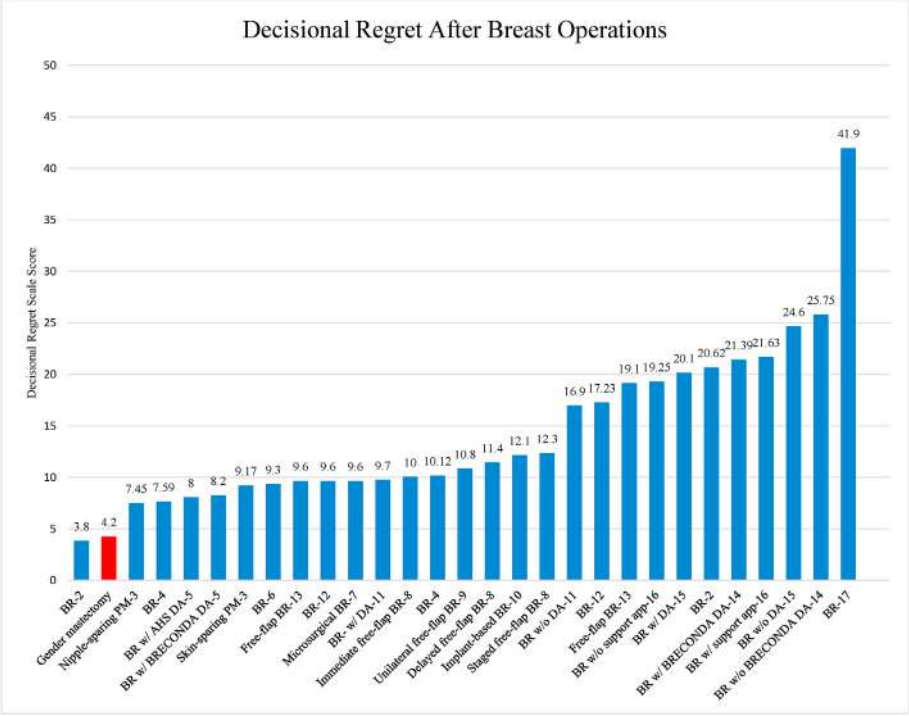

Fig. 2. Decision Regret Scale scores after breast operations. Gender affirming surgery shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

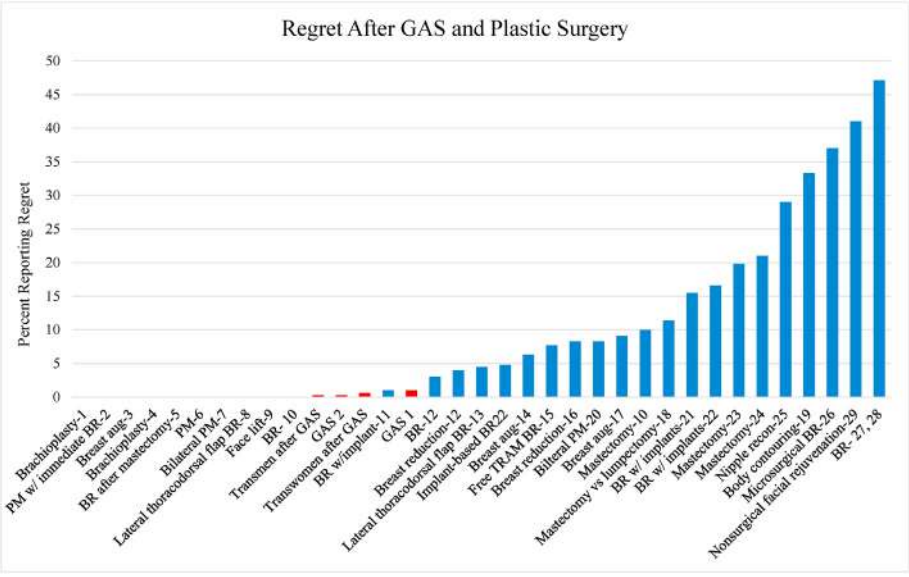

Fig. 3. Percentage of patients reporting regret. Gender affirming surgery shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

into breast reconstruction reported very high levels of regret. In fact, Sheehan et al. report that 27.6 % of patients had mild regret and 19.5 % had moderate to strong regret, resulting in a combined 47.1 % of patients experiencing some form of regret after breast reconstruction.[16]

The Decision Regret Scale contains 5 items that are rated on a 5-point Likert scale.[17] Scores are converted to a 100-point scale, with higher scores corresponding to higher levels of regret. While not used in all papers, the DRS can be broken down into three categories. A score of 0 indicates no regret, a score of 1–25 indicates mild regret, and a score greater than 25 suggests the patient has moderate to severe regret.[18] In this systematic review, a wide range of DRS scores after breast reconstruction was evident, with scores ranging from 3.8 to 41.9 (Supplemental Table 2). DRS scores after rhinologic surgery were the lowest, with mean scores of 0.0 and 5.0 in patient groups who were verbally consented and consented via video, respectively.[19] The highest DRS scores were seen after breast reconstruction, with mean DRS of 41.9.[20] Multiple papers focused on the ability for decision aids used during pre-operative decision making to decrease regret after breast reconstruction and noted significant decreases in reported regret.[21–27]

Lastly, several papers included in the systematic review investigated regret qualitatively, often by interviewing patients (Supplemental Table 3). One patient noted regret after undergoing breast reconstruction

surgery due to the pain and distress she suffered secondary to multiple debridements.[28] Other patients expressed regret after breast reconstruction, wishing that they were engaged in more shared decision-making discussions. One patient stated, "I regret that I didn't have both of them removed at the time. Had I known what I know now … I would've had both breasts removed."[29]

3.2. Regret after gender-affirming surgery

A study performed in Amsterdam retrospectively examined 6,793 patients who attended a gender identity clinic in Amsterdam from 1972 to 2015 and found **0.6 %** and **0.3 %** of transwomen and transmen reported experiencing regret after gender affirming surgery, respectively. The authors noted that reasons for regret could be divided into three categories. True regret was defined as regretting having GAS. Social regret involved losing touch with loved ones or being fired from a job because of GAS. Lastly, some participants reported feeling non-binary and no longer feeling satisfied with their surgical result. Average time to experiencing regret was 130 months (more than 10 years) post-operatively.[30]

In 2021, a systematic review and meta-analysis was completed which assessed 27 studies, including a total of 7,928 transgender individuals. One third of the included individuals underwent transmasculine procedures, while the remaining two thirds underwent transfeminine procedures. Of the 7,928 individuals included in the analysis, **1.0 %** expressed regret. The most common reason for post-operative regret was "difficulty/dissatisfaction in life with the new gender role." Another common reason was failure of surgery to achieve their aesthetic surgical goals. The authors hypothesized that the rate of regret established by this metanalysis was lower than a previously established rate from 1993 due to increased rigor in the selection process before gender affirming surgery.[31]

Another study surveyed all surgeons registered for the 2016 World Professional Association for Transgender Health and the 2017 US Professional Association for Transgender Health. Most respondents practiced in the United States and had surgically treated at least 100 transgender or gender-nonconforming patients. Of the 30 % of surgeons that completed the survey, 61 % respondents had treated at least one patient who experienced regret or requested reversal of a procedure. Overall, the calculated rate of regret after gender affirming surgery was **0.2%-0.3 %**. Of the 62 patients that respondents reported had sought reversal surgery, reasons for reversal included surgical complications, continued evolution of their gender identity, rejection or alienation from social support, and difficulty in romantic relationships.[5]

Recently, research from the University of Michigan demonstrated low levels of regret after gender-affirming mastectomy in a cross-sectional study. On average, respondents underwent surgery 3.6 years before the survey. The median Decision Regret Scale score was 0.0. Further, of the 139 respondents, zero requested reversal procedures.[32]

In February 2024, the 2022 US Transgender Survey Early Insight report was published, providing data from 92,329 binary and nonbinary transgender people. This report noted that 97 % of respondents who had undergone gender-affirming surgery reported that they were "a lot more satisfied" or "a little more satisfied" with their lives.[33]

3.3. Regret after elective surgical procedures

Weight-loss surgery, similar to gender affirming surgery, has seen a global increase in popularity in the past decade.[34] A 2017 study interested in long-term bariatric surgery outcomes asked patients who underwent bariatric surgery in 2004 to rate their satisfaction and open-endedly share comments regarding their experience. Of the 155 patients who participated in the study, **1.9 %** of respondents explicitly stated regret at having undergone bariatric surgery.[35] Patients who were younger at the time of surgery or who had not checked in with their surgeon or primary care doctor recently reported worse experiences. Interestingly, the responders who reported a negative experience had the greatest weight change and all participants in the negative experience group did lose weight. This study did require participants to express regret in a face-to-face manner, which may limit its validity.

A large study from 2019 examined rates of regret after Roux-En-Y gastric bypass surgery versus gastric banding surgery. Of the 205 participants who underwent Roux-En-Y surgery, **5.1 %** reported regret four years after surgery. Of the 188 patients who underwent gastric banding, **19.5 %** did not think they made the right decision and would not undergo weight-loss surgery again.[36]

Regret has been studied extensively in patients undergoing sterilization surgery. A 1999 study aimed to establish the probability of regret after tubal sterilization and identify risk factors for regret by interviewing women 14 years after surgery. Of the 11,232 women aged 18–44 that were included, **20.3 %** of women aged 30 or under at the time of tubal sterilization expressed regret, and **5.9 %** of women over the age of 30 at the time of surgery expressed regret.[37] This study did not investigate the reason for participants' regret. A more recent study from 2016 included 837 women ages 25–45 who underwent tubal sterilization surgery and found that **28 %** of participants reported regret. Risk factors for experiencing post-operative regret were increased time since sterilization and having a reason other than not wanting children for undergoing sterilization (i.e., health problems, situational, other reasons). Post sterilization regret was also noted to be associated with depressive symptoms after controlling for sociodemographic characteristics.[38]

Treatment of prostate cancer has increasingly incorporated robot-assisted procedures. A UK study published in 2020 explored rates of decisional regret after robot-assisted radical prostatectomy in 106 participants. **30 %** of participants reported "high regret." Regret was associated with increased length of time from surgery and lower sexual function scores.[39]

Ventral and inguinal hernia repair are two of the most common elective surgeries performed in the US. A recent study retrospectively reviewed 8,315 patients who underwent elective ventral and inguinal hernia repair and completed a decision regret survey from 2017 to 2020. Of patients that underwent ventral hernia repair, **11 %** reported regret. Risk factors associated with regret included complications and readmission after surgery. In the inguinal hernia group, **9 %** reported regret-regret was associated with readmission and follow-up ED visits.[40]

Elective diverticulitis surgery is also a relatively common procedure that is left to the patient and physician's discretion. A cross-sectional study completed in 2021 that included 133 adult patients treated for diverticulitis between 2014 and 2019 demonstrated that 29 % of participants ultimately underwent elective colectomy as treatment for diverticulitis and **32 % of those patients** reported decision regret.[41]

3.4. Regret after non-surgical life decisions

Deciding whether or not to have children is a massive life decision. The Gallup Organization asked Americans over age 45 with children how many children they would like to have if they could "do it once again." **7 %** of respondents chose '0 children.' In a similar survey of Germans with children, **8 %** fully agreed with the statement, "if I could choose today once again, I would not want to have children." Another 11 % of respondents "rather agreed" with the statement. Similar research in a Polish population revealed approximately **13 %** of parents manifest regret regarding having children.[42]

Regret after sexual experience is a commonly discussed form of regret. A 2002 questionnaire administered to college-students revealed that **71.9 %** of sexually active students expressed regret about engaging in sexual activity at least once. Regression analyses noted that the only significant predictor of regret was the number of sexual partners of the respondent.[43]

Regret after getting tattooed is another infamous type of regret after a relatively permanent body modification. A survey study conducted in New Orleans in 2015 found that **16.2 %** of participants regretted a

current tattoo and **21.2 %** were interested in tattoo removal.[44] A South American metanalysis found that the most common reasons stated for tattoo removal were dissatisfaction with the tattoo itself or how it was made and issues with the tattoo being displayed at work.[45]

Regret after marriage and divorce has been thoroughly researched using online surveys. Civic Science, an opinion research organization, polled 1,900 married participants and noted that **31 %** said, given a redo, they would not marry their spouse again.[46] Another online survey of married Britons reported that **23 %** of respondents would not marry their partner if they could go back in time.[47] Conversely, a 2016 survey of 460 divorcees reported that **27 %** of women and **32 %** of men regretted their decision to divorce.[48]

4. Discussion

This systematic review and literature review was designed to provide a framework to understand regret after gender affirming surgery in the context of other elective medically necessary surgeries as well as major life decisions. Unfortunately, some people seek to limit access to gender-affirming services, most vehemently gender-affirming surgery, and use post-operative regret as reason that care should be denied to all patients. This over-reaching approach erases patient autonomy and does not honor the careful consideration and multidisciplinary approach that goes into making the decision to pursue gender-affirming surgery. This review demonstrates that there is lower regret after GAS, which is less than 1 %, than after many other decisions, both surgical and otherwise.[31] Many plastic surgery operations included in our systematic review resulted in significantly higher rates of regret, up to 47.1 % in one breast reconstruction study.[16] Regret after GAS is also significantly lower than rates of regret following other elective surgeries, such as Roux-En-Y surgery (5.1 %), tubal sterilization (28 %), and robot-assisted prostatectomy (30 %).[36,38,39] These operations, while associated with higher rates of post-operative regret, are not restricted and policed like gender-affirming surgery. Further, regret after GAS is significantly lower than regret after important non-surgical life decisions, such as having children (7–8%) and getting a tattoo (16.2 %).[42,49]

The low rate of regret after gender-affirming surgery may be partially attributed to the stringent prerequisites that patients complete before being scheduled for surgery. Most recent studies involved patients who were treated under the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) version 7, released in 2011. Version 7 recommended that prior to gender-affirming mastectomy, patients are required to have a letter of support from a mental-health professional.[50] If a patient desires genital reconstructive surgery, hysterectomy, or orchiectomy, two letters of support are required in addition to a year of hormonal therapy and living fulltime in their congruent gender role.[50] While this approach has minimized post-operative regret, patients and advocates argued that it was medical gatekeeping and significantly stigmatized patients. WPATH SOC version 8, released in 2022, removes the mental health letter for chest surgery, reduces the letters from 2 to 1 for genital surgery, and decreases the duration of hormonal therapy to 6 months.[51] Future studies will evaluate the impact of the new SOC guidelines on patient-reported regret.

De-transitioning, also known as continued gender transition, has been exhaustively covered in the mainstream and conservative media and is an emerging area of study in gender affirming care. A 2020 study surveyed individuals who had “de-transitioned” or returned to the gender corresponding to their sex assigned at birth. To be included, patients must have discontinued gender-affirming medications or reversed gender-affirming surgery. Over half, 60 % of participants, stated they chose to de-transition because they had become more comfortable identifying as the gender corresponding to their sex assigned at birth. Other participants reported that they came to understand that they identified as lesbian, gay, or bisexual and not transgender.[52] Interestingly, some participants in the study reported regret in their decision to de-transition after transitioning.

It is important to note that reported regret after any surgery is likely underestimated due to patients not seeking additional care, loss to follow up, patients not sharing their satisfaction with their decision-making with their surgeons or going elsewhere for additional care. Within the transgender and gender non-conforming patient community, there is reluctance to disclose regret in care due to fear of further stigmatizing gender affirming care and limiting access for other patients. In fact, one survey noted that only 24 % of participants informed their clinician they had detransitioned.[52] Rates of de-transition after GAS are one way to assess regret, but this measure does not account for patients who regret undergoing GAS and do not choose surgery to alleviate this regret.

Research on regret after gender-affirming surgery poses unique challenges, as patients may fear that their regret could be weaponized against the transgender community. Those who seek to limit access to GAS often use regret as a key element in their arguments and in proposed legislation. Further, there is not currently a patient-reported outcome measure (PROM) to assess outcomes after gender-affirming surgery in all patient populations (transgender and non-binary), and the complex social, surgical, and politico legal aspects of surgical transition. Introduction and validation of a GAS PROM will improve our ability to evaluate patients’ preoperative goals and understand factors that impact post-operative regret.

Postoperative regret should be included in all discussions with patients in the informed consent process, not just in gender affirmation surgery. The multifactorial nature of regret inclusive of gender identify, social and sexual relationships, goals and expectations of the surgery, and potential complications should be embraced as part of the decision-making process so patients can make the best decision for themselves. As always, multidisciplinary care inclusive of mental health services should be emphasized to support patients who do experience regret.

5. Conclusion

This systematic review highlights that regret following gender-affirming surgery is remarkably low, below 1 %, compared to various elective surgeries and important life decisions. The findings challenge the restrictive narrative based on regret as a reason to limit access to gender-affirming services. The review emphasizes the careful considerations and evolving standards in the decision-making process for GAS, balancing the need to minimize regret while addressing concerns about medical gatekeeping. The call to incorporate discussions about postoperative regret in the informed consent process extends beyond GAS, underscoring the importance of a multifactorial understanding of regret and the necessity for multidisciplinary care to support patients who may experience regret. Overall, this review advocates for a nuanced and empathetic approach to ensure patient-centered care and respect for individual autonomy in the context of gender-affirming surgery and beyond.

CRediT authorship contribution statement

Sarah M. Thornton: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Armin Edalatpour:** Writing – review & editing. **Katherine M. Gast:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

This work has not been published previously, it is not under consideration for publication elsewhere, and its publication is approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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References

1. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students — 19 States and large urban school districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(3):67–71. https://doi.org/10.15585/mmwr.mm6803a3.
2. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. *Int Rev Psychiatr*. 2016;28(1):44–57. https://doi.org/10.3109/09540261.2015.1115753.
3. Scott KB, Thuman J, Jain A, Gregoski M, Herrera F. Gender-affirming surgeries: a national surgical quality improvement project database analyzing demographics, trends, and outcomes. *Ann Plast Surg*. 2022;88(5):S501–S507. https://doi.org/10.1097/SAP.0000000000003157.
4. Almazan AN, Keuroghlian AS. Association between gender-affirming surgeries and mental health outcomes. *JAMA Surg*. 2021;156(7):611–618. https://doi.org/10.1001/jamasurg.2021.0952.
5. Narayan SK, Hontscharuk R, Danker S, et al. Guiding the conversation—types of regret after gender-affirming surgery and their associated etiologies. *Ann Transl Med*. 2021;9(7). https://doi.org/10.21037/atm-20-6204, 605-605.
6. Wilson A, Ronnekleiv-Kelly SM, Pawlik TM. Regret in surgical decision making: a systematic review of patient and physician perspectives. *World J Surg*. 2017;41(6):1454–1465. https://doi.org/10.1007/s00268-017-3895-9.
7. Hurwitz DJ, Jerrod K. L-brachioplasty: an adaptable technique for moderate to severe excess skin and fat of the arms. *Aesthetic Surg J*. 2010;30(4):620–629. https://doi.org/10.1177/1090820X10380857.
8. Isern AE, Tengrup I, Loman N, Olsson H, Ringberg A. Aesthetic outcome, patient satisfaction, and health-related quality of life in women at high risk undergoing prophylactic mastectomy and immediate breast reconstruction. *J Plast Reconstr Aesthetic Surg*. 2008;61(10):1177–1187. https://doi.org/10.1016/j.bjps.2007.08.006.
9. Munhoz AM, Fells K, Arruda E, et al. Subfascial transaxillary breast augmentation without endoscopic assistance: technical aspects and outcome. *Aesthetic Plast Surg*. 2006;30(5):503–512. https://doi.org/10.1007/s00266-006-0017-8.
10. Modolin Modolin Modolin Modolin Modolin Improved Double-Fuse Technique for Post-Bariatric Brachioplasty Improved Double-Fuse Technique for Post-Bariatric Brachioplasty Improved Double-Fuse Technique for Post-Bariatric Brachioplasty Improved Double-Fuse Technique for Post-Bariatric Brachioplasty Improved Double-Fuse Technique for Post-Bariatric Brachioplasty Improved Double-Fuse Technique for Post-Bariatric Brachioplasty.
11. Rassaby J, Hill D. Patients' perceptions of breast reconstruction after mastectomy. *Med J Aust*. 1983;2(4):173–176. https://doi.org/10.5694/j.1326-5377.1983.tb122398.x.
12. Keller K, Meisel C, Grübling N, Petzold A, Wimberger P, Kast K. Patient-reported satisfaction after prophylactic operations of the breast. *Breast Care*. 2019;14(4):217–223. https://doi.org/10.1159/000496398.
13. Josephson U, Wickman M, Sandelin K. Initial experiences of women from hereditary breast cancer families after bilateral prophylactic mastectomy: a retrospective study. *Eur J Surg Oncol*. 2000;26(4):351–356. https://doi.org/10.1053/ejso.1999.0897.
14. Lossing C, Elander A, Gewalli F, Holmström H. The Lateral Thoracodorsal Flap In Breast Reconstruction: A Long Term Follow Up Study.
15. Pascali M, Botti C, Botti G. Face lifting in bald male patients: new trends and specific needs. *Plast Reconstr Surg*. 2020;145(1):60–69. https://doi.org/10.1097/PRS.0000000000006397.
16. Sheehan J, Sherman KA, Lam T, Boyages J. Regret associated with the decision for breast reconstruction: the association of negative body image, distress and surgery characteristics with decision regret. *Psychol Health*. 2008;23(2):207–219. https://doi.org/10.1080/14768320601124899.
17. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making*. 2003;23(4):281–292. https://doi.org/10.1177/0272989X03256005.
18. Harcourt D, Russell C, Hughes J, White P, Nduka C, Smith R. Patient satisfaction in relation to nipple reconstruction: the importance of information provision. *J Plast Reconstr Aesthetic Surg*. 2011;64(4):494–499. https://doi.org/10.1016/j.bjps.2010.06.008.
19. Penn JP, Nallani R, Dimon EL, et al. Educational informed consent video equivalent to standard verbal consent for rhinologic surgery: a randomized controlled trial. *Am J Rhinol Allergy*. 2021;35(6):739–745. https://doi.org/10.1177/1945892421992659.
20. Lee CNH, Pignone MP, Deal AM, et al. Accuracy of predictions of patients with breast cancer of future well-being after immediate breast reconstruction. *JAMA Surg*. 2018;153(4). https://doi.org/10.1001/jamasurg.2017.6112.
21. Luan A, Hui KJ, Remington AC, Liu X, Lee GK. Effects of A Novel decision aid for breast reconstruction: a randomized prospective trial. *Ann Plast Surg*. 2016;76:S249–S254. https://doi.org/10.1097/SAP.0000000000000722.
22. Paraskeva N, Tollow P, Clarke A, et al. A multi-centred sequential trial comparing PEGASUS, an intervention to promote shared decision making about breast reconstruction with usual care. *J Plast Reconstr Aesthetic Surg*. 2022;75:37. https://doi.org/10.1186/ISRCTN18000391.
23. Mardinger C, Steve AK, Webb C, Sherman KA, Temple-Oberle C. Breast reconstruction decision aids decrease decisional conflict and improve decisional satisfaction: a randomized controlled trial. *Plast Reconstr Surg*. 2023;151(2):278–288. https://doi.org/10.1097/PRS.0000000000009830.
24. Sowa Y, Inafuku N, Tsuge I, et al. Development and implementation of a decision aid for post-mastectomy breast reconstruction for Japanese women with breast cancer: a field-testing study. *Breast Cancer*. 2023;30(4):570–576. https://doi.org/10.1007/s12282-023-01447-4.
25. Sherman KA, Shaw LKE, Winch CJ, et al. Reducing decisional conflict and enhancing satisfaction with information among women considering breast reconstruction following mastectomy: results from the BRECONDA randomized controlled trial. In: *Plastic and Reconstructive Surgery*. vol. 138. Lippincott Williams and Wilkins; 2016:592e–602e. https://doi.org/10.1097/PRS.0000000000002538.
26. Lam WWT, Chan M, Or A, Kwong A, Suen D, Fielding R. Reducing treatment decision conflict difficulties in breast cancer surgery: a randomized controlled trial. *J Clin Oncol*. 2013;31(23):2879–2885. https://doi.org/10.1200/JCO.2012.45.1856.
27. Fang SY, Lin PJ, Kuo YL. Long-term effectiveness of a decision support app (Pink Journey) for women considering breast reconstruction surgery: Pilot randomized controlled trial. *JMIR Mhealth Uhealth*. 2021;9(12). https://doi.org/10.2196/31092.
28. Hickey OT, Nugent NF, Burke SM, Hafeez P, Mudrakouski AL, Shorten GD. Persistent pain after mastectomy with reconstruction. *J Clin Anesth*. 2011;23(6):482–488. https://doi.org/10.1016/j.jclinane.2011.01.009.
29. Hasak JM, Myckatyn TM, Grabinski VF, Philpott SE, Parikh RP, Politi MC. Stakeholders' perspectives on postmastectomy breast reconstruction: recognizing ways to improve shared decision making. *Plast Reconstr Surg Glob Open*. 2017;5(11). https://doi.org/10.1097/GOX.0000000000001569.
30. 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. https://doi.org/10.1016/j.jsxm.2018.01.016.
31. Bustos VP, Bustos SS, Mascaro A, et al. Regret after gender-affirmation surgery: a systematic review and meta-analysis of prevalence. *Plast Reconstr Surg Glob Open*. 2021. https://doi.org/10.1097/GOX.0000000000003477. Published online.
32. Bruce L, Khouri AN, Bolze A, et al. Long-term regret and satisfaction with decision following gender-affirming mastectomy. *JAMA Surg*. 2023. https://doi.org/10.1001/jamasurg.2023.3352. Published online August 9.
33. James SE, Herman JL, Durso LE, Heng-Lehtinen R. *Early Insights: A Report of the 2022 U.S. Transgender Survey*. 2024.
34. Bartosiak K, Janik MR, Walędziak M, Paśnik K, Kwiatkowski A. Effect of significant postoperative complications on decision regret after laparoscopic sleeve gastrectomy: a case–control study. *Obes Surg*. 2022;32(8):2591–2597. https://doi.org/10.1007/s11695-022-06113-w.
35. Turrentine FE, Mehaffey JH, Mehaffey RL, Mullen MG, Schirmer BD, Hallowell PT. Patient reported outcomes 10 years after roux-en-Y gastric bypass. *Obes Surg*. 2017;27(9):2253–2257. https://doi.org/10.1007/s11695-017-2641-6.
36. Wee CC, Fleishman A, McCarthy AC, Hess DT, Apovian C, Jones DB. Decision regret up to 4 Years after gastric bypass and gastric banding. *Obes Surg*. 2019;29(5):1624–1631. https://doi.org/10.1007/s11695-019-03772-0.
37. Hillis SD, Marchbanks PA, Ratliff Tylor L, et al. *Poststerilization Regret: Findings from the United States Collaborative Review of Sterilization*. vol. 93. 1999.
38. Shreffler KM, Greil AL, McQuillan J, Gallus KL. Reasons for tubal sterilisation, regret and depressive symptoms. *J Reprod Infant Psychol*. 2016;34(3):304–313. https://doi.org/10.1080/02646838.2016.1169397.
39. Lindsay J, Uribe S, Moschonas D, et al. Patient satisfaction and regret after robot-assisted radical prostatectomy: a decision regret analysis. *Urology*. 2021;149:122–128. https://doi.org/10.1016/j.urology.2020.12.015.
40. Howard R, Ehlers A, Delaney L, et al. Incidence and trends of decision regret following elective hernia repair. *Surg Endosc*. 2022;36(9):6609–6616. https://doi.org/10.1007/s00464-021-08766-7.
41. Cohan JN, Orleans B, Brecha FS, et al. Factors associated with decision regret among patients with diverticulitis in the elective setting. *J Surg Res*. 2021;261:159–166. https://doi.org/10.1016/j.jss.2020.12.019.
42. Piotrowski K. How many parents regret having children and how it is linked to their personality and health: two studies with national samples in Poland. *PLoS One*. 2021;16(7 July). https://doi.org/10.1371/journal.pone.0254163.
43. Oswalt SB, Cameron KA, Koob JJ. Sexual regret in college students. *Arch Sex Behav*. 2005;34(6):663–669. https://doi.org/10.1007/s10508-005-7920-y.
44. Liszewski W, Kream E, Helland S, Cavigli A, Lavin BC, Murina A. The demographics and rates of tattoo complications, regret, and unsafe tattooing practices. *Dermatol Surg*. 2015;41(11):1283–1289. https://doi.org/10.1097/DSS.0000000000000500.
45. Rivera FP. A highlight on reasons for tattoo regrets and removal. *Medical Lasers*. 2021;10(2):106–110. https://doi.org/10.25289/ml.2021.10.2.106.
46. Acklin M. Maybe Date Your Spouse. Civic Science. Published August 8, 2018. Accessed January 9, 2024. https://civicscience.com/maybe-date-your-spouse/.
47. Almost a quarter of Britons regret marriage: survey. Reuters. Published August 9, 2007. Accessed January 9, 2024. https://www.reuters.com/article/idUSL12352704/.
48. Maximets N. How Many Couples Regret Divorce | The Latest Statistics. OnlineDivorce. Published March 29, 2022. Accessed January 9, 2024. https://www.onlinedivorce.com/blog/how-many-couples-regret-divorce/.
49. Liszewski W, Kream E, Helland S, Cavigli A, Lavin BC, Murina A. The demographics and rates of tattoo complications, regret, and unsafe tattooing practices: a cross-sectional study. *Dermatol Surg*. 2015;41(11):1283–1289. https://doi.org/10.1097/DSS.0000000000000500.
50. Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People The World Professional Association for Transgender Health. Accessed December 3, 2023. www.wpath.org.
51. 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;23:1–259. https://doi.org/10.1080/26895269.2022.2100644.
52. 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. https://doi.org/10.1007/s10508-021-02163-w.

Revisión Cass: Contexto de la Discusión y Claves de Análisis

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Revisión Cass:
Contexto de la discusión y claves de análisis

Preparado por:[a]
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Presentación

Este texto es un 'documento de trabajo' que entrega orientaciones para contextualizar y comprender el estado de los servicios de identidad de género del sistema de salud de Reino Unido, particularmente las discusiones que han surgido tras el lanzamiento del informe final de la denominada Revisión Cass en abril de 2024. Nos interesa facilitar el acceso a información breve y sencilla que permita situar el debate en sus coordenadas científicas, políticas y sociales. Al ser un documento de trabajo, esperamos ir actualizándolo conforme avanza la discusión.

Con este fin, identificamos una serie de dimensiones de análisis que suelen repetirse en las conversaciones que circulan en redes sociales y en los medios de comunicación y prensa: cuestiones vinculadas al contexto que origina la Revisión Cass, cuestiones de tipo metodológicas que son propias de la naturaleza del informe, así como asuntos relacionados con la evidencia en torno a la salud afirmativa de género y sus efectos sobre la salud de las personas.

Nos interesa informar de manera responsable y cuidadosa, evitando instalar el pánico y reconociendo los límites que tenemos desde nuestras profesiones y disciplinas, así como los límites que implica el informarse de discusiones que ocurren fuera de nuestro país, en ritmos y formatos que no se corresponden con nuestra realidad local ni con nuestro idioma, y que muchas veces nos obligan a pronunciarnos sin disponer de toda la información que quisiéramos. Por lo mismo, la escritura de este documento nos ha tomado tiempo y cautela—después de todo, estamos hablando de un informe de 388 páginas (!). Creemos que ése es el ritmo que cuida y que mejor acompaña un proceso de estas características.

Junto con lo anterior, nos interesa también combatir la desinformación (incluyendo información imprecisa y, a veces, derechamente falsa) y *mala fe* con que diversos medios de comunicación en el mundo, en el Reino Unido y en Chile, junto a ciertos "feminismos" y sectores de la sociedad civil, han comunicado los hallazgos del informe. Hacemos esto teniendo presentes a las personas trans y no binarias de todas las edades, especialmente niñes[b] y adolescentes, sus familias y cuidadores, quienes se han visto al centro un debate que les deshumaniza y amenaza con privarles del acceso a una salud digna, respetuosa y comprometida con la defensa de sus derechos. Esperamos que este texto lo puedan usar y distribuir entre sus redes, para que más personas se informen y sepan qué está ocurriendo con esta discusión.

Mayo 2024

[a] Ambes autores contribuimos por igual en la escritura, revisión y organización de este documento. Por cuestiones de orden, nuestros nombres figuran en orden alfabético.
[b] Para una lectura más accesible, este documento utiliza el lenguaje inclusivo que usa la E en lugar de la X para incluir a todos los géneros, y volver el texto accesible a quienes leerán el documento utilizando lectores de pantalla.

Contexto de la discusión

Algunos antecedentes relevantes

Caso *Bell versus Tavistock*:

- En octubre de 2019, en el Reino Unido, se presentó una revisión judicial (denuncia) contra el *Gender Identity Development Service* (Servicio/Unidad de Desarrollo de la Identidad de Género, en inglés GIDS)[c], por parte de la "señora A" y Keira Bell, quien comenzó un tratamiento con bloqueadores puberales[d] a sus 16 años.
  - La denuncia cuestionaba si las personas menores de 18 años podían dar su consentimiento al uso de bloqueadores de la pubertad. En el centro de la demanda estaba el arrepentimiento de Keira Bell por su propia transición.
  - El 1 de diciembre de 2020, el tribunal falló a favor de Bell, señalando que resultaba altamente improbable que menores de 16 años tuviesen la madurez suficiente para consentir al uso de bloqueadores puberales. Como consecuencia, el NHS cambió el proceso de acceso a los bloqueadores de la pubertad, estableciendo que sería competencia de un tribunal decidir si es en el "interés superior" de la persona empezar con un tratamiento farmacológico.
- En septiembre de 2021, el Tribunal de Apelaciones anuló la sentencia del Alto Tribunal en el caso Bell versus Tavistock, que, en primera instancia, prohibió de hecho el acceso a tratamientos médicos vitales a jóvenes trans, a menos que tuvieran una orden judicial.[1]
- La decisión del Tribunal restableció la validez de la prueba de Gillick** (Gillick competence) e insistió en que corresponde al médico junto con quien consulta y su familia o cuidadores tomar decisiones caso a caso en materias concernientes a su salud, respetándose el principio de autonomía corporal.
  - **La prueba o Competencia de Gillick es el resultado de una sentencia histórica de 1985 (*Gillick contra West Norfolk y Wisbech AHA*) que permite a personas menores de 18 años acceder a la asistencia médica sin el consentimiento de sus padres si se determina que comprenden los efectos posibles y probables del tratamiento.[2]
  - La *competencia de Gillick* (como instrumentos y principio) ha sido materia de cuestionamiento e impugnación legal por parte de grupos conservadores en casos que van más allá del acceso a la salud de género afirmativa, como por ejemplo el acceso de menores de 18 años al aborto y a su salud sexual y reproductiva en general.

Cierre del Gender Identity Development Service (GIDS) del Tavistock and Portman NHS Trust:

- En julio de 2022, el NHS anunció que el GIDS sería sustituido por dos centros regionales en Londres y en el Noroeste para descentralizar y ofrecer un enfoque más "holístico" a la atención trans-afirmativa. Dicha decisión se concretó el año 2023 siguiendo las recomendaciones de una revisión independiente elaborada por la Dra. Hillary Cass, quien concluyó –tal como lo habían

[c] El NHS (*National Health Service* o Servicio Nacional de Salud) es el sistema de salud pública de Inglaterra. El GIDS (*Gender Identity Development Service* o Servicio de Desarrollo de la Identidad de Género) es la única clínica del Reino Unido especializada en identidad de género para niños y jóvenes.

[d] Los bloqueadores puberales son fármacos que se indican para detener la producción de hormonas sexuales que inducen los cambios corporales asociados a la pubertad.

manifestado organizaciones trans y usuaries del servicio durante años– que el GIDS no estaba a la altura de la creciente demanda y que era necesaria una mejor atención integral.[e]

- Pese a que la decisión anterior se presentó públicamente como una solución frente a la necesidad de reducir las listas de espera, el cierre del GIDS se enmarca dentro de un contexto social, político y de salud más amplio[3]:
  - En relación con las perspectivas en disputa, sería posible identificar al menos dos: 1) críticas que surgen desde quienes se oponen a la salud trans afirmativa (ej. feministas "críticas de género" o trans-excluyentes) y 2) desde quienes han criticado la demora y tiempos de espera excesivos a los que se somete a quienes consultan, antes de su ingreso al sistema.

- ***Tiempos de espera:*** Algunas de las decisiones que motivaron el cierre del GIDS (ej. tiempos/listas de espera) cuestionan el mito en torno a la supuesta "prisa" (*rush*) con que niñes y adolescentes inician sus tratamientos de hormonización y/o transición de género:[4]
  - Investigaciones recientes que recogen testimonios de niñes y adolescentes y sus familias, apuntan a que los tiempos de espera para una primera sesión dentro del GIDS ocurre en un promedio de 1,066 días.[5] Hasta fines de mayo de 2022:
    - 5,035 personas se encontraban en lista de espera.
    - Se realizaron, en promedio, 200 derivaciones por mes.
    - Las derivaciones hechas el año 2019 recién estaban siendo atendidas en una primera sesión en mayo de 2022.
  - Información disponible a través de la página web del Servicio de Disforia de Género de la Región Norte (NRGDS) muestra que:
    - "En marzo de 2024, la persona que encabeza la lista de espera para su sesión de evaluación inicial ha esperado 70 meses (5 años y 10 meses) para obtener una hora y, en la actualidad, sigue a la espera de que se le asigne una".[6]

Ambiente Hostil: Disparidades en Salud y Violencia Transfóbica

- En su visita al Reino Unido e Irlanda del Norte en abril y mayo de 2023, Víctor Madrigal-Borloz, Experto Independiente de Naciones Unidas sobre la protección contra la violencia y la discriminación por motivos de orientación sexual o identidad de género, manifestó su preocupación por la "extrema presión y hostilidad" que experimentan las personas y organizaciones LGBT, la cual se exacerba por un debate político que cuestiona sus derechos y, en algunos casos, su propia existencia.[7]

- A partir de 2016, los medios de comunicación han contribuido a producir una "guerra cultural" respecto de los derechos de las personas trans, amplificando la desinformación y generando pánico moral respecto de la atención de salud trans-afirmativa, particularmente en relación a las infancias trans.[8–10]
  - Siguiendo la explicación que propone Stuart Hall et al. (1978) con relación al pánico moral, en el momento en que los medios comienzan a hablar de "aumentos repentinos y dramáticos" en los números o 'casos' y cuando hacen referencia a la supuesta "novedad" de un 'fenómeno', sería posible hablar de los inicios del pánico moral.[11] Respecto de las personas trans, esto se ve reflejado en coberturas que no respetan sus pronombres o nombres sociales y que insisten en la idea de 'contagio social', 'ideología transgénero', 'moda', 'peligro' o

[e] GIDS ha sido objeto de investigaciones periodísticas y análisis controversiales por décadas. Quienes quieran profundizar en los principales debates, les sugerimos leer críticamente la investigación periodística de Hannah Barnes (*Time to Think: The Inside Story of the Collapse of the Tavistock's Gender Service for Children*) y escuchar el capítulo sobre *Puberty Blockers* del podcast *Prominent Corrections*, el cual responde a muchos de los sesgos contenidos en la investigación de Barnes, los cuales no han sido cubiertos por la prensa tradicional en Reino Unido.

‘amenaza’, como si las infancias trans fuesen un ‘fenómeno’ reciente o producto de las redes sociales y la pornografía.[12–14]

- ***Disparidades en salud y crímenes de odio:*** El informe sobre salud LGBTQ+ elaborado por la organización LGBT Stonewall en 2018, reveló que en el Reino Unido existen tasas elevadas de depresión, ansiedad y otras formas de angustia en la población LGBTQ+ en comparación con la población no LGBTQ+, observándose también un riesgo de suicidio significativamente elevado en todos los grupos LGBTQ+.[15,16]
  - Al respecto, la política nacional de prevención del suicidio y el plan de acción LGBT del gobierno británico reconocen que las personas LGBTQ+ necesitan enfoques adaptados y locales para apoyar su salud mental.[17]
  - Una revisión sistemática de 2021 sobre la evidencia del impacto del COVID-19 sobre la salud y el bienestar de la población LGBTQ+ arrojó que no existirían investigaciones específicas sobre el impacto de la pandemia sobre esta población. Esto último sería preocupante, dadas las desigualdades en salud que presenta dicho grupo respecto de sus pares heterosexuales y cisgénero. La escasez de evidencia se explicaría debido a la falta de recopilación sistemática de datos sobre orientación sexual e identidad de género, posiblemente como consecuencia de la homofobia y transfobia institucionalizada.[18]
  - El informe 2023 de ILGA-Europa muestra un aumento de los crímenes de odio en Inglaterra y Gales, siendo los transfóbicos los que más han aumentado, con un 56%, seguidos por los homo y lesbofóbicos con un 41%. Estos se atribuirían, en parte, a un aumento de la cobertura anti-trans en los medios de comunicación y a los ataques recientes contra la salud trans-afirmativa.
    - Recientemente, el 11 de febrero de 2023, la adolescente trans de dieciséis años, Brianna Ghey, fue apuñalada hasta su muerte por dos jóvenes de 15 años. Su crimen fue motivado, en parte, por la transfobia.[19]
  - Hace 5 años, y durante el período liderado por 4 diferentes jefes de gobierno, Reino Unido inició un proceso de consulta para implementar una ley que prohibiera las prácticas de conversión.[20]
    - La intención del Gobierno era publicar los resultados de la consulta y el proyecto legislativo en 2022. A finales de marzo de ese año, se filtró un documento en el que se detallaba la intención de no prohibir en absoluto las terapias de conversión. Tras intensas protestas, el Gobierno anunció que seguiría adelante con la prohibición de las prácticas de conversión para personas LGB (lesbianas, gays y bisexuales), pero que no lo haría para las personas trans.[21]

La Revisión Cass

El Cass Review o *Revisión Cass* (2024) es una revisión independiente encargada en 2020 por el NHS a la pediatra Dra. Hillary Cass con el fin de proporcionar recomendaciones sobre los servicios de atención de género disponibles en infancia y adolescencia. Tras un informe provisional publicado en 2022, Cass publicó sus conclusiones finales en abril de 2024 en un informe titulado *Revisión independiente de los servicios de identidad de género para niños y jóvenes: Informe final*.[22]

- El equipo liderado por Cass encargó una serie de estudios a la Universidad de York. Ésta realizó revisiones sistemáticas de la evidencia disponible respecto de varias intervenciones afirmativas de género, incluidos el uso de bloqueadores de la pubertad, de hormonas sexuales cruzadas, la transición social y las medidas de apoyo psicosocial.
  - La Revisión tuvo como objetivo garantizar que quienes se cuestionan su identidad de género o experimentan disforia de género durante la infancia o adolescencia, puedan recibir una atención de alto nivel, integral, segura y efectiva (p. 20).
- El informe de la Revisión Cass publicado en abril de 2024 advierte en contra de la tendencia a establecer generalizaciones respecto de la experiencia de niñes y adolescentes que cuestionan su identidad de género, reconociendo su diversidad de trayectorias. En relación con esto último, señala que el "sentido de identidad de les jóvenes no es fijo y puede cambiar en el tiempo", agregando que no debiesen existir "jerarquías en cuanto a la identidad de género o la forma en que ésta se expresa, ya sea social o médicamente. Nadie debe sentir la necesidad de invalidar su propia experiencia por temor a que se refleje negativamente en otras identidades" (p. 21).
  - El informe señala también que, "para algunes, el mejor resultado será la transición, mientras que otres resolverán su angustia de otras maneras. Algunes pueden hacer su transición y luego de/retransitar y/o arrepentirse". El NHS debe atender a todes quienes buscan ayuda, independiente de sus trayectorias (p. 21).
  - Cass recomienda también que todes les profesionales del sistema de salud del NHS deben formarse "sobre cómo trabajar con sensibilidad y eficacia con jóvenes trans, no binarios y que cuestionan su género" (p. 38).

¿Qué dice y qué no dice la Revisión Cass?

- Lo primero es señalar que la Revisión no hace referencia a evidencia alguna que dé cuenta de posibles 'daños' (físicos o psicológicos) causado por la transición social, el uso de bloqueadores puberales y/o de hormonas cruzadas.[f]
- A diferencia de lo que algunos medios han reportado, la Revisión Cass no generó datos nuevos. Más bien, revisó la evidencia disponible sobre los efectos de prácticas afirmativas de género en la salud física y mental de niñes y adolescentes trans y que cuestionan su identidad.
  - En este sentido, la Revisión no recomienda prohibir el uso y acceso a bloqueadores de la pubertad (Final Report - FAQs).
  - Tampoco recomienda prohibir la transición social para ningún grupo de edad. Cass recomienda que niñes pre-puberales y sus familias puedan acceder tempranamente al apoyo

[f] En Reino Unido, el periódico *The Times* difundió una noticia cuyo titular leía: "1.000 familias demandarán a la clínica de género Tavistock". La supuesta demanda y los números de familias demandantes nunca han existido. Esta noticia ha sido amplificada de manera irresponsable por múltiples medios y organizaciones anti-trans como 'evidencia' de los daños a los que han sido sometidos niñes y adolescentes trans. En enero de este año, el mismo medio publicó que dicha demanda no existe.

necesario por parte de profesionales calificados para tomar decisiones relacionadas con la transición social (Final Report - FAQs).
    - El informe reconoce que no existe una definición única de transición social y valora la diversidad de trayectorias que ésta puede tener.
    - El apoyo que les niñes y sus familias puedan recibir es vital para reconocer variaciones comunes de la expresión y roles de género. En este sentido, Cass recomienda evitar decisiones apresuradas y sugiere evaluar la implementación de transiciones "parciales" en diálogo con les niñes y sus familias para permitir cierta flexibilidad y apertura a trayectorias diversas, no profundizando en qué consiste dicha parcialidad (p. 32).

Evidencia respecto del uso de bloqueadores de pubertad y hormonas cruzadas

- La Revisión Cass afirma que la evidencia con relación al uso de bloqueadores de la pubertad y de hormonas masculinizantes/feminizantes es "débil", lo cual no significa que las intervenciones sean malas o dañinas. Llegan a esta conclusión a partir de decisiones metodológicas que han sido críticamente cuestionadas, a las que nos referiremos más adelante. Esto es importante dado que las conclusiones a las que llega la Revisión Cass difieren sustancialmente de evidencia robusta respecto de los beneficios de la transición social y el uso de bloqueadores de pubertad y hormonas.[23–34]
    - Respecto del uso de bloqueadores de la pubertad, el informe reconoce la existencia de "beneficios claramente definidos en circunstancias muy limitadas" (p. 32), y se describen como "potenciales" los riesgos que pudiesen existir en relación con sus usos.
    - Con relación al uso de hormonas cruzadas, los autores de las revisiones sistemáticas del equipo de la Universidad de York concluyeron que se requieren "investigaciones de alta calidad que evalúen los resultados de las intervenciones hormonales en adolescentes con disforia/incongruencia de género" (p. 33), agregando que existirían pocos estudios que hayan realizado un seguimiento a largo plazo.
        - Dado lo anterior, concluyen que "no se pueden extraer conclusiones sobre el efecto en la disforia de género, la satisfacción corporal, la salud psicosocial, el desarrollo cognitivo o la fertilidad. Sigue habiendo incertidumbre acerca de los resultados sobre la estatura/crecimiento, la salud cardiometabólica y ósea" (p. 33).
        - Al mismo tiempo, señalan que "el tratamiento hormonal puede mejorar la salud psicológica", concluyendo que se requieren "investigaciones sólidas con un seguimiento a largo plazo" que permitan reforzar este hallazgo (p. 33).

Evidencia respecto de quienes han de/retransicionado

- La Revisión Cass cita una auditoría del NHS sobre jóvenes trans inscritos en el GIDS, en la que se constató un número extremadamente bajo de de/retransición (p. 168):
    - Se auditaron 3,499 pacientes, de los cuales sólo 3,306 fueron incorporados en el análisis.
    - "Menos de 10 pacientes volvieron a su género [registrado al nacer], todes elles eran mujeres, y se confirmó que todes menos une habían recibido bloqueadores de la pubertad como primera intervención. Estos pacientes habían recibido una media de 6,5 consultas antes de ser remitidos a endocrinología (rango 3-10 consultas)" (p. 168).
    - La cifra anterior no sólo es baja, sino que además queda claro que incluso las personas que de/retransicionaron recibieron varias consultas de evaluación separadas en el tiempo (en promedio 6,5 consultas) antes de ser derivadas a un especialista endocrino. Por tanto, en el contexto de esta auditoría, les niñes sí recibieron evaluación previamente antes de iniciar un tratamiento hormonal, el cual no se prescribe de manera "precipitada" ni apurada, como suele reportearse.
    - Respecto de esto último, resulta fundamental señalar que las guías clínicas actuales para la atención de niñes y adolescentes trans, no binaries y de género no conforme recomiendan el

paso inicial sea la realización de una evaluación integral de las necesidades y el contexto de apoyo de quien consulta.[29,35] La indicación de bloqueo puberal se realiza sólo cuando existe evidencia clínica del inicio de la pubertad en casos donde este bloqueo puede mejorar (o prevenir el deterioro) del bienestar de le niñe o adolescente.[29,35] Esta evaluación e indicación de tratamiento deben ser realizadas por profesionales con experiencia y capacitación técnica.[29,35] Si bien en otros contextos se admite la prescripción por otras especialidades o profesionales, en el contexto chileno esta indicación solamente es realizada por especialistas en endocrinología pediátrica.

¿El mayor escándalo en la historia de la medicina?

- Algunos medios de prensa dentro y fuera de Reino Unido han titulado la cobertura de la Revisión Cass como *el mayor escándalo de la medicina*. Esto no sólo es irresponsable y mal intencionado, sino que da cuenta de la falta de ética con que es tratado el tema en los medios de comunicación, los que han contribuido a instalar el pánico en torno al tratamiento de género afirmativo. La Revisión Cass no da cuenta de evidencia alguna de "daño" respecto del uso de bloqueadores de pubertad, transición social o uso de hormonas cruzadas—y esto no es una interpretación.
  - Sin embargo, existen otros daños y perjuicios que parecieran no llamar la atención de Cass. La Revisión no examina la evidencia que sí existe respecto del daño que han causado las restricciones autoritarias y abusivas de acceso a la salud afirmativa que se han implementado contra las infancias trans en algunos estados en Estados Unidos y en el NHS en Inglaterra. Tampoco revisan la evidencia que da cuenta del trato abusivo al que se somete a les niñes cuando profesionales de la salud evalúan su caso, el tipo de preguntas intrusivas al que se les expone y los efectos perjudiciales que tienen los tiempos de espera sobre su salud mental y física.[7,36–40]

Composición del equipo que realizó la Revisión

- La Dra. Cass fue seleccionada para dirigir el proceso que se conoció como la *Revisión Cass* debido a su "independencia", es decir, porque era una médica sin conocimientos ni experiencia profesional en la atención sanitaria a niñes y adolescentes trans.
  - El problema es que quienes conformaron el equipo de trabajo tampoco tienen experiencias en salud trans (como investigadores o usuaries). De acuerdo a un artículo académico publicado por Cal Horton,[41] los Términos de Referencia originales publicados en los reportes preliminares excluyeron explícitamente a personas con expertise en temas trans del órgano de gobierno de la Revisión, dejando fuera también a quienes son expertes por experiencia, es decir, quienes han tenido experiencias directas como usuaries del GIDS:
    - "El Cass Review, por su diseño, priorizó a profesionales cisgénero sin experiencia en atención sanitaria trans. Dentro de este diseño no hubo ninguna consideración respecto de medidas que hubiesen aminorado el riesgo de sesgo cisnormativo[g] en la estructura de liderazgo."[41]
    - La inclusión de integrantes de la comunidad que se estudia e investiga en las distintas etapas de una investigación se considera una buena práctica en el diseño de estudios, especialmente cuando estos refieren a la experiencia de comunidades minorizadas.

[g] Mecanismo identificado por Cal Horton (2024) en su análisis de los reportes preliminares de la Revisión Cass para describir un tipo de sesgo que puede conducir a que investigadores vean las infancias trans "como un problema o una desviación inherente", haciendo de las experiencias trans una vivencia "sospechosa, problemática o patológica" (p. 7). Los prejuicios cisnormativos, afirma Horton, establecen jerarquías de valor entre vidas trans y cis, favoreciendo las interpretaciones, sensibilidades y privilegios que provienen de grupos cisgénero, los cuales permean la sociedad, instituciones y campos disciplinares.

La Revisión Cass versus las revisiones comisionadas

¿Qué es una revisión sistemática?

- Las revisiones sistemáticas son un método para sintetizar evidencia científica que responde a una pregunta de investigación específica de una forma transparente y reproducible, buscando incorporar toda la evidencia disponible y evaluando su calidad.[42]
  - Uno de los elementos importantes que la definen son la definición de una estrategia de búsqueda que se fija desde el inicio y no se ajusta a conveniencia. Ello implica utilizar en la revisión toda la evidencia disponible y no sólo aquella que se ajusta a las ideas de quien la realiza.

La Revisión Cass NO es una revisión sistemática

- Un punto crítico es que el informe final de la Revisión Cass es una revisión NO sistemática en sí misma.[h]

- El reporte incluye los hallazgos de 6 revisiones sistemáticas realizadas por un equipo de investigación liderado por Jo Taylor de la Universidad de York (Inglaterra), dos artículos de evaluación de guías clínicas, y un artículo de investigación original basado en una encuesta. Las seis revisiones evaluaron las siguientes áreas:
  - Cambios en el número y el perfil de pacientes derivados a equipos especializados en género.[43]
  - Efecto de la transición social en infancia y adolescencia.[44]
  - Efecto de intervenciones psicosociales en infancia y adolescencia consultante por "incongruencia de género".[45]
  - Efecto de la supresión puberal.[46]
  - Efecto de la terapia hormonal cruzada.[47]
  - Protocolos o vías de abordaje y tratamiento utilizados en servicios especializados en género.[48]

- Solamente las revisiones sistemáticas, revisiones de guías clínicas y el artículo sobre la encuesta fueron sometidos a revisión por pares (*peer review*)[i]. El informe final de la revisión Cass no es una publicación de revista científica y no tuvo revisión externa.

Problemas metodológicos identificados en el informe

Problemas de rigurosidad en el uso de evidencia científica

- El reporte final de la Revisión Cass contiene recomendaciones y aseveraciones que exceden muy significativamente el contenido de las revisiones sistemáticas (por ejemplo, todo lo referido al neurodesarrollo infantojuvenil o la capacidad de consentimiento).
  - Ello implica que, el en resto del informe, se utilizan referencias a estudios que no formaron parte de las revisiones sistemáticas, por lo que es posible que exista investigación y evidencia que difiere de las aseveraciones hechas por Cass, pero que no fueron incluidas ni consideradas en el reporte.
    - En el ejemplo anterior sobre el neurodesarrollo, el informe correlaciona directamente la evidencia sobre la madurez de la corteza cerebral prefrontal con la capacidad de tomar

[h] Algunas críticas a la revisión han usado el nombre "Reporte" o "Informe Cass" (en inglés, *Cass Report*) para hacer la diferencia respecto de las revisiones sistemáticas que fueron incluidas en el reporte final.

[i] La revisión externa de pares (peer-review) es uno de los mecanismos que existen para garantizar la calidad de una publicación científica, la validez, impacto y/o replicabilidad de los hallazgos. En este proceso participan dos o más investigadores con expertise en el tema, quienes no tienen relación con quienes realizaron la investigación evaluada y cuya identidad es anónima.

decisiones a largo plazo. Los estudios de neuroimágenes no evalúan directamente el desarrollo de las funciones ejecutivas y claramente señalan que las curvas poblacionales no deben ser asumidas como trayectorias individuales.[49] Es decir, hay variabilidad individual importante en los ritmos de maduración, y no hay "números mágicos" como punto de criterio certero para la maduración.
    - El informe Cass sugiere tener un enfoque pediátrico/juvenil hasta los 25 años argumentando que solo entonces el cerebro y las funciones ejecutivas están completamente maduros. Seguir este raciocinio abriría un vacío lógico si es que no se revisaran todas las decisiones que una persona hasta los 25 años es capaz de tomar asumiendo que no tiene capacidad completa de evaluar las consecuencias de largo plazo. Esta lógica presupondría revisar toda capacidad de decisión (para intervenciones médicas o incluso la responsabilidad penal) e inclusive el concepto de mayoría de edad. El informe no se hace cargo de estas implicancias al sugerir el cambio en el modelo de atención.

- Toda la investigación cualitativa a la que se aduce en el informe no está publicada en ninguna revista científica, por lo que no fue sometida a ninguna evaluación externa de pares para revisar su calidad, métodos y conclusiones. Aun cuando las revisiones sistemáticas encargadas por Cass a la Universidad de York pasaron la revisión por pares, ello no implica necesariamente que no tengan falencias, las cuales, a su vez, impactan la forma en que Cass interpretó sus hallazgos y recomendaciones. Algunas de las falencias de las revisiones incluyen:
    - La inclusión de heterogeneidad significativa en los criterios de inclusión utilizados para seleccionar la evidencia:
        - En supresión puberal, se incluyen varios tipos de medicamentos con mecanismos y resultados esperables muy diferentes (por ejemplo, progestinas que solo detienen los sangrados menstruales junto con análogos de GnRH, el tratamiento estándar).
        - En intervenciones psicosociales, se incluyen esquemas de psicoterapia junto con intervenciones de módulos de auto instrucción o grupos de apoyo.
        - En transición social, se incluyen estudios que evalúan solo el cambio de nombre social y estudios evaluando cambios de aspecto y presentación.
    - Es esperable que introduciendo esta heterogeneidad en lo que se está evaluando, haya heterogeneidad en los resultados observados. Luego esta heterogeneidad en los resultados observados se instrumentaliza para afirmar que la evidencia es no concluyente.
    - Asegurar criterios claros que definan una intervención específica es central en las directrices técnicas para la realización de revisiones sistemáticas.[50,51]

- Aun cuando estas revisiones señalan que son parte de un mismo protocolo, llama la atención que cada una utilizó herramientas diferentes para categorizar la calidad de la evidencia, sin proveer un razonamiento. Diferentes herramientas pueden arrojar resultados diferentes. Al chequear el protocolo original, es posible comprobar que los autores modificaron los métodos preestablecidos para evaluar la calidad de la evidencia.[52] Dado que no se entrega un razonamiento, se deja espacio a la posibilidad de que se hayan acomodado las herramientas para obtener un determinado resultado.

- Incluso más allá del método de evaluación de la evidencia, una vez evaluada, este juicio es subjetivo. Esto es evidente en el elevado número de estudios considerados de calidad "moderada" que apoyan intervenciones como la terapia hormonal cruzada, que luego no fueron considerados en las conclusiones.

- Las revisiones sistemáticas son muchísimo más breves que el Cass review, y sus conclusiones son mucho más cautelosas que el reporte completo, pues sólo pueden basarse en la evidencia que se encontró sistemáticamente. El reporte incluye otras fuentes no sistemáticas.

Inconsistencias en la evaluación de la validez de la evidencia: El sistema GRADE

- Existe una inconsistencia en la evaluación de calidad de la evidencia. Las revisiones sistemáticas ocupan escalas de evaluación basadas en el contenido de los artículos de investigación, mientras que el informe final Cass utiliza el sistema GRADE (*Grading of Recommendations, Assessment, Development, and Evaluations*).
  - En este sistema, las revisiones sistemáticas y ensayos clínicos aleatorios (en inglés, *randomized clinical trials* (RCT)) están por sobre cualquier estudio observacional (no experimental).
  - El sistema GRADE se basa en el diseño de los estudios y no en su contenido. Cuando este método es sobre-simplificado puede llevar a reduccionismos graves. Por ejemplo, evaluar todo estudio observacional como de baja calidad, sin considerar su contenido.
  - Las propias guías GRADE establecen que evidencia de "baja calidad" puede ser el sustento de recomendaciones clínicas claras.[53]
  - De hecho, estudios han demostrado que tanto en la indicación de fármacos en pediatría como las guías de la OMS en gran parte se basan en evidencia que GRADE categoriza como de "baja calidad" o "débil".[54,55] Algunos ejemplos de indicaciones médicas sin soporte de "alta calidad" para los estándares de la revisión Cass incluyen el paracetamol para el dolor de espalda[56] y los propios bloqueadores puberales para niñxs cisgénero con pubertad precoz.[57]

- El problema está en cómo se presenta a una audiencia general la evidencia usando la etiqueta de "baja calidad" o "débil" sin explicación técnica del término.[41] Esto es aún más problemático en el caso de los medios de comunicación.

- Más aún, la inexistencia de estudios RCT como justificación de una supuesta incapacidad de fundamentar decisiones es extremadamente riesgosa en salud pública. El mismo argumento ha sido usado para cuestionar los fundamentos del uso de mascarillas para el COVID y contra el uso de vacunas.[58,59]

Falta de conexión con el contexto y las condiciones materiales que moldean las experiencias de tránsito y de acceso a la salud trans-afirmativa

- Las revisiones y el reporte Cass recomiendan realizar estudios RCT como única forma de resolver incertidumbres respecto de la evidencia en torno al uso de bloqueadores puberales y tratamientos hormonales:
  - Tanto las revisiones sistemáticas como el reporte Cass en su conjunto, instrumentalizan la ausencia de estudios tipo RCT para argumentar que la evidencia existente es de baja calidad. Para remediar lo anterior y generar más evidencia, proponen además realizar estudios RCT para testear las intervenciones.
  - En la práctica, eso implicaría asignar aleatoriamente a niñes y adolescentes a recibir tratamiento (ej. bloqueadores hormonales u hormonas cruzadas) o un placebo, condicionando la atención de salud afirmativa a que participen de un estudio: es decir, se condiciona la entrega de medicamentos que son vitales para su desarrollo, salud mental y física, aumentando la angustia e incertidumbre de quienes llevan años esperando recibir atención.
  - Esta sugerencia está completamente desligada de la experiencia de tránsito de niñes y adolescentes trans, no binaries y de género expansivo, además de estar desligada del conocimiento de quienes trabajan directamente con esta población.
  - Esto lleva a una sugerencia éticamente cuestionable en un ámbito donde académicxs han expuesto las razones por las cuales los estudios RCT para estas intervenciones no son viables ni éticos.[60]

- La interpretación de los hallazgos no fue adecuadamente contrastada con cambios a nivel macro en infancia y adolescencia. Por ejemplo:
  - La atención que se pone sobre la identificación de autismo no es contextualizada con la controversia actual alrededor del incremento de identificación de autismo a nivel global.[61]
  - La falta de respuesta a intervenciones psicosociales no es contrastada con la realidad de que incluso la psicoterapia tiene un efecto limitado en tratar la depresión en población general infantojuvenil,[62] más aún en el caso de una población sistemáticamente vulnerada.

- La interpretación de los hallazgos fue hecha totalmente desconectada de la experiencia de personas trans. Por ejemplo:
  - Se estableció la expectativa de un claro efecto positivo y homogéneo de la transición social, los bloqueadores puberales o el tratamiento hormonal cruzado. Dado que ese efecto no se encontró, entonces se desestima la intervención.
  - Puesto de otra forma, el razonamiento es "si transitar socialmente, bloquear la pubertad o el tratamiento hormonal no se asocian con mejorías en la depresión, ansiedad o suicidalidad, *entonces* estas intervenciones no son útiles."
  - Por un lado, las prácticas afirmativas en salud, así como las experiencias de transición (social, legal, médicas) son diversas y no se pueden homogeneizar. No todas las personas trans realizan los mismos cambios, no todas desean hormonarse ni optan por cirugías de modificación corporal.
  - Por otro lado, existe un problema en asumir que una persona dejará de tener los estresores sociales y experiencias de marginación y violencia sólo por transitar socialmente o recibir intervenciones médicas. Esto desconoce todo el contexto macro de la experiencia trans en una sociedad cisnormativa, las barreras de acceso a la salud y los tiempos de espera que el mismo informe Cass reconoce, por nombrar sólo algunos factores.
  - Otro ejemplo sería sugerir que el consumo de pornografía online estaría vinculado con la disforia de género (ver comentario anterior sobre 'pánico moral'). En una sección del informe, Cass reflexiona acerca de la cuestión generacional y la influencia que tendrían distintos estresores sobre las actitudes y comportamientos de quienes consultan en el NHS debido a su identidad de género (la denominada 'Generación Z'). En el punto 7.20 (p. 110), Cass cita una publicación de Karin Nadrowski para sugerir que "la exploración con jóvenes que cuestionan su género debe considerar su interacción con contenidos pornográficos". Esta sugerencia no tiene ningún fundamento científico ni evidencia alguna. Es una sugerencia muy dañina y poco rigurosa que estigmatiza y vuelve a instalar la sospecha respecto de las supuestas causas de la disforia e identidad de género, su supuesto 'contagio' y 'moda' entre jóvenes.

- La interpretación de los hallazgos fue hecha con estándares inconsistentes a la hora de evaluar la evidencia disponible:
  - Los bloqueadores puberales, tratamientos hormonales e incluso la transición social son sometidas a un juicio de existencia de RCT que las avalen. En contraste, la propuesta del informe Cass sobre "acompañamientos" psicosociales no se basan en la existencia de estudios similares que lo avalen.
  - Se acusan problemas de representatividad de los estudios clínicos que se encontraron en la revisión, pero no se señala cuál sería el método adecuado de reclutamiento de pacientes. ¿Cómo conseguir una muestra aleatoria de personas trans y no binarias? Por otro lado, los problemas de representatividad no parecen ser un problema cuando se incluyen estudios sobre de/retransición de baja calidad, sin señalar el tamaño muestral que representan e incluso replicando gráficos con faltas ortográficas (p.189).

- La interpretación de los hallazgos fue hecha en comparación a un estándar poco claro y sin evidencia. Por ejemplo:
  - En el análisis del número de personas derivadas a unidades de género en el tiempo, se acusa un incremento “mayor a lo esperable a la aceptación social actual” de la disidencia sexo-genérica. ¿Cuál es ese estándar esperable?
  - Sin ninguna estimación clara y real de qué parte de la población general es trans y no binaria, ¿cuál es la evolución estándar esperable para la demanda de un servicio necesario que antes no existía y no se ofrecía, en un contexto que además es tremendamente hostil hacia la población consultante?

Conclusión

El Informe o Revisión Cass es un documento controvertido, que dará espacio a debates sobre su rigurosidad científica. Sus implicancias son de gran escala por estar respaldado por instituciones gubernamentales de salud que son referencia internacional. Este informe se generó en un contexto político y social tremendamente hostil hacia las personas trans y no binarias y su metodología científica debe entenderse en ese contexto.

El informe no generó datos nuevos, no dio cuenta de evidencia alguna sobre supuestos “daños”, ni es en sí una revisión sistemática, como se ha presentado hacia el público en diversos medios. El informe no recomienda la suspensión total de las intervenciones médicas ni recomienda prohibir la transición social o el cierre de las clínicas de género. El informe sí promueve un enfoque holístico en la atención de personas trans, no binarias y de género no conforme en la infancia y adolescencia, respecto de lo cual nos sentimos convocades a colaborar en conjunto con quienes llevan años trabajando en estas temáticas, tanto desde la academia como desde la sociedad civil.

Pese a lo anterior, el informe contiene recomendaciones que contradicen las guías de tratamiento internacionales vigentes y afirmaciones que exceden muy significativamente el contenido de las revisiones sistemáticas. La metodología científica del informe ya está siendo objeto de críticas y los hallazgos no se deben considerar como reflejo universal de toda la investigación ni experiencia clínica existente. Después de todo, es una revisión que encarga el NHS en respuesta a una problemática específica local que no es del todo replicable.

Muchas de las recomendaciones del informe no dialogan con la realidad de las personas trans ni sus experiencias de tránsito diversas siendo, además, potencialmente dañinas para su dignidad. La desinformación, tergiversación de los hallazgos y usos políticos del informe para restringir aún más el acceso a la salud trans-afirmativa nos parecen particularmente graves, especialmente cuando son los medios de comunicación y las redes sociales quienes amplifican la desinformación para producir pánico y confirmar sus propios prejuicios respecto de la salud de género afirmativa.

Con todo, es de suma importancia que respondamos de manera coordinada, atingente y fundamentada en evidencia científica y principios éticos universales. Esto es importante en las conversaciones con quienes no tienen experiencia en salud trans y no binaria, y que desean hacerse una opinión informada. El presente documento tiene como fin entregar herramientas para establecer diálogos informativos y responsables. Durante este período aún más difícil de lo habitual, nuestra invitación es a actuar de manera colectiva y cuidándonos entre todes.

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Referencias

1. Siddique H, correspondent HSL affairs. Appeal court overturns UK puberty blockers ruling for under-16s. *The Guardian*. https://www.theguardian.com/society/2021/sep/17/appeal-court-overturns-uk-puberty-blockers-ruling-for-under-16s-tavistock-keira-bell. Published September 17, 2021. Accessed May 10, 2024.
2. Walsh R. A blow to the rights of transgender children. British Psychological Society. Published December 3, 2020. Accessed May 7, 2024. https://www.bps.org.uk/psychologist/blow-rights-transgender-children
3. Osserman J. Psychoanalysis and Trans: A Study of Two Psychosocial Scenes. In: Frosh S, Vyrgioti M, Walsh J, eds. *The Palgrave Handbook of Psychosocial Studies*. Springer International Publishing; 2024:1-20. doi:10.1007/978-3-030-61510-9_13-1
4. McKay K, Kennedy E, Wright T, Young B. Thinking Time, Shifting Goalposts and Ticking Time Bombs: Experiences of Waiting on the Gender Identity Development Service Waiting List. *Int J Environ Res Public Health*. 2022;19(21):13883. doi:10.3390/ijerph192113883
5. Barras A, Carlile A. *"Everything Feels Stacked against Us." Two Years on: Understanding the Impact of the 2020 Bell v Tacistock Case on Transgender, Non-Binary, and Gender Diverse Children, Young People and Their Families*. Mermaids; Goldsmiths, University of London; 2022. Accessed May 7, 2024. https://mermaidsuk.org.uk/wp-content/uploads/2022/12/BvT-short-report-December-2022.pdf
6. Waiting list/waiting times. Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust. Accessed May 7, 2024. https://www.cntw.nhs.uk/services/northern-region-gender-dysphoria-service-specialist-service-walkergate-park/waiting-list-waiting-times/
7. Madrigal-Borloz V. *United Nations Independent Expert on Protection against Violence and Discrimination Based on Sexual Orientation and Gender Identity. Country Visit to the United Kingdome of Great Britain and Northern Ireland (24 April - 5 May 2023): End of Mission Statement*. United Nations; 2023. Accessed May 8, 2024. https://www.ohchr.org/sites/default/files/documents/issues/sexualorientation/statements/eom-statement-UK-IE-SOGI-2023-05-10.pdf
8. Amery F, Mondon A. Othering, peaking, populism and moral panics: The reactionary strategies of organised transphobia. *The Sociological Review*. Published online April 16, 2024:00380261241242283. doi:10.1177/00380261241242283
9. Pearce R, Erikainen S, Vincent B. TERF wars: An introduction. *The Sociological Review*. 2020;68(4):677-698. doi:10.1177/0038026120934713
10. Faye S. *Trans: Un alegato por un mundo más justo y más libre*. Traducción de Rosa María García; 2022.
11. Hall S, Critcher C, Jefferson T, Clarke J, Roberts B. *Policing the Crisis: Mugging, the State, and Law and Order*. 1978th edition. Palgrave; 1978.
12. Phipps A. *Me, Not You: The Trouble with Mainstream Feminism*. Manchester University press; 2020.

13. Gill-Peterson J. *Historias de La Infancia Trans*. Bellaterra Edicions; 2022. https://www.bellaterra.coop/es/libros/historias-de-la-infancia-trans
14. Serano J. All the Evidence Against Transgender Social Contagion. Medium. Published May 26, 2023. Accessed May 10, 2024. https://juliaserano.medium.com/all-the-evidence-against-transgender-social-contagion-f82fbda9c5d4
15. Bachmann CL, Gooch B. *LGBT in Britain: Health Report*. Stonewall Foundation; YouGov; 2018. Accessed May 8, 2024. https://www.stonewall.org.uk/system/files/lgbt_in_britain_health.pdf
16. Yıldız E. Suicide in sexual minority populations: A systematic review of evidence-based studies. *Archives of Psychiatric Nursing*. 2018;32(4):650-659. doi:10.1016/j.apnu.2018.03.003
17. Government Equalities Office. *LGBT Action Plan*.; 2018. Accessed May 8, 2024. https://assets.publishing.service.gov.uk/media/5b39e91ee5274a0bbef01fd5/GEO-LGBT-Action-Plan.pdf
18. McGowan VJ, Lowther HJ, Meads C. Life under COVID-19 for LGBT+ people in the UK: systematic review of UK research on the impact of COVID-19 on sexual and gender minority populations. *BMJ Open*. 2021;11(7):e050092. doi:10.1136/bmjopen-2021-050092
19. Williams Z. Remember Brianna Ghey's name, not her killers' – and confront the transphobia that dogged her. *The Guardian*. https://www.theguardian.com/commentisfree/2024/feb/02/brianna-ghey-name-killers-transphobia-children. Published February 2, 2024. Accessed May 8, 2024.
20. Jowett A, Brady G, Goodman S, Pillinger C, Bradley L. *Conversion Therapy: An Evidence Assessment and Qualitative Study*. Government Equalities Office; Coventry University; 2020. Accessed May 12, 2024. https://pure.coventry.ac.uk/ws/portalfiles/portal/44880617/2020_12_15_Conversion_Therapy_Reserach_Report_AJ_edited_clean_4_.pdf
21. Ban Conversion Therapy Coalition. Protecting trans victims of gender identity conversion practices. Published online 2022. Accessed May 8, 2024. https://static1.squarespace.com/static/5efc4344362f4379c92231da/t/62629af0ff5cf66e052c1a99/1650629361587/BCT+briefing_22+April+2022.pdf
22. Cass H. *Independent Review of Gender Identity Services for Children and Young People: Final Report*.; 2024. Accessed May 10, 2024. https://cass.independent-review.uk/home/publications/final-report/
23. Horton C. The importance of child voice in trans health research: a critical review of research on social transition and well-being in trans children. *International Journal of Transgender Health*. 2023;0(0):1-18. doi:10.1080/26895269.2023.2295381
24. Endocrine Society. Transgender Health: An Endocrine Society Position Statement. Published December 16, 2020. Accessed May 8, 2024. https://www.endocrine.org/advocacy/position-statements/transgender-health
25. Poteat T, Davis AM, Gonzalez A. Standards of Care for Transgender and Gender Diverse People. *JAMA*. 2023;329(21):1872. doi:10.1001/jama.2023.8121
26. Rafferty J, COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON ADOLESCENCE, et al. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. *Pediatrics*. 2018;142(4):e20182162. doi:10.1542/peds.2018-2162
27. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2):e20191725. doi:10.1542/peds.2019-1725
28. de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, 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
29. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*. 2022;23(sup1):S1-S259. doi:10.1080/26895269.2022.2100644
30. Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature. *Child and Adolescent Mental Health*. 2021;26(1):3-14. doi:10.1111/camh.12437

31. 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). doi:10.1371/journal.pone.0261039
32. Lavender R, Shaw S, Maninger JK, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. *LGBT health*. 2023;(101616707). doi:10.1089/lgbt.2022.0201
33. 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. *International journal of pediatric endocrinology*. 2020;2020(101516111):8. doi:10.1186/s13633-020-00078-2
34. Chen D, Berona J, Chan YM, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *The New England journal of medicine*. 2023;388(3):240-250. doi:10.1056/NEJMoa2206297
35. 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
36. Horton C. "I Was Losing That Sense of Her Being Happy"—Trans Children and Delaying Social Transition. *LGBTQ+ Family: An Interdisciplinary Journal*. 2022;18(2):187-203. doi:10.1080/27703371.2022.2076002
37. Horton C. "It felt like they were trying to destabilise us": Parent assessment in UK children's gender services. *International Journal of Transgender Health*. 2023;24(1):70-85. doi:10.1080/26895269.2021.2004569
38. Horton C. Experiences of Puberty and Puberty Blockers: Insights From Trans Children, Trans Adolescents, and Their Parents. *Journal of Adolescent Research*. 2024;39(1):77-103. doi:10.1177/07435584221100591
39. BBC. Transgender patients could face years-long wait for NHS treatment.https://www.bbc.com/news/uk-68602939. Published March 20, 2024. Accessed May 8, 2024.
40. Rose E. bricks that built bodies. Transsexual Heretic. Published February 28, 2023. Accessed May 10, 2024. https://eliottrose.substack.com/p/bricks-that-built-bodies
41. Horton C. The Cass Review: Cis-supremacy in the UK's approach to healthcare for trans children. *International Journal of Transgender Health*. 2024;0(0):1-25. doi:10.1080/26895269.2024.2328249
42. Lame G. Systematic Literature Reviews: An Introduction. *Proceedings of the Design Society: International Conference on Engineering Design*. 2019;1(1):1633-1642. doi:10.1017/dsi.2019.169
43. Taylor J, Hall R, Langton T, Fraser L, Hewitt CE. Characteristics of children and adolescents referred to specialist gender services: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326681
44. Hall R, Taylor J, Hewitt CE, et al. Impact of social transition in relation to gender for children and adolescents: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326112
45. Heathcote C, Taylor J, Hall R, et al. Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326347
46. Taylor J, Mitchell A, Hall R, et al. Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326669
47. Taylor J, Mitchell A, Hall R, Langton T, Fraser L, Hewitt CE. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326670
48. Taylor J, Hall R, Langton T, Fraser L, Hewitt CE. Care pathways of children and adolescents referred to specialist gender services: a systematic review. *Archives of Disease in Childhood*. Published online April 9, 2024. doi:10.1136/archdischild-2023-326760
49. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience & Biobehavioral Reviews*. 2006;30(6):718-729. doi:10.1016/j.neubiorev.2006.06.001

50. Page MJ, McKenzie JE, Bossuyt PM, et al. Declaración PRISMA 2020: una guía actualizada para la publicación de revisiones sistemáticas. *Rev Esp Cardiol*.
51. Stern C, Lizarondo L, Carrier J, et al. Methodological guidance for the conduct of mixed methods systematic reviews. *JBI Evidence Synthesis*. 2020;18(10):2108-2118. doi:10.11124/JBISRIR-D-19-00169
52. Urquhart E. Methods Change Raises New Questions of Bias in Cass Review. Assigned. Accessed May 8, 2024. https://www.assignedmedia.org/breaking-news/york-preregistration-turban-mmat-nos
53. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*. 2011;64(4):401-406. doi:10.1016/j.jclinepi.2010.07.015
54. Alexander PE, Bero L, Montori VM, et al. World Health Organization recommendations are often strong based on low confidence in effect estimates. *Journal of Clinical Epidemiology*. 2014;67(6):629-634. doi:10.1016/j.jclinepi.2013.09.020
55. Meng M, Zhou Q, Lei W, et al. Recommendations on Off-Label Drug Use in Pediatric Guidelines. *Front Pharmacol*. 2022;13. doi:10.3389/fphar.2022.892574
56. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet*. 2014;384(9954):1586-1596. doi:10.1016/S0140-6736(14)60805-9
57. Luo X, Liang Y, Hou L, Wu W, Ying Y, Ye F. Long-term efficacy and safety of gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis. *Clinical Endocrinology*. 2021;94(5):786-796. doi:10.1111/cen.14410
58. Prasad V. Hospitals that reinstate universal masking with flimsy surgical masks are anti-science. Published December 26, 2021. Accessed May 1, 2024. https://www.drvinayprasad.com/p/hospitals-that-reinstating-universal
59. Prasad V. The only real solution to vaccine skepticism: We need more randomized trials and a new phase IV safety system. Published December 26, 2021. Accessed May 1, 2024. https://www.drvinayprasad.com/p/the-only-real-solution-to-vaccine
60. Ashley F, Tordoff DM, Olson-Kennedy J, Restar AJ. Randomized-controlled trials are methodologically inappropriate in adolescent transgender healthcare. *International Journal of Transgender Health*. 2023;0(0):1-12. doi:10.1080/26895269.2023.2218357
61. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: A systematic review update. *Autism Research*. 2022;15(5):778-790. doi:10.1002/aur.2696
62. Cuijpers P, Karyotaki E, Ciharova M, et al. The effects of psychological treatments of depression in children and adolescents on response, reliable change, and deterioration: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2023;32(1):177-192. doi:10.1007/s00787-021-01884-6

PRESS RELEASE

Endocrine Society Statement in Support of Gender-Affirming Care

Washington, DC May 08, 2024

We stand firm in our support of gender-affirming care. Transgender and gender-diverse people deserve access to needed and often life-saving medical care.

NHS England's recent report, the Cass Review, does not contain any new research that would contradict the recommendations made in our **Clinical Practice Guideline** on gender-affirming care.

The guideline, which cites more than 260 research studies, recommends a very conservative approach to care, with no medical intervention prior to puberty. Estimates indicate only a fraction of transgender and gender-diverse adolescents opt to take puberty-delaying medications, which have been used to treat early puberty in youth for four decades.

- The guideline recommends beginning treatment with puberty-delaying medications that are generally reversible.
- As adolescents grow older and can provide informed consent, then hormone therapy can be considered.
- Our guideline suggests waiting until an individual has turned 18 or reached the age of majority in their country to undergo gender-affirming

genital surgery.

Our Clinical Practice Guidelines are developed using a **robust and rigorous process** that adheres to the highest standards of trustworthiness and transparency as defined by the Institute of Medicine (now the National Academy of Medicine). Our guideline development panels spend years developing each guideline based on a thorough review of medical evidence, author expertise, rigorous scientific review, and a transparent process. More than 18,000 Endocrine Society members worldwide have an opportunity to comment on guideline drafts prior to publication.

The Society is in the process of updating the 2017 Clinical Practice Guideline. It was one of **six selected** for a routine update. The process will incorporate the latest research and conduct systematic reviews to provide guidance on the safe and effective treatment of gender incongruence and dysphoria from an endocrine perspective.

We agree that increased funding for youth and adult transgender health research programs is needed to close the gaps in knowledge regarding transgender medical care and should be made a priority.

Although the scientific landscape has not changed significantly, misinformation about gender-affirming care is being politicized. In the United States, 24 states have enacted laws or policies barring adolescents' access to gender-affirming care, according to the **Kaiser Family Foundation.** In seven states, the policies also include provisions that would prevent at least some adults over age 18 from accessing gender-affirming care.

Cisgender teenagers, together with their parents or guardians, are deemed competent to give consent to various medical treatments. Teenagers who have gender incongruence and their parents and guardians should not be discriminated against.

Transgender and gender-diverse teenagers, their parents, and physicians should be able to determine the appropriate course of treatment. Banning evidence-based medical care based on misinformation takes away the ability of parents and patients to make informed decisions.

Medical evidence, not politics, should inform treatment decisions.

About Endocrine Society

Endocrinologists are at the core of solving the most pressing health problems of our time, from diabetes and obesity to infertility, bone health, and hormone-related cancers. The Endocrine Society is the world's oldest and largest organization of scientists devoted to hormone research and physicians who care for people with hormone-related conditions.

The Society has more than 18,000 members, including scientists, physicians, educators, nurses, and students in 122 countries. To learn more about the Society and the field of endocrinology, visit our site at **www.endocrine.org**. Follow us on X (formerly Twitter) at **@TheEndoSociety** and **@EndoMedia**.

Endocrine Society Guideline recommends healthy adults under the age of 75 take the recommended daily allowance of vitamin D

June 03, 2024

Healthy adults under the age of 75 are unlikely to benefit from taking more than the daily intake of vitamin D recommended by the Institutes of Medicine (IOM) and do not require testing for vitamin D levels, according to a new Clinical Practice Guideline issued today by the Endocrine Society. For children, pregnant people, adults older than 75 years and adults with high-risk prediabetes, the guideline recommends vitamin D higher than the IOM recommended daily allowance.

PRESS RELEASE Meetings & Events

ENDO 2024 press conferences to highlight male birth control, anti-obesity medications

May 21, 2024

Researchers will delve into emerging research in diabetes, obesity, reproductive health and other aspects of hormone health during the Endocrine Society's ENDO 2024 news conferences June 1-4.

PRESS RELEASE

Lily Ng and Douglas Forrest of NIDDK win 2024 Endocrine Images Art Competition

May 16, 2024

The Endocrine Society is delighted to announce that Lily Ng, PhD, and Douglas Forrest, Ph.D., have won the Society's 2024 Endocrine Images Art Competition for their image of the astrocyte cell that expresses type 2 deiodinase.

PRESS RELEASE

Endocrine Society and European Society of Endocrinology publish joint guideline on

glucocorticoid-induced adrenal insufficiency

May 13, 2024

The joint guideline is designed to help clinicians manage patients who have, or are at risk of developing, glucocorticoid-induced adrenal insufficiency. At least 1% of the global population uses chronic glucocorticoid therapy as anti-inflammatory or immune-suppressive agents.

PRESS RELEASE

Endocrine Society names Andrews as new Editor-in-Chief of Endocrinology

April 25, 2024

The Endocrine Society has appointed Zane B. Andrews, Ph.D., of Monash University in Melbourne, Australia, as Editor-in-Chief of its flagship basic science journal, Endocrinology.

AMERICAN PSYCHOLOGICAL ASSOCIATION

P Policy Statement on ffirming Evidence-Based Inclusive Care for Transgender, Gender Diverse, and Nonbinary Individuals, ddressing Misinformation, and the Role of Psychological Practice and Science

FEBRU RY 2024

Consistent with the merican Psychological ssociation's mission to promote the advancement, communication, and application of psychological science and knowledge to benefit society and improve lives, this Policy Statement affirms P 's support for unobstructed access to healthcare and evidence-based clinical care for transgender, gender-diverse, and nonbinary children, adolescents, and adults, and for increased public accessibility to timely and accurate information founded in clinical and psychological science. Evidence-based clinical care, including gender-affirming care, should be noncoercive, adaptive to and centered on the needs of the individual receiving care, and rooted in psychological and clinical science, including recognition of gender diversity as a part of normal human diversity as well as recognition of limits in the current state of scientific knowledge.

Furthermore, this policy statement addresses the spread of misleading and unfounded narratives that mischaracterize gender dysphoria and affirming care, likely resulting in further stigmatization, marginalization, and lack of access to psychological and medical supports for transgender, gender diverse, and nonbinary individuals. Misinformation further creates distress and confusion for families and loved ones of transgender, gender-diverse, and nonbinary individuals, as they make decisions about their healthcare. The primary goal is to encourage psychologists to unite in their support for access to psychological and all appropriate healthcare services and treatment for transgender, gender-diverse, and nonbinary individuals.

Policy Statement:

WHERE S gender diversity is present throughout the lifespan and has been present throughout history (Gill-Peterson, 2018; Hunt, 2016; Stryker, 2017); and

WHERE S gender-based bias and mistreatment (e.g., discrimination, violence, non-affirmation, or rejection in response to gender diversity) pose significant harm, including risk of suicide, to the well-being of children, adolescents, adults, and families. (Delozier et al., 2020; Kosciw et al., 2022; Puckett et al., 2023; Trevor Project, 2023); and

WHERE S transgender, gender diverse, and nonbinary individuals experiencing systemic discrimination and mistreatment targeting their gender identity or expression, may also face racial, ethnic, socioeconomic, religious, and other forms of discrimination, translated into greater discrimination and psychological distress than their counterparts (Castro-Ramirez et al., 2021; Hendricks & Testa, 2012; Lefevor et al., 2019; Lytle et al., 2016; Turban et al., 2020; van der Miesen et al., 2020); and

WHERE S gender-related distress is a complex and nuanced psychological experience, informed by a rapidly evolving basis in new scientific findings and advances, which often requires specialized understanding and expertise (P , 2015; Coleman et al., 2022); and

WHERE S psychologists often play a vital role in assisting individuals experiencing gender dysphoria and their parents, caregivers, and families, offering valuable insights into their mental health and well-being (P , 2015; dickey & Puckett, 2023; Hughto et al., 2015); and

WHERE S psychologists can play an important and essential role in facilitating the support for client-led exploration of gender identity, assisting individuals in navigating their unique experiences (P , 2015; Coleman et al., 2022); and

WHERE S affirming mental health services provided by psychologists can positively contribute to the holistic care of individuals participating in gender-affirming healthcare or experiencing gender dysphoria, gender incongruence, and/or distress associated with discrimination and mistreatment (nzani et al., 2019; Expósito-Campos et al., 2023; Hembree et al.,2017; Wittlin et al., 2023; World Health Organization, 2022); and

WHERE S legislative efforts to restrict access to care have involved the dissemination of misleading and unfounded narratives (e.g., mischaracterizing gender dysphoria as a manifestation of traumatic stress or neurodivergence, and equating affirming care for transgender, gender-diverse, and nonbinary youth with child abuse), creating a distorted perception of the psychological and

medical support necessary for these youth and creating a hostile environment that adversely affects their mental health and wellbeing (P , 2023; shley, 2023; Hughto et al., 2022; Kremen et al., 2021; McNamara et al., 2022); and

WHERE S such misinformation is widely disseminated through formal and informal networks, yet credible scientific evidence has not been widely disseminated and is not readily accessible to the public, having the potential to further stigmatize and marginalize all transgender, gender-diverse, and nonbinary individuals, hindering their access to indicated and necessary healthcare, worsening existing geographic disparities in healthcare access, and fostering an environment that may lead to discrimination (DuBois et al., 2023; Goldenberg et al., 2020; Weixel & Wildman, 2022); and

WHERE S state bans on gender-affirming care and the imposition of legal penalties on providers engaging in evidence-based care disregard the comprehensive body of psychological and medical research supporting the positive impact of gender-affirming treatments, which include as a standard of care noncoercive, developmentally appropriate support for gender exploration and decision-making in alleviating psychological distress and improving overall well-being for transgender, gender diverse, and nonbinary individuals across the lifespan (chille et al., 2020; shley, 2023; Green et al., 2022; Ramos et al., 2021; Tordoff et al., 2022); and

WHERE S state bans on gender-affirming care disrupt not only the role of providers in offering evidence-based care but also obstruct patient and parental rights in shared decision-making (Clark & Virani, 2021); and

WHERE S the imposition of such bans poses a direct threat to the mental health and emotional well-being of transgender, gender-diverse, and nonbinary youth, exacerbating the already high rates of depression, anxiety, and suicide attempts among this vulnerable population (breu et al., 2022a; breu et al., 2022b; Hughes et al., 2021; Kidd et al., 2021); and

WHERE S obstructing access to psychological and medical interventions, including gender-affirming care, heightens the risk of negative mental health outcomes among children, adolescents, and adults; (Chen et al., 2023; McGregor et al. 2023; Turban et al., 2020; Turban, et al. 2022; van der Miesen et al., 2020);

THEREFORE, BE IT RESOLVED that the merican Psychological ssociation (P) steadfastly supports evidence-based clinical care for all children, adolescents, and adults inclusive of gender identity and expression; and

THEREFORE, BE IT RESOLVED that the P upholds the rights of all individuals to unbiased health insurance coverage, rejecting discrimination based on gender identity and advocating for the inclusion of gender-affirming care, including psychological care; and

THEREFORE, BE IT RESOLVED that the P underscores the necessity for access to comprehensive, gender-affirming healthcare for transgender, gender-diverse, and nonbinary children, adolescents, and adults; and

THEREFORE, BE IT RESOLVED that the P underscores the importance of an accurate understanding of evidence-based care—highlighting the continuous need for research and expansion of the scientific foundation to further ensure full access to competent and reliable healthcare—s as essential to promoting inclusivity; protecting the rights of transgender, gender-diverse, and nonbinary individuals; and ensuring that they receive the necessary support and full healthcare attention, inclusive of psychological and medical care, in a compassionate and affirming manner; and

THEREFORE, BE IT RESOLVED that the P supports efforts to address and rectify the dissemination of false information to ensure the well-being and dignity of transgender, gender-diverse, and nonbinary individuals; and

THEREFORE, BE IT RESOLVED that the P opposes state bans on gender-affirming care, which are contrary to the principles of evidence-based healthcare, human rights, and social justice, and which should be reconsidered in favor of policies that prioritize the well-being and autonomy of transgender, gender-diverse, and nonbinary individuals; and

THEREFORE, BE IT RESOLVED that insurance plans should extend coverage for healthcare services tailored to the developmental needs of children, adolescents, and adults identifying as transgender, gender-diverse, or nonbinary, encompassing both psychological and medical gender-affirming care; and

THEREFORE, BE IT RESOLVED that equitable health insurance access is necessary to facilitate essential gender-affirming care, including access to mental health supports; and

THEREFORE, BE IT RESOLVED that the P opposes efforts to obstruct access to evidence-based interventions for children, adolescents, and adults, advocating for inclusive healthcare coverage without gender-based discrimination; and

THEREFORE, BE IT FURTHER RESOLVED that the P emphasizes the importance of psychological and medical care from an intersectional perspective, which takes into consideration the many facets of an individual's experience and provides services that are antidiscriminatory in all areas, including opposing racial, ethnic, socioeconomic, religious, and gender-based discrimination; and

THEREFORE, BE IT FURTHER RESOLVED that the P urges support for policies facilitating access to comprehensive, gender-affirming healthcare for children, adolescents, and adults, recognizing the positive impact on mental health outcomes; and

THEREFORE, BE IT FURTHER RESOLVED that the P encourages insurance providers to offer coverage addressing the healthcare needs of children, adolescents, and adults who identify as transgender, gender diverse, or nonbinary; and

THEREFORE, BE IT FURTHER RESOLVED the P affirms the essential role and legal rights of parents and caregivers in taking action to ensure the well-being of children and adolescents while honoring their expressed gender identity, including involvement in the process of healthcare decision-making, as well as the role of parents, caregivers, and providers in supporting developmentally appropriate youth self-advocacy.

REFERENCES

breu, R. L., Sostre, J. P., Gonzalez, K. ., Lockett, G. M., & Matsuno, E. (2022). "I am afraid for those kids who might find death preferable": Parental figures' reactions and coping strategies to bans on gender-affirming care for transgender and gender diverse youth. *Psychology of Sexual Orientation and Gender Diversity, 9*(4), 500–510. https://doi.org/10.1037/sgd0000495

breu, R. L., Sostre, J. P., Gonzalez, K. ., Lockett, G. M., & Matsuno, E., Mosley, D. V. (2022b). Impact of gender-affirming care bans on transgender and gender diverse youth: Parental figures' perspective. *Journal of Family Psychology, 36*(5), 643–652.

chille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, ., & Wilson, T. . (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. *International Journal of Pediatric Endocrinology*, *2020*, 1–5. https://doi.org/10.1186/s13633-020-00078-2

merican Psychological ssociation. (2015). Guidelines for psychological practice with transgender and gender nonconforming people. *merican Psychologist*, *70*, 832–864. https://doi.org/10.1037/a0039906

merican Psychological ssociation. (2023). *Using psychological science to understand and fight health misinformation.* merican Psychological ssociation. https://www.apa.org/pubs/reports/health-misinformation

nzani, ., Morris, E. R., & Galupo, M. P. (2019). From absence of microaggressions to seeing authentic gender: Transgender clients' experiences with micro affirmations in therapy. *Journal of LGBT Issues in Counseling*, *13*(4), 258–275. https://doi.org/10.1080/15538605.2019.1662359

shley, F. (2023). Interrogating gender-exploratory therapy. *Perspectives on Psychological Science*, *18*(2), 472–481. https://doi.org/10.1177/17456916221102325

Castro-Ramirez, F., l-Suwaidi, M., Garcia, P. Rankin, O., Ricard, J. R., & Nock, M. K. (2021). Racism and poverty are barriers to the treatment of youth mental health concerns, *Journal of Clinical Child & dolescent Psychology*, *50*, 534–546. https://doi.org/10.1080/15374416.2021.1941058

Chen, D., Berona, J., Chan, Y., Ehrensaft, D., Garofalo, R., Hidalgo, M. ., Rosenthal, S. M., Tishelman, . C., & Olson-Kennedy, J. (2023). Psychosocial functioning in transgender youth after 2 years of hormones. *The New England Journal of Medicine*, *388*(3), 240–250. https://doi.org/10.1056/nejmoa2206297

Clark, B. ., & Virani, . (2021). This wasn't a split second decision: n empirical ethical analysis of transgender youth capacity, rights and authority to consent to hormone therapy. *Journal of Bioethical Inquiry*, *18*(1),1510164. https://doi.org/10.1007/s11673-020-10086-9

Coleman, E., Radix, . E., Bouman, W. P., Brown, G. R., De Vries, . L., Deutsch, M. B., … & rcelus, J. (2022). Standards of care for the health of transgender and gender diverse people, version 8. *International Journal of Transgender Health*, *23*(sup1), S1–S259. https://doi.org/10.1080/26895269.2022.2100644

Delozier, . M., Kamody, R. C., Rodgers, S., & Chen, D. (2020). Health disparities in transgender and gender expansive adolescents: topical review from a minority stress framework. *Journal of Pediatric Psychology*, *45*(8), 842–847. https://doi.org/10.1093/jpepsy/jsaa040

dickey, l. m., & Puckett, J. . (2023). *ffirmative counseling for transgender and gender diverse clients.* Hogrefe Publishing.

DuBois, L. Z., Puckett, J. ., Price, S. F., Kuehn, K., Lash, B., Walker, T., … & Juster, R. P. (2023). The impact of sociopolitical events on transgender people in the US. *Bulletin of pplied Transgender Studies*, *2*(1–2), 1–26. http://doi.org/10.57814/sdx3-7y41

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: systematic review. *Clinical Psychology Review*, *100*, 102229. https://doi.org/10.1016/j.cpr.2022.102229

Gill-Peterson, J. (2018). *Histories of the transgender child.* University of Minnesota Press.

Goldenberg, T., Reisner, S.L., Harper, G.W., Gamarel, K.H., Stephenson, R. (2020). State-level transgender-specific policies, race/ethnicity, and use of medical gender affirmation services among transgender and other gender diverse people in the United States. *The Milbank Quarterly*, *98*(3), 802–846. https://doi.org/10.1111/1468-0009.12467

Green, . E., DeChants, J. P., Price, M. N., & Davis, C. K. (2022). ssociation of gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth. *Journal of dolescent Health*, *70*, 643–649. https://doi.org/10.1016/j.jadohealth.2021.10.036

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W.J, Hassan Murad, Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: n Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, *102*(11), 3869–3903. https:// doi.org/10.1210/jc.2017-01658.

Hendricks, M. L., & Testa, R. J. (2012). conceptual framework for clinical work with transgender and gender nonconforming clients: n adaptation of the Minority Stress Model. *Professional Psychology: Research and Practice*, *43*(5), 460–467. https://doi.org/10.1037/a0029597.

Hughes, L. D., Kidd, K. M., Gamarel, K. E., Operario, D., & Dowshen, N. (2021). "These laws will be devastating": Provider perspectives on legislation banning gender-affirming care for transgender adolescents. *Journal of dolescent Health*, *69*, 976–982. https://doi.org/10.1016/j.jadohealth.2021.08.020

Hughto, J. M. W., Reisner, S. L., & Pachankis, J. E. (2015). Transgender stigma and health: critical review of stigma determinants, mechanisms, and interventions. *Social Science & Medicine*, *147*, 222–231. https://doi.org/10.1016/j.socscimed.2015.11.010

Hughto, J. M., Meyers, D. J., Mimiaga, M. J., Reisner, S. L., & Cahill, S. (2022). Uncertainty and confusion regarding transgender non-discrimination policies: implications for the mental health of transgender mericans. *Sexuality Research and Social Policy*, *19*(3), 1069–1079. https://doi.org/10.1007/s13178-021-00602-w

Hunt, S. (2016). *n introduction to the health of two-spirit people: Historical, contemporary, and emergent issues*. National Collaborating Center for boriginal Health. https://www.ccnsa-nccah.ca/docs/emerging/RPT-HealthTwoSpirit-Hunt-EN.pdf

Kidd, K. M., Sequeira, G. M., Paglisotti, T., Katz-Wise, S. L., Kazmerski, T. M., Hillier, ., ... & Dowshen, N. (2021). "This could mean death for my child": Parent perspectives on laws banning gender-affirming care for transgender adolescents. *Journal of dolescent Health*, *68*, 1082–1088. https://doi.org/10.1016/j.jadohealth.2020.09.010

Kosciw, J. G., Clark, C. M., & Menard, L. (2022). *The 2021 National School Climate Survey: The experiences of LGBTQ+ youth in our nation's schools*. GLSEN. https://www.glsen.org/sites/default/files/2022-10/NSCS-2021-Full-Report.pdf

Kremen, J., Williams, C., Barrera, E. P., Harris, R. M., McGregor, K., Millington, K., ... & Roberts, S. (2021). ddressing legislation that restricts access to care for transgender youth. *Pediatrics*, *147*(5), e2021049940. https://doi.org/10.1542/peds.2021-049940

Lefevor, G. T., Janis, R. ., Franklin, ., & Stone, W. M. (2019). Distress and therapeutic outcomes among transgender and gender nonconforming people of color. *The Counseling Psychologist*, *47*(1), 34–58. https://doi.org/10.1177/0011000019827210

Lytle, M. C., Blosnich, J. R., & Kamen, C. (2016). The association of multiple identities with self-directed violence and depression among transgender individuals. *Suicide & Life-Threatening Behavior*, *46*(5), 535–544. https://doi.org/https://doi.org/10.1111/sltb.12234

McGregor, K., McKenna, J. L., Williams, C. R., Barrera, E. P., & Boskey, E. R. (2023). ssociation of pubertal blockade at Tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. *Journal of dolescent Health*. https://doi.org/10.1016/j.jadohealth.2023.10.028

McNamara, M., Lepore, C., Istott, ., Kamody, R., Kuper, L., Szilagyi, N., ... & Olezeski, C. (2022). Scientific misinformation and gender affirming care: tools for providers on the front lines. *Journal of dolescent Health*, *71*(3), 251–253. https://doi.org/10.1016/j.jadohealth.2022.06.008

Puckett, J. ., boussouan, . B., Ralston, . L., Mustanski, B., & Newcomb, M. E. (2023). Systems of cissexism and the daily production of stress for transgender and gender diverse people. *International Journal of Transgender Health, 24(1)*, 113–126. https://doi.org/10.1080/26895269.2021.1937437

Ramos, G. G. F., Mengai, . C. S., Daltro, C. . T., Cutrim, P. T., Zlotnik, E., & Beck, . P. . (2021). Systematic review: Puberty suppression with GnRH analogues in adolescents with gender incongruity. *Journal of Endocrinological Investigation*, *44*, 1151–1158. https://doi.org/10.1007/S40618-020-01449-5

Stryker, S. (2017). *Transgender history* (2nd ed.). Seal Press.

Trevor Project. (2023). *2023 U.S. National Survey on the Mental Health of LGBTQ Young People*. https://www.thetrevorproject.org/survey-2023/assets/static/05_TREVOR05_2023survey.pdf

Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, . S. (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics*, *145*(2), e20191725. https://doi.org/10.1542/peds.2019-1725

Turban, J. L., King, D., Köbe, J., Reisner, S. L., & Keuroghlian, . S. (2022). ccess to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLOS ONE*, *17*(1), e0261039. https://doi.org/10.1371/journal.pone.0261039

van der Miesen, . I. R., Steensma, T. D., de Vries, . L. C., Bos, H., & Popma, . (2020). Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers. *Journal of dolescent Health*, *66*(6), 699–704. https://doi.org/10.1016/j.jadohealth.2019.12.018

Weixel, T., & Wildman, B. (2022). Geographic distribution of clinical care for transgender and gender-diverse youth. *Pediatrics*, *150*(6), e2022057054. https://doi.org/10.1542/peds.2022-057054

Wittlin, N. M., Kuper, L. E., & Olson, K. R. (2023). Mental health of transgender and gender diverse youth. *nnual Review of Clinical Psychology*, *19*, 207–232. https://doi.org/10.1146/annurev-clinpsy-072220-020326

World Health Organization. (2022). *ICD-11: International classification of diseases* (11th revision). https://icd.who.int/en

Joint statement EPATH and WPATH

To: NHS England Specialised Commissioning: england.scengagement@nhs.net

Re: NHS Puberty blocker policy

Public consultation, NHS England: would like to hear what patients, parents and carers, clinicians, providers and other interested parties think about the proposed interim clinical policy:

The policy proposition is that puberty suppressing hormones (PSH) are not recommended to be available as a routine commissioning option for treatment of children and adolescents who have gender incongruence or dysphoria.

1. In what capacity are you responding?

European Professional Association for Transgender Health (EPATH) and The World Professional Association for Transgender Health (WPATH).

The European Professional Association for Transgender Health (EPATH) and the World Professional Association for Transgender Health (WPATH) are deeply concerned over the NHS England Interim Clinical Policy: Puberty suppressing hormones for children and adolescents who have gender incongruence or dysphoria.

Transgender and gender diverse young people across the United Kingdom are facing a health care access crisis. The closure of the NHS Tavistock Clinic's Gender Identity Development Service (GIDS), with no new clinical hubs fully operational yet, has left young transgender and gender diverse people and families with no opportunity to obtain care. This is in breach of the main Principles of the NHS Constitution. We urge NHS England to immediately revise the proposed guidelines and work to strengthen equitable access to gender-affirming health care services for transgender and gender diverse youth across the nation.

2. Are you responding on behalf of an organisation?

On behalf of the Associations EPATH and WPATH; The aims of the Associations, which it may pursue at international level in any country, are: (1) to promote mental, physical and social health of transgender people in Europe/globally; (2) to increase the quality of life among transgender people in Europe/globally ; and (3) to ensure transgender people's rights for

healthy development and well-being (for further information see The Bylaws at www.wpath.org and www.epath.eu).

EPATH and WPATH are concerned about the current situation in the UK for transgender and gender diverse young people, as it significantly risks compromising their health. At present, the former care provider, the NHS Tavistock Clinic's Gender Identity Development Service (GIDS), is not scheduling any new patient appointments for those on the waiting list and the two new proposed (clinical) hubs are not (fully) operational. While the existence of long waiting lists has already compromised the access to transgender healthcare severely, the current situation leaves transgender and gender diverse young people and their families seeking appropriate medical treatments without *any* possibility to receive such care.

Additionally, EPATH and WPATH are concerned about the policy proposition that puberty suppressing hormones are not recommended to be available as a routine commissioning option for the treatment of adolescents who have gender incongruence or dysphoria. EPATH and WPATH support the scientific and consensus-based clinical recommendations of WPATH's Standards of Care Version 8 (SOC8) Adolescent Chapter. We are concerned that the proposed policy proposition is not according to these Standards of Care, which recommend, among other recommendations, the use of puberty blocking hormones and other medical affirming interventions, when certain criteria are fulfilled. The complete lack of access to this treatment will impact the lives of transgender youth in the United Kingdom permanently, as the physical changes from their endogenous puberty are irreversible.

3. Has all the relevant evidence been taken into account?

The National Institute for Health and Care Excellence (NICE) review was published in 2020, which reviewed 9 studies regarding both *clinical effectiveness* (studies concerning associations of puberty blockers and outcomes regarding gender dysphoria, mental health and quality of life), as well as *safety* (studies concerning associations of puberty blockers and physical health parameters, based on the PICO format (population, intervention, control, and outcomes). In short, for children and adolescents with gender dysphoria, these address questions regarding: 1) clinical effectiveness; 2) short-term and long-term safety; and 3) cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention.

The selected studies by NICE only focused on the effects of puberty blockers, therefore studies that evaluated a combination of blockers, hormones, and/or surgeries were excluded. This resulted in the inclusion of 9 studies fulfilling the criteria for the defined PICO, while 11 studies were excluded. All selected studies were graded based on the GRADING system as providing 'VERY LOW' evidence. In subsequent stakeholder testing (2023), 8 stakeholders suggested 19 identifiable and unique references that might have been erroneously omitted from the evidence review or literature surveillance report, which were assessed to *not* fall within PICO and search methodology, with one exception: de Vries et al., 2014. It was concluded that the de Vries et al., 2014 study does fall within the PICO format and search methodology as set out by NICE. It

indicates that use of GnRH analogues along with other interventions (e.g., multidisciplinary care) improves body image outcomes after gender affirming surgery. However, this evidence does not materially affect the conclusions of the existing evidence review. (Post-Engagement Evidence Report on Interim PSH Policy for Gender Incongruence or Dysphoria).

There are additional studies that are of relevance and should be considered to be incorporated within the NICE review:

Kuper, L. E., Stewart, S., Preston, S., Lau, M., & Lopez, X. (2020). Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*, *145*(4), e20193006. https://doi.org/10.1542/peds.2019-3006

Effectiveness studies on blockers, hormones or both.

- **Wiepjes et al.**, (2018).
Wiepjes, C. M., Nota, N. M., de Blok, C. J. M., Klaver, M., de Vries, A. L. C., Wensing-Kruger, S. A., de Jongh, R. T., Bouman, M. B., Steensma, T. D., Cohen-Kettenis, P., Gooren, L. J. G., Kreukels, B. P. C., & den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *The Journal of Sexual Medicine*, *15*(4), 582–590. https://doi.org/10.1016/j.jsxm.2018.01.016
Report the % of adolescents that stopped blockers (1.9%).

- **van der Miesen et al.**, (2020).
van der Miesen, A. I. R., Steensma, T. D., de Vries, A. L. C., Bos, H., & Popma, A. (2020). Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *The Journal of Adolescent Health : Official publication of the Society for Adolescent Medicine*, *66*(6), 699–704. https://doi.org/10.1016/j.jadohealth.2019.12.018
A cross sectional study comparing psychological functioning of transgender adolescents on blockers with baseline transgender adolescents as well as cisgender general population peers; transgender adolescents on blockers functioned better then baseline and comparable to cisgender same age peers.

- **Arnoldussen et al.**, (2022).
Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., & de Vries, A. L. C. (2022). Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT Health*, *9*(4), 238–246. https://doi.org/10.1089/lgbt.2020.0494
Showing improvement in self-perception on baseline (adolescents) compared to post-treatment (young adulthood).

- van der Loos et al., (2022).
van der Loos, M. A. T. C., Hannema, S. E., Klink, D. T., den Heijer, M., & Wiepjes, C. M. (2022). Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *The Lancet. Child & Adolescent Health*, *6*(12), 869–875. https://doi.org/10.1016/S2352-4642(22)00254-1

Showing continuation rates of hormone use (98%) after puberty suppression of up to 20 years after it's start.

- **Nos et al.**, (2022).
Nos, A. L., Klein, D. A., Adirim, T. A., Schvey, N. A., Hisle-Gorman, E., Susi, A., & Roberts, C. M. (2022). Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. *Journal of the American Medical Association* , *5*(11), e2239758. https://doi.org/10.1001/jamanetworkopen.2022.39758
These findings suggest that clinicians can offer GnRH analogues to transgender and gender-diverse adolescents during pubertal development for mental health and cosmetic benefits without an increased likelihood of subsequent use of gender-affirming hormones.

Other studies concerning safety have also been published. These include:

- **Schagen et al.**, (2020).
Schagen, S. E. E., Wouters, F. M., Cohen-Kettenis, P. T., Gooren, L. J., & Hannema, S. E. (2020). Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *The Journal of Clinical Endocrinology and Metabolism*, *105*(12), e4252–e4263. https://doi.org/10.1210/clinem/dgaa604
During 2 years of GnRHa treatment, Bone mineral apparent density (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.

- **Boogers et al.**, (2022).
Boogers, L. S., Wiepjes, C. M., Klink, D. T., Hellinga, I., van Trotsenburg, A. S. P., den Heijer, M., & Hannema, S. E. (2022). Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. *The Journal of Clinical Endocrinology and Metabolism*, *107*(9), e3805–e3815. https://doi.org/10.1210/clinem/dgac349
Growth decelerated during GnRH analogues and accelerated during gender-affirming hormone therapy (GAHT). After regular-dose treatment, adult height was slightly lower than predicted at start of GnRH analogues, likely due to systematic overestimation of predicted adult height (PAH) as described in boys from the general population, but not significantly different from target height. High-dose ethinyl estradiol (EE) resulted in greater reduction of adult height than high-dose estradiol, but this needs to be weighed against possible adverse effects.

- **Arnoldussen et al.**, (2022).
Arnoldussen, M., Hooijman, E. C., Kreukels, B. P., & de Vries, A. L. (2022). Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clinical Child Psychology and Psychiatry*, *27*(4), 1069–1076. https://doi.org/10.1177/13591045221091652
Evaluating associations between baseline IQ (before blockers, hormones and surgeries) and post-treatment young adulthood educational level.

Moreover, WPATH published, as aforementioned, the 8th edition of its Standards of Care for the Health of Transgender and Gender Diverse People.

Coleman, E., Radix, A. E., Bouman, W. P., Brown, G. R., de Vries, A. L. C., Deutsch, M. B., Ettner, R., Fraser, L., Goodman, M., Green, J., Hancock, A. B., Johnson, T. W., Karasic, D. H., Knudson, G. A., Leibowitz, S. F., Meyer-Bahlburg, H. F. L., Monstrey, S. J., Motmans, J., Nahata, L., Nieder, T. O., … Arcelus, J. (2022). Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*, *23*(Suppl 1), S1–S259. https://doi.org/10.1080/26895269.2022.2100644

Regarding the evidence for treatment of transgender and gender diverse adolescents, SOC8 states: "Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible. A short narrative review is provided instead." While systematic reviews are important in areas of medicine where the evidence is robust, in gender health for minors, our organization believes it is important to simultaneously 1) acknowledge the state of the evidence; 2) develop guidelines that promote a careful and comprehensive approach, while 3) continuing to promote and advocate for continued research and scientific advancements that will further contribute to honed clinical practice recommendations in the future. SOC8 concluded: "although the existing samples reported on relatively small groups of youth (e.g., n = 22 - 101 per study) and the time to follow-up varied across studies (6 months - 7 years), this emerging evidence base indicates a general improvement in the lives of transgender adolescents who, following careful and comprehensive assessment, receive medically necessary gender-affirming medical treatment. Further, rates of reported regret during the study monitoring periods are low. Taken as a whole, the data show early medical intervention - as part of broader combined assessment and treatment approaches focused on gender dysphoria and general well-being - can be effective and helpful for many transgender adolescents seeking these treatments."

Also, regarding the state of the evidence, it is important to stress again that more outcome data are desirable and while controlled trials would provide stronger evidence, they are neither feasible nor ethical. Regarding the feasibility issues, e.g., an untreated control group, this will be highly unlikely since eligible adolescents rarely refrain from treatment. Furthermore, treatment preference may lead to non- participation or withdrawal from a randomized trial of the group without GnRH. Finally, blinding will be impossible due to the clinically evident effects of treatment (or lack thereof). An alternative might be a waiting-list control group, something that might become feasible with the present long waiting-lists, although still unethical, since puberty develops further while these adolescents will be on the waiting list with life-long (undesired physical) consequences. Other options would be between-clinic comparisons with different treatment approaches, although between-clinic contexts might differ in so many respects that a robust comparison may be extremely challenging. Therefore, the most feasible and preferred option are rigorous longitudinal studies using appropriate outcome measures to provide valuable evidence on the effects and safety of GnRH analogues, of which the Dutch cohort studies are an example.

It is also important to realize that, at present, the NHS is defining the outcome measures for gender affirming medical treatments (improvement of psychological functioning or quality of life), however this falls short. Additional outcomes, such as the improvement of gender dysphoria, satisfaction with care, trends of detransition (and why) are all important to capture *in addition to* improvement of psychological functioning and/or quality of life. Simply put, for many transgender youth who appropriately receive gender affirming medical care, quality of life *may* improve, however many other aspects of the human experience can detrimentally impact quality of life in unforeseen ways. It is alarming that the totality of appropriate outcome measures are not being taken into account when making one-size-fits-all policy decisions.

Despite the many areas in medicine where the evidence is low (see e.g., Eating Disorders guidelines of NICE) recommendations are published without the same degree of criticism or scrutiny that gender affirming medical interventions encounter. Considering the definition of low evidence can be subjective and is often based on study biases (due to low numbers or lack of controls), the need for recommendations and guidance is even *more* necessary in these circumstances. For example, there was low evidence regarding many of the approaches followed during the start of the COVID-19 pandemic, yet careful recommendations were made. All clinical practice guideline recommendations, whether the available evidence is considered as being of high quality or very low quality, require both a judicious consideration of the relevant evidence and consensus from the panel regarding both the interpretation of the evidence and the trade-off between the benefit(s) versus the harm or burden of the recommended health intervention.

Summing up, systematic reviews alone are not enough to make robust clinical recommendations. The Standards of Care version 8, consistent with clinical guidelines in other aspects of medicine, provide recommendations that are based on several factors, including but not limited to the available research. The hallmark recommendation in the Adolescent chapter of SOC8 is for well-qualified and well-trained providers to conduct a comprehensive biopsychosocial assessment in order to determine treatment priorities and sequence, which means medical treatments may or may not be indicated in a particular clinical scenario. This careful recommendation is made because of the limited amount of studies that inform the totality of available evidence, not in spite of it.

4. Does the equality and health inequalities impact assessment reflect the potential impact that might arise as a result of the proposed changes?

While formulating the adolescent SOC8 statements, medical ethics and human rights perspectives were also considered. This seems extremely important in transgender care for adolescents, apart from evidence regarding efficacy and safety. The Adolescent Chapter in the SOC8 refers to, for example, the fact that allowing irreversible puberty to progress in adolescents who experience gender incongruence is not a neutral act given that it may have immediate and lifelong harmful effects for the transgender young person (Giordano, 2008; Giordano & Holm, 2020; Kreukels & Cohen-Kettenis, 2011). From a human rights perspective, considering gender diversity as a normal and expected variation within the broader diversity of

the human experience, it is an adolescent's right to participate in their own decision-making process about their health and lives, including access to gender health services (Amnesty International, https://www.amnesty.org.uk/press-releases/amnesty-international-uk-and-liberty-joint-statement-puberty-blockers).

Giordano S. (2008). Lives in a chiaroscuro. Should we suspend the puberty of children with gender identity disorder? *Journal of Medical Ethics*, *34*(8), 580–584. https://doi.org/10.1136/jme.2007.021097

Giordano, S., & Holm, S. (2020). Is puberty delaying treatment 'experimental treatment'? *International Journal of Transgender Health*, *21*(2), 113–121. https://doi.org/10.1080/26895269.2020.1747768

Kreukels, B. P., & Cohen-Kettenis, P. T. (2011). Puberty suppression in gender identity disorder: the Amsterdam experience. *Nature Reviews. Endocrinology*, *7*(8), 466–472. https://doi.org/10.1038/nrendo.2011.78

5. Are there any changes or additions you think need to be made to this policy?

It is also important to provide context on systematic reviews and how they inform clinical practice. A systematic review cannot, and should not be used as an exclusive arbiter to determine whether a particular model of care is evidence-based or not. There are many ways of obtaining evidence, which can be obtained both from the scientific literature and expert clinical consensus. While the importance of randomized control trials were stressed in early descriptions of evidence-based medicine, they are rarely performed as it is unethical and impractical to randomize subjects to treatment groups or lack thereof.

Rather, evidence-based medicine is about using the best available evidence to guide clinical decision-making and the development of practice guidelines, which provide guidance on how to ethically use the evidence, whether from randomized trials, observational studies, physiological experiments, case series, case reports, or the experience of individual (or a group of) clinicians, to optimally help patients make the best decisions consistent with their circumstances and values. Thus, all guidelines should be evidence-based, even when the evidence is of very low quality. The guideline development process and the recommendation should include a systematic review of the literature and rigorous assessment of the quality of the evidence. But in addition, the evidence requires interpretation (whether from randomized trials or case reports) and, in the context of guidelines, a consensus process must determine that interpretation. This need for interpretation is important because most observations are theory-laden and conclusions regarding the phenomenon of interest can only be drawn in the context of existing theoretical understanding and shared sets of values.

On occasion, the evidence is so compelling that answers to such questions are obvious and beyond dispute. Far more often, the answers are less obvious and require evaluation and, in the

context of guidelines, a series of expert consensus recommendations. Every recommendation in the Standards of Care for the Health of Transgender and Gender Diverse People – Version 8 (SOC8) was agreed upon through a Delphi consensus process (in addition to reviewing the available scientific literature, whether through systematic reviews or short narrative reviews of the existing research), necessitating 75% agreement from the international and multidisciplinary committee of 120 experts in the field. The hallmark recommendation in the Adolescent chapter of SOC8 is for well-qualified and well-trained providers to conduct a comprehensive biopsychosocial assessment in order to determine treatment priorities and sequence, which means medical treatments may or may not be indicated in a particular clinical scenario.

The proposed NHS Policy regarding Puberty Suppressing Hormones is currently based on decisions that 1) Seems to Assume a treatment model (e.g., "gender affirming model") is the stance driving the WPATH SOC8 Adolescent chapter when it is not; 2) seems to Promote a one-size-fits-all approach when the complexity of the human experience necessitates a broader (yet still careful and ethical) framework, as is the case in SOC8; 3) seems to be Predicated on the notion that a systematic review can be the sole arbiter of what constitutes sufficient evidence for treatment recommendations, when that is not the case in other areas of medicine; and lastly, 4) Isolated cases of regret or rare discontinuance of treatment exist, but do not diminish the validity of treatment for the many transgender and gender diverse adolescents who meet the criteria as specified in the SOC8.

In summary, WPATH and EPATH stress the importance of maintaining access to care for all transgender and gender diverse populations, regardless of age of diagnosis.

Sincerely,

Annelou L.C. de Vries, MD, PhD, EPATH President, on behalf of the European Professional Association for Transgender Health

Marci L Bowers, MD, WPATH President, on behalf of the World Professional Association for Transgender Health

References

- Kuper et al., (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy
- Wiepjes et al., (2018) The Amsterdam Cohort of Gender Dysphoria Study (1972e2015)/ Trends in Prevalence, Treatment, and Regrets
- van der Miesen et al. (2020) Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers
- Arnoldussen et al., (2022) Self-Perception of Transgender Adolescents after Gender-Affirming Treatment- A Follow-Up Study into Young Adulthood

- van der Loos et al., (2022) Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence- a cohort study in the Netherlands
- Nos et al., (2022) Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents
- Schagen (2020) Bone development in transgender adolescents treated with GnRH analogues and subsequently gender affirming hormones
- Boogers (2022) Trans girls grow tall- adult height is unaffected by GnRH analogue and estradiol treatment
- Arnoldussen et al., (2022) Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents

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Clinical Research Article

Clinical Research Article

Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones

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Abbreviations: 1CTP, carboxyterminal cross-linked telopeptide of type I collagen; aBMD, areal bone mineral density; ANOVA, analysis of variance; BMAD, bone mineral apparent density; BMD, bone mineral density; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analogue; P1NP, N-terminal propeptide of type-1 collagen; PBM, peak bone mass.

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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,

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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.

Key Words: bone mineral density, bone, GnRH analogue, sex steroids, gender dysphoria, transgender, adolescents

Over the last decades, children diagnosed with gender dysphoria have increasingly come to the attention of the psychomedical care system and clinicians recognize their suffering, aggravated by the somatic changes of puberty (1, 2). The development of secondary sex characteristics can be temporarily halted with gonadotropin-releasing hormone analogue (GnRHa) treatment (3). This offers the adolescent the opportunity to explore their wish to pursue gender-affirming treatment, while no longer experiencing the agonizing development of secondary sex characteristics due to endogenous puberty, which are incongruent with gender identity. Birth-assigned girls must be at least in Tanner breast stage 2 with clear palpable mammary tissue, while birth-assigned boys must have reached Tanner stage G2 before initiating treatment with GnRHa (3, 4). If no contraindications exist, sex steroids consistent with the affirmed gender are added to the GnRHa treatment at an age where adolescents can give informed consent to such treatment, usually at approximately 16 years (3). There is much discussion about this age, since 16 years is considered a late age to induce puberty in adolescents.

In young adults, peak bone mass (PBM) is higher in men than in women (5). Sex steroids play an essential role in the establishment of gender differences in bone mass, both through direct effects and indirect effects, for example, via differences in muscle mass and insulin-like growth factor (6). Puberty is an important period in determining adult bone mineral content (6). Together, these findings strengthen the notion that maximizing bone mineral accrual during adolescence may be important in the prevention of osteoporosis and fractures at older age.

One of the primary concerns when using GnRHa in adolescents for a prolonged period of time is the potential decrease in bone mineral density (BMD) (3, 7). The suppression of the endogenous sex steroids to stop pubertal development, as recommended by current guidelines, may potentially interfere with the normal pubertal bone mass increment and reduce PBM. Therefore, assessment of BMD every 1 to 2 years is recommended (3). Three studies in adolescents diagnosed with gender dysphoria receiving GnRHa and gender-affirming hormone treatment reported decreases in areal BMD (aBMD) and bone mineral apparent density (BMAD) z-scores during GnRHa treatment, although not all significant (8-10). Little difference was noted in change of BMAD z-scores between early- and late-pubertal groups as defined by bone age (8). Catch-up of bone mineral accrual during subsequent gender-affirming hormone treatment may be incomplete (8-10). One study investigated bone markers and showed a decrease of carboxyterminal cross-linked telopeptide of type I collagen (1CTP) and N-terminal propeptide of type-1 collagen (P1NP) during GnRHa and during subsequent gender-affirming hormone treatment which was interpreted as evidence of decreased bone turnover (8). All these studies compared data at the start of GnRHa treatment, at the start of gender-affirming hormones and one endpoint, either 12–24 months after the start of gender-affirming hormone therapy or age 22 years. However, this does not provide information on the course of BMD during treatment. Do BMD z-scores continue to decline with prolonged use of GnRHa? How long do BMD z-scores continue to increase during GAH treatment? These questions remain unanswered. Now that increasing numbers of adolescents undergo this treatment, possibly starting at younger ages, there is a clear need for such data. Therefore we set out to describe the course of BMD during 2 years of GnRHa therapy and during 3 years of subsequent gender-affirming hormone treatment in a large group of adolescents diagnosed with gender dysphoria, with measurements at yearly intervals. We also investigated whether the outcome was influenced by the pubertal stage, as defined by Tanner stage, at which GnRHa treatment was started. In addition, we report data from a small subgroup with more prolonged GnRHa treatment.

Methods

Subjects and protocol

Subjects were adolescents fulfilling *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria for gender identity disorder (the term used at the time) (11) and eligible for treatment according to existing guidelines at that time (4, 12, 13). The design of the study was observational and prospective, and individuals were included from 1998 to 2009. The first phase of treatment consisted of intramuscular injections of GnRHa 3.75 mg (Triptorelin-CR (Ferring Pharmaceuticals, Denmark). The first 2 injections were administered with a 2-week interval followed by injections every 4 weeks to suppress endogenous sex steroid production. To induce female pubertal development in

transgirls, oral estrogens were prescribed in an increasing dosage over a period of 2 years as previously described (4). Male puberty in transboys was induced by administering Sustanon (a mixture of testosterone propionate, -fenylpropionate, -isocaproate and -decanoate) intramuscularly in increasing doses over a period of 2 years (14). In subjects who were 16 years of age or older at the start of pubertal suppression, gender-affirming hormones were started at half the adult dose and increased to the adult dose after 6 months. A dose of 2 mg 17beta-estradiol per day and 125 mg testosterone-esters per 2 weeks was considered an adult dose. From 45 subjects, some data were also included in previous studies by Vlot et al (8) and Klink et al (10), but those studies only reported results at 3 time points: at the start of GnRHa, at the start of gender-affirming hormones, and after 2 years of gender-affirming hormones (8) or age 22 years (10), and they did not describe a detailed course of BMD and bone markers over several years of GnRHa or gender-affirming hormone treatment.

Different effects of treatment might be expected depending on the pubertal stage at baseline. A previous study used a bone age cutoff of 14 and 15 years for transboys and transgirls, respectively, to define early- and late-pubertal groups (8). However, especially for transboys, bone age 14 years signifies the final stages of puberty and near completion of linear growth rather than midpuberty. In the current study, Tanner stage was used to define early- and late-pubertal groups, with the early-pubertal group defined as Tanner stage 2 or 3 at the start of GnRHa treatment, and the late-pubertal group as Tanner stage 4 or 5.

Bone densitometry

Dual-energy x-ray absorptiometry (DXA) was performed before GnRHa administration and then every subsequent year using Hologic QDR 4500 (Hololgic Inc., Waltham, MA, USA). Likewise, at the start of gender-affirming hormone treatment, a DXA scan was performed, with yearly measurements thereafter. Areal BMD (aBMD, g/cm^2) of the lumbar spine, nondominant hip, and whole body, as well as the bone mineral content of the whole body (BMC-WB, g) were measured. To calculate z-scores based on age and sex, the National Health and Nutrition Examination Surveys (NHANES) references values were used. Because changes in aBMD might partly be due to altered growth during treatment, we also studied BMAD (g/cm^3) calculated as described by Ward et al (15). BMAD z-scores were calculated using LMS data from an English reference population (15). To calculate z-scores the reference population of the birth-assigned sex was used. For adolescents older than 17 years no reference values of BMAD are available; therefore, reference values of 17 year-olds were used to calculate the z-score at older ages (15).

Serum bone markers

Markers of bone formation (P1NP, P3NP, and osteocalcin) and of bone resorption (1CTP) were determined in fasting blood samples, drawn before noon on the same days as the DXA scans, and stored at –20 °C.

Osteocalcin was measured by an immunometric assay (Colorimetric, BioSource, Nivelles, Belgium) (lower detection limit of 0.4 nmol/L; inter-assay coefficient of variation (CV) for the whole range <10%). Serum 1CTP, P1NP, and P3NP levels were measured using a radioimmunoassay (Orion Diagnostica, Espoo, Finland). The lower ranges of detection were 1 µg/L for 1CTP, 5 µg/L for P1NP, and 1µg/L for P3NP. The inter-assay CV for the whole range of 1CTP was 7% and for P1NP 8%. The CV for P3NP was 6% at 4.2 µg/L and 8% at 6.2 µg/L.

Statistical analyses

Independent *t* tests were used to ascertain differences between the ages of the transgirls and transboys. To analyze changes in BMAD over time, data were analyzed using a linear mixed model. A full factorial model was chosen as fixed part of the model, ie, a model consisting of time (3 or 4 levels), pubertal stage (early/late), and sex and all possible interactions (ie, three 2-way and one 3-way interactions). An unstructured covariance matrix was used as random part of the model. An advantage of the linear mixed model approach above traditional repeated measurements analysis of variance (ANOVA) is that all acquired data are included in the analyses and no data are lost due to incomplete data sets.

Differences in aBMD during a more prolonged period of GnRHa treatment were calculated using the related samples Wilcoxon Signed Ranked test.

All data on BMAD, and z-scores are presented as estimated marginal means and standard error of the mean. The statistical package was SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval

The study was placed on the International Standard Randomized Controlled Trial Number register and ascribed registration number ISRCTN 81574253 (www.isrctn.com). Approval by the local medical ethical committee was obtained. Informed consent for the study was obtained from all adolescents, and if aged <18 years also from their parents.

Results

A total of 54 transgirls and 73 transboys started treatment according to this protocol. For 51 transgirls and 70 transboys, DXA scans were available at the start of GnRHa administration and these individuals were included in the analyses. There were no significant differences between the ages of the transgirls and the transboys at the start of GnRHa administration (Table 1).

A total of 36 transgirls and 42 transboys received gender-affirming hormone treatment in addition to GnRHa treatment. The transboys were slightly but significantly older at start of gender-affirming hormone treatment than the transgirls (Table 1). The ratio of subjects who were in early and in late puberty was not different in the group evaluated for the effects of gender-affirming hormone treatment compared with the group analyzed during GnRHa treatment alone.

Anthropometric data and data on pubertal development of the subjects at baseline are shown in Table 1. All adolescents had sex characteristics typical of the sex assigned at birth and none had signs of a difference/disorder of sex development. None of the adolescents had a bone fracture during the study.

Changes during 2 years of GnRHa treatment

Bone mineral apparent density. Changes in aBMD and aBMD z-scores are shown in Table 2. BMAD of the lumbar spine did not change during 2 years of GnRHa treatment in the transgirls or the early pubertal transboys ($P = 0.84$, $P = 0.09$, and $P = 0.69$, respectively) (see Fig. 1, Table 2). In the late-pubertal transboys, a small but significant decrease in BMAD of the lumbar spine was found.

BMAD of the femoral neck showed a significant decrease in the late-pubertal transgirls and in both groups of transboys ($P = 0.007$, $P = 0.015$, and $P < 0.001$, respectively) (see Fig. 1, Table 2). The small decrease in the early pubertal transgirls was not significant ($P = 0.31$).

Bone mineral apparent density z-scores. At the start, z-scores of the BMAD at both locations were higher in the transboys than in the transgirls. The BMAD z-score of the lumbar spine significantly decreased in all 4 groups ($P \leq 0.001$) (see Fig. 1, Table 2). The BMAD z-scores of the femoral neck significantly decreased in all groups ($P = 0.006$, $P = 0.002$, and $P < 0.001$) except for the early-pubertal transgirls ($P = 0.25$). Four transgirls had a z-score of the hip below −2 after 2 years of GnRHa treatment and 3 individuals had a z-score of the lumbar spine below −2. Two transboys had a z-score of the hip below −2 whereas none of the transboys had a z-score of the lumbar spine below −2 after 2 years of GnRHa treatment.

Bone mineral density during prolonged GnRHa treatment. Because the average age at the start of GnRHa treatment was more than 14 years, most individuals were not treated with GnRHa for more than 2 years

Table 1. Characteristics at the Start of GnRHa Treatment and at the Start of Gender-Affirming Hormone Treatment

Start GnRHa		Transgirls (n = 51)	Transboys (n = 70)	*P* value
	Age in years, mean ± SD	14.1 ± 1.7	14.5 ± 2.0	n.s.
	Pubertal group: Early/late	15/36	14/56	n.s.
	Height in cm, mean ± SD	169.0 ± 8.9	162.2 ± 8.8	<0.001
	Weight in kg, mean ± SD	57.9 ± 12.9	56.2 ± 14.7	n.s.
	BMI in kg/m^2, mean ± SD	20.1 ± 3.3	21.3 ± 4.2	n.s.
	Serum estradiol in pmol/L, median [IQR]		Early: 113.5 [63.5–129.3] Late: 121 [83.5–231.5]	
	Serum testosterone in nmol/L, median [IQR]	Early: 3.8 [2.15–6.15] Late: 13 [10.3–17.8]		
Start gender-affirming hormones		Transgirls (n = 36)	Transboys (n = 42)	
	Age in years, mean ± SD	16.2 ± 1.2	16.9 ± 1.1	0.005
	Pubertal group: Early/late	10/26	5/37	n.s.
	Duration of GnRHa use before start GAH, years	2.0 ± (0.94)	1.8 ± (1.11)	n.s.
	Height in cm, mean ± SD	176.5 ± 7.3	167.1 ± 7.4	0.005
	Weight in kg, mean ± SD	66.7 ± 11.9	63.5 ± 11.5	n.s.
	BMI in kg/m^2, mean ± SD	21.1 ± 3.2	22.8 ± 4.0	n.s.

Abbreviations: BMI, body mass index; GAH, gender-affirming hormones; GnRHa, gonadotropin-releasing hormone analogue; IQR, interquartile range; n.s., not significant; SD, standard deviation.

Table 2. aBMD and BMAD During 2 Years of GnRHa Treatment

	Transgirls					
	Early Pubertal		Late-Pubertal			
	0 mo	24 mo	0 mo	24 mo	*p*1	*p*2
aBMD_LS g/cm^2	0.73 (0.03)	0.75(0.03)	0.79 (0.02)	0.82 (0.02)	<0.05	<0.05
Z-score	−0.67 (0.26)	−1.26 (0.24)	−0.33 (0.17)	−0.92 (0.17)	<0.05	<0.05
aBMD_hip g/cm^2	0.81 (0.03)	0.86 (0.03)	0.87 (0.02)	0.89 (0.02)	<0.05	n.s.
Z-score	−0.49 (0.24)	−0.93 (0.21)	−0.43 (0.16)	−1.01 (0.15)	<0.05	<0.05
Whole body BMD g/cm^2	0.90 (0.02)	0.92 (0.02)	0.95 (0.01)	0.95 (0.01)	<0.05	n.s.
Z-score	−0.56 (0.24)	−1.51 (0.20)	−0.51 (0.16)	−1.62 (0.15)	<0.05	<0.05
BMAD_LS g/cm^3	0.20 (0.01)	0.20 (0.01)	0.20 (0.01)	0.21 (0.0!)	n.s.	n.s.
Z-score	−0.33 (0.33)	−1.19 (0.34)	−0.65 (0.20)	−1.21 (0.22)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.01)	0.27 (0.01)	0.28 (0.01)	0.26 (0.01)	n.s.	<0.05
Z-score	−0.94 (0.27)	−1.23 (0.35)	−1.01 (0.17)	−1.56 (0.25)	n.s.	<0.05
	Transboys					
	Early-pubertal		Late-pubertal			
	0 mo	24 mo	0 mo	24 mo	*p*1	*p*2
aBMD_LS g/cm^2	0.75 (0.03)	0.80 (0.03)	0.95 (0.01)	0.92 (0.01)	<0.05	<0.05
Z-score	−0.28 (0.27)	−1.04 (0.26)	0.38 (0.14)	−0.71 (0.14)	<0.05	<0.05
aBMD_hip g/cm^2	0.79 (0.03)	0.83 (0.03)	0.93 (0.01)	0.89 (0.02)	<0.05	<0.05
Z-score	0.09 (0.26)	−0.50 (0.24)	0.46 (0.13)	−0.56 (0.13)	<0.05	<0.05
Whole body BMD g/cm^2	0.88 (0.02)	0.92 (0.02)	1.03 (0.01)	1.01 (0.01)	<0.05	<0.05
Z-score	−0.28 (0.27)	−0.82 (0.24)	0.66 (0.13)	−0.40 (0.13)	<0.05	<0.05
BMAD_LS g/cm^3	0.22 (0.01)	0.22 (0.01)	0.25 (0.01)	0.24(0.01)	n.s.	<0.05
Z-score	−0.15 (0.29)	−0.86 (0.30)	0.33 (0.14)	−0.56 (0.17)	<0.05	<0.05
BMAD_hip g/cm^3	0.30 (0.01)	0.28 (0.01)	0.32 (0.01)	0.30 (0.01)	<0.05	<0.05
Z-score	−0.23 (0.25)	−0.94 (0.30)	0.04 (0.12)	−0.54 (0.18)	<0.05	<0.05

aBMD and BMAD during 2 years of GnRHa treatment. Values are presented as estimated marginal means ± standard error. *p1* represents the *P* value between the start and after 2 years of treatment for the early pubertal groups. *p2* represents the *P* value between start and after 2 years of treatment for the late-pubertal groups. For changes per year of treatment see Fig. 1.

Abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMD, bone mineral density; LS, lumbar spine.

before gender-affirming hormone treatment was started. However, a few younger individuals were treated for up to 4 years. The aBMD values of the lumbar spine and hip in 4 transboys and 11 transgirls remained stable during 3 years of GnRHa treatment. The z-scores on the other hand declined (Table 3).

Serum bone markers. At baseline, there were no significant differences in serum levels of any of the 4 bone markers (P1NP, P3NP, osteocalcin, 1CTP) between the early- and late-pubertal groups of transgirls (Fig. 2). In the transboys, baseline serum levels of all 4 bone markers were significantly higher in those in early puberty compared to those in later puberty.

After 2 years of GnRHa treatment serum levels of all 4 bone markers showed a significant decrease in both groups of transgirls and in early-pubertal transboys, which was most marked during the first year of treatment (Fig. 2). Serum levels of P3NP and 1CTP showed a smaller but significant decrease in late-pubertal transboys whereas serum levels of P1NP and osteocalcin did not change in this group.

Changes during 3 years of gender-affirming hormone treatment

After an average of 1.89 years (± 1.03 year) of GnRHa administration, gender-affirming hormones were added to the treatment. Both early-pubertal groups were on GnRHa for a significantly longer time (2.5 years in transgirls (n = 7) and 4.0 years in transboys (n = 3)) when compared with both late-pubertal groups (1.5 years in transgirls and 1.7 years in transboys) ($P < 0.001$).

Bone mineral apparent density. Changes in aBMD and aBMD z-scores are shown in Table 4. A significant increase in BMAD of the lumbar spine was found in all 4 groups

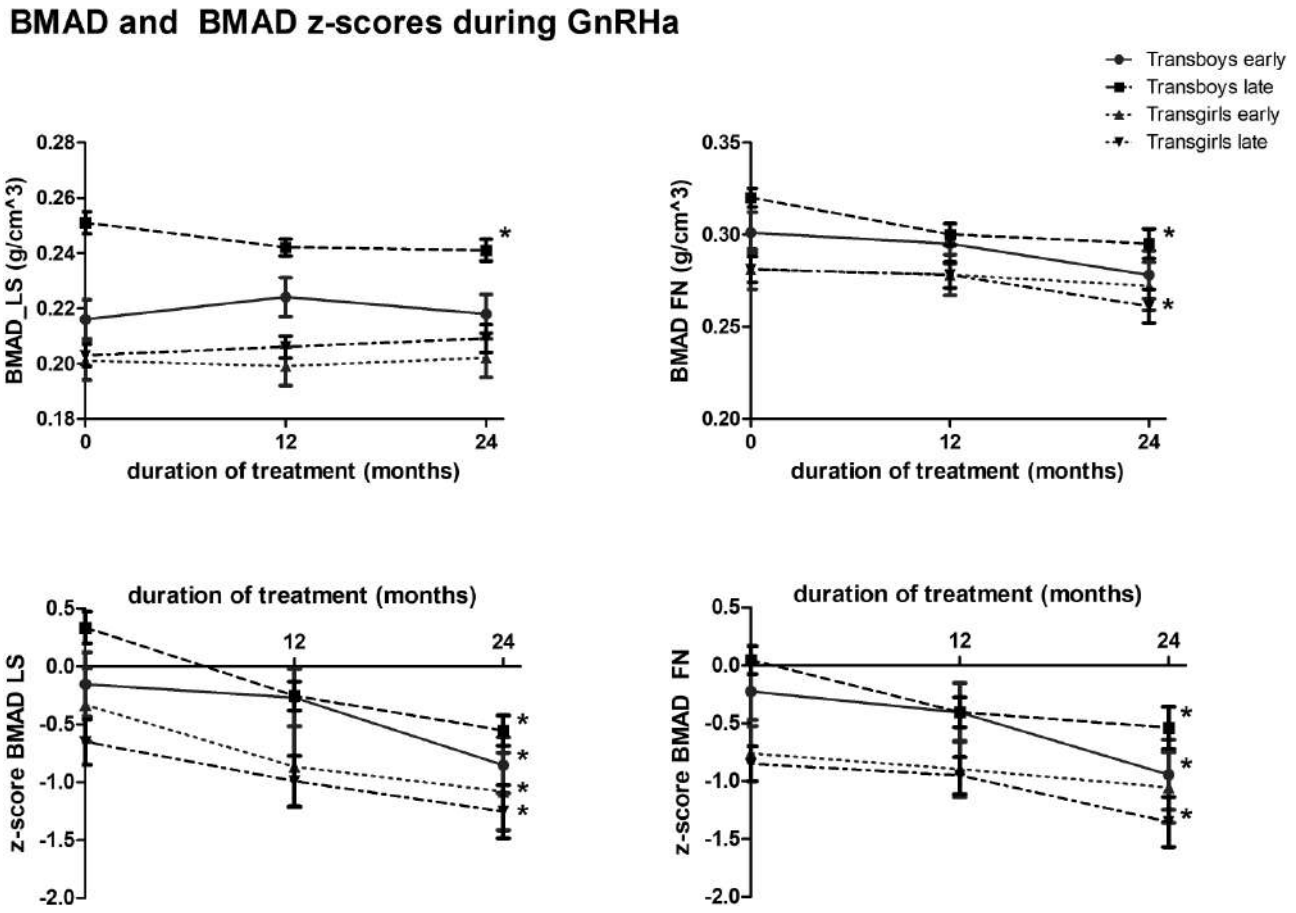

Figure 1. Estimated marginal means and standard error of the mean of BMAD prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by an asterisk. Abbreviations: BMAD: bone mineral apparent density; FM, femoral neck; LS, lumbar spine.

($P < 0.001$) after 3 years of gender-affirming hormone treatment (Fig. 3, Table 4). The BMAD of the femoral neck showed a significant increase in both groups of transgirls and in the early-pubertal transboys ($P < 0.05$). In the late-pubertal transboys the increase was not significant.

Bone mineral apparent density z-scores. The BMAD z-scores of the lumbar spine significantly increased in all 4 groups (Fig. 3, Table 4). Z-scores of the femoral neck showed a significant increase in both groups of transgirls and in the early pubertal transboys. The increase of the z-score in late-pubertal transboys was not significant.

Three transgirls had a z-score of the femoral neck below –2 and 3 individuals had a z-score of the lumbar spine below –2 after 3 years of gender-affirming hormone treatment. None of the transboys had a z-score below –2 after 3 years of gender-affirming hormone treatment.

Serum bone markers. The mean serum levels of the bone markers prior to gender-affirming hormone administration are shown in Fig. 4. Serum levels of P1NP, P3NP, and 1CTP were significantly higher in the early pubertal transgirls than in the late-pubertal transgirls. In the transboys, baseline serum levels of P1NP and P3NP were significantly higher in the early pubertal group compared with the late-pubertal group. Levels of all 4 markers changed little in the late-pubertal transboys, whereas in the early pubertal transboys and late-pubertal transgirls, osteocalcin, P1NP, and P3NP showed a pronounced decrease during the first year of gender-affirming hormone treatment, after which levels stabilized. Remarkably, in the early-pubertal transgirls an initial increase in the P1NP, P3NP, and 1CTP levels was found followed by a decrease. After 3 years of gender-affirming hormone treatment, all 4 bone markers had significantly decreased in both early and late-pubertal transgirls. In transboys, osteocalcin, P1NP, and 1CTP significantly decreased. In both early and late-pubertal transboys, serum levels of P3NP did not significantly change.

Discussion

This study examined the impact of puberty suppression and subsequent addition of gender-affirming hormones

Table 3. aBMD and aBMD Z-Scores During 3 Years of GnRHa Treatment

Sex	Age at Start (Range)	Duration GnRHa(yrs)		Start	12 Months	24 Months	36 Months	*P*
Transgirls	12.6 (12.1-12.8)	3.45 (0.43)	aBMD LS (g/cm^2) mean(± SD) (n = 4)	0.73 (0.9)	.74 (0.10)	0.77 (0.11)	0.77 (0.11)	0.14
			Z-score LS mean (± SD) (n = 4)	−0.43 (1.41)	−0.92 (1.40)	−1.05 (1.31)	−1.15 (1.00)	0.07
			aBMD Hip (g/cm^2) mean (± SD) (n = 4)	0.80 (0.04)	0.82 (0.4)	0.83 (0.05)	0.85 (0.06)	0.07
			Z-score hip mean (± SD) (n = 4)	−0.18 (0.50)	−0.65 (0.34)	−1.08 (0.42)	−1.08 (0.42)	0.007
Transboys	12.7 (11.9-14.0)	3.30 (0.50)	aBMD LS (g/cm^2) mean (± SD) (n)	0.85 (0.13) (11)	0.88 (0.10) (11)	0.90 (0.11) (11)	0.90 (0.9) (11)	0.29
			Z-score LS mean (± SD) (n)	0.42 (1.01) (9)	−0.52 (0.83) (10)	−0.35 (0.96) (11)	−0.53 (0.78) (11)	0.008
			aBMD Hip (g/cm^2) mean (± SD) (n)	0.88 (0.09) (9)	0.88 (0.71) (11)	0.87 (0.08) (11)	0.88 (0.09) (11)	0.95
			Z-score hip mean (± SD) (n)	0.86 (0.71) (8)	0.40 (0.71) (8)	−0.18 (0.67) (9)	−0.30 (0.67) (10)	0.12

Abbreviations: aBMD, areal bone mineral density; LS, lumbar spine; SD, standard deviation.

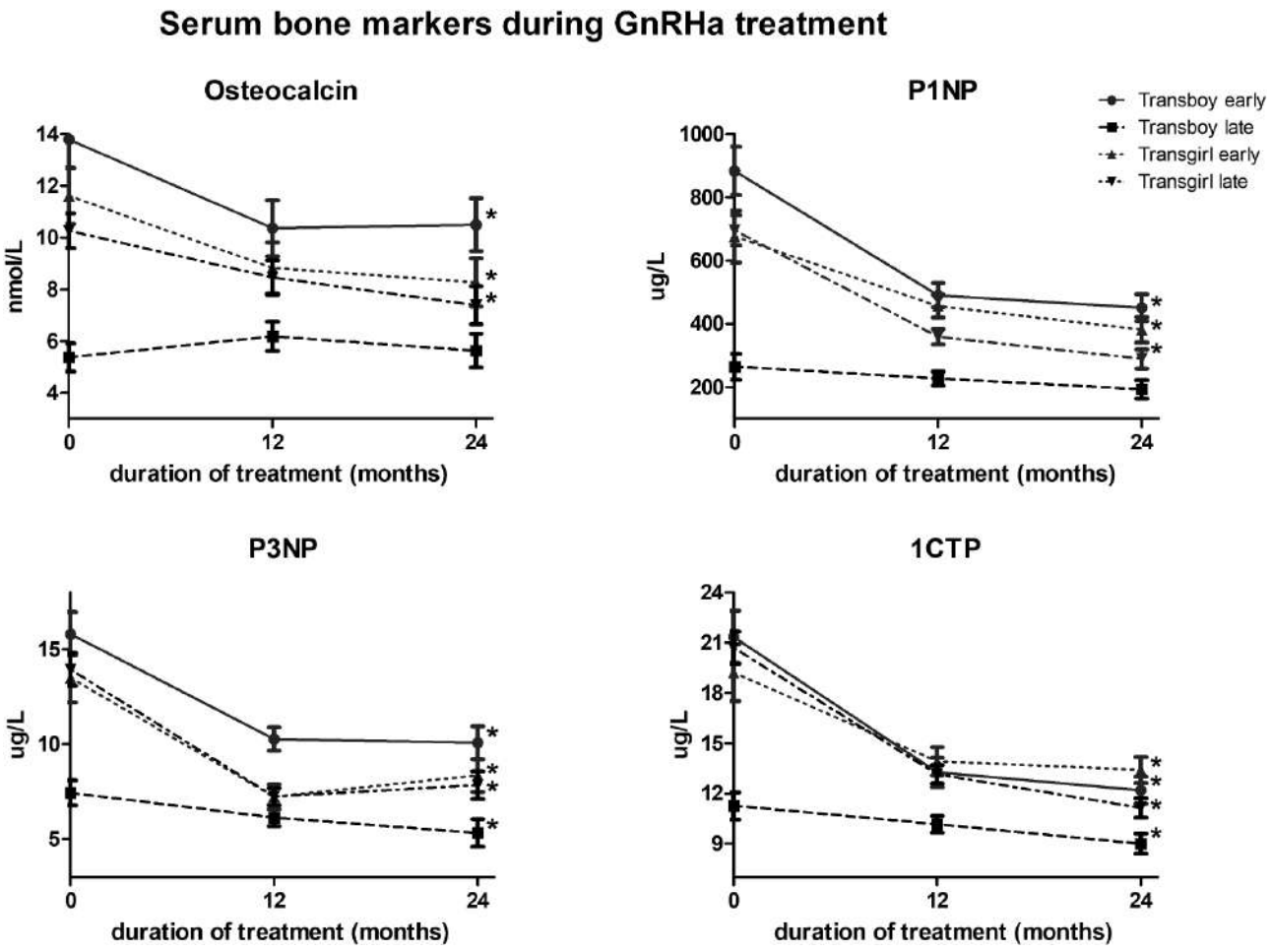

Figure 2. Estimated marginal means and negative standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by asterisk.

Table 4. aBMD and BMAD During 3 Years of Gender-Affirming Hormone Treatment in Addition to GnRHa Treatment

	Transgirls					
	Early-Pubertal		Late-Pubertal			
	0	36	0	36	*p*1	*p*2
aBMD_LS g/cm^2	0.77 (0.03)	0.95 (0.04)	0.83 (0.02)	0.95 (0.03)	<0.05	<0.05
Z-score	−1.37 (0.30)	−0.82 (0.39)	−0.99 (0.19)	−1.05 (0.25)	<0.05	n.s.
aBMD_hip g/cm^2	0.87 (0.03)	1.02 (0.04)	0.88 (0.02)	0.96 (0.02)	<0.05	<0.05
Z-score	−0.99 (0.23)	−0.09 (0.28)	−0.86 (0.14)	−0.70 (0.18)	<0.05	n.s.
Whole body BMD g/cm^2	0.93 (0.02)	1.06 (0.06)	0.96 (0.01)	0.98 (0.04)	<0.05	n.s.
Z-score	−1.67 (0.23)	−1.22 (0.28)	−1.42 (0.14)	−1.48 (0.18)	<0.05	n.s.
BMAD_LS g/cm^3	0.20 (0.08)	0.24 (0.09)	0.21 (0.05)	0.24 (0.06)	<0.05	<0.05
Z-score	−1.39 (0.36)	−0.49 (0.40)	−1.29 (0.23)	−0.50 (0.25)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.01)	0.31 (0.02)	0.27 (0.01)	0.27 (0.01)	<0.05	<0.05
Z-score	−0.88 (0.23)	−0.35 (0.37)	−1.36 (0.20)	−1.21 (0.24)	<0.05	<0.05
	Transboys					
	Early-pubertal		Late-pubertal			
	0	36	0	36	*p*1	*p*2
aBMD_LS g/cm^2	0.82 (0.04)	1.02 (0.07)	0.90 (0.02)	0.99 (0.02)	<0.05	<0.05
Z-score	−1.30 (0.43)	0.11 (0.58)	−0.68 (0.16)	−0.26 (0.22)	<0.05	<0.05
aBMD_hip g/cm^2	0.83 (0.04)	1.02 (0.06)	0.88 (0.02)	0.96 (0.02)	<0.05	<0.05
Z-score	−0.82 (0.33)	0.59 (0.43)	−0.50 (0.12)	0.12 (0.16)	<0.05	<0.05
Whole body BMD g/cm^2	0.94 (0.03)	1.11 (0.10)	1.02 (0.01)	1.10 (0.03)	n.s.	<0.05
Z-score	−1.06 (0.32)	0.21(0.43)	−0.30 (0.12)	−0.05 (0.16)	<0.05	<0.05
BMAD_LS g/cm^3	0.22(0.01)	0.26 (0.01)	0.24 (0.01)	0.26 (0.01)	<0.05	<0.05
Z-score	−1.01 (0.49)	0.12 (0.51)	−0.61 (0.18)	−0.04 (0.18)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.02)	0.32 (0.02)	0.30 (0.01)	0.32 (0.01)	<0.05	n.s.
Z-score	−0.71 (0.37)	0.01 (0.43)	−0.41 (0.14)	−0.10 (0.16)	<0.05	n.s.

aBMD and BMAD during 3 years of GnRHa plus gender-affirming hormone treatment. Values are presented as estimated marginal means ± standard error. *p1* represents the *P* value between start and after 3 years of treatment for the early-pubertal groups. *p2* represents the *P* value between start and after 3 years of treatment for the late-pubertal groups.

For changes per year of treatment see Fig. 2.

Abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMD, bone mineral density; LS, lumbar spine.

on bone development in adolescents diagnosed with gender dysphoria. At the start of GnRHa treatment, aBMD and BMAD values were within the normal range. However, transgirls had z-scores well below zero, whereas these were close to zero in transboys. This finding is consistent with previous studies (8, 10, 16-18) and may be explained by differences in lifestyle and exercise intensity between transgirls and transboys. A recent study showed that high-school transgirls have a higher intake of fast-food and are less physically active than transboys (19). In a different cohort of transgender adolescents we found vitamin D levels <50 nmol/L in 74% of transboys and 78% of transgirls starting GnRHa treatment ((9) and unpublished data). However, these findings do not explain why BMD z-scores are lower in transgirls than in transboys. Alternatively, it may be hypothesized that biological factors that act during intrauterine or early development and are involved in the development of gender dysphoria, are also related to bone development programming. For example, a whole-exome sequencing study in transgender individuals found 21 variants in 19 genes associated with estrogen activated pathways of sexually dimorphic brain development (20). These variants in estrogen receptor–activated pathways might also play a role in bone mineral acquisition.

During GnRHa treatment we observed a decline of aBMD and BMAD z-scores in line with previous studies (8-10). In transgirls a decrease of aBMD z-scores was also reported with the use of the anti-androgenic progestin cyproterone acetate (18). In contrast, 1 study showed that in transboys treated with the progestin lynestrenol for an average of 11.6 months aBMD z-scores were stable or increased (18). If these results are confirmed, also with more prolonged treatment duration, the better safety profile with regard to bone health is an important point to discuss with adolescents. In particular, older transboys who have already

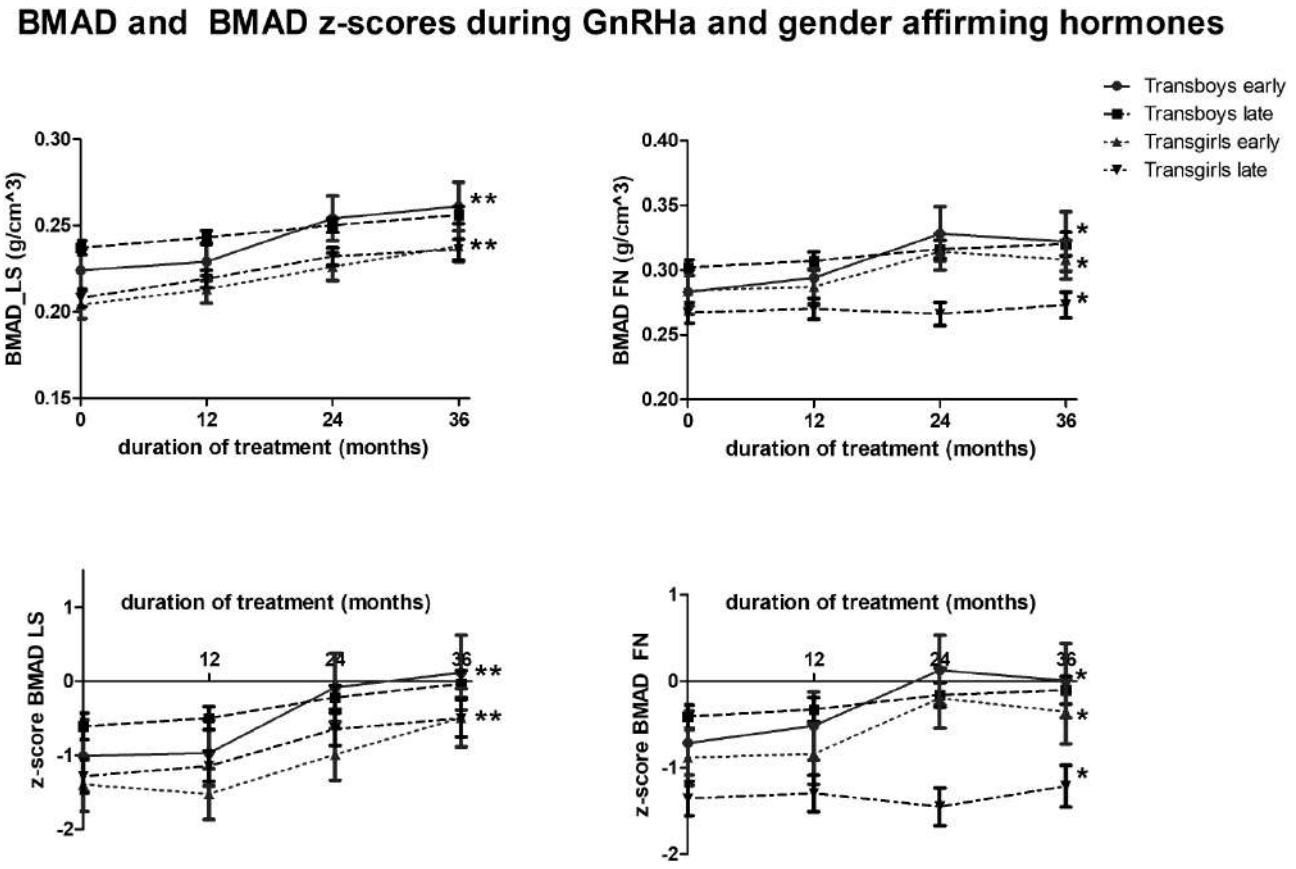

Figure 3. Estimated marginal means and standard error of the mean of BMAD prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

completed breast development may prefer lynestrenol to GnRHa treatment.

In most individuals with prolonged (3-4 years) GnRHa treatment, no further decrease in aBMD z-scores was observed in the last year, suggesting that z-scores might stabilize. Data from a larger cohort of adolescents treated with GnRHa for longer periods of time are needed, especially now that adolescents are presenting at younger ages at gender identity clinics and starting treatment at the onset of puberty.

During gender-affirming hormone treatment, a significant increase in the BMAD of the lumbar spine was found in all groups, and of the femoral neck in all but the late-pubertal transboys. In line with previous studies, BMAD z-scores were close to zero in transboys after 3 years of testosterone treatment (8-10). The increase in z-scores was most pronounced in the early pubertal transboys whose z-scores were slightly higher after 3 years of androgen treatment than at the start of GnRHa treatment.

The BMAD z-scores remained well below zero in transgirls in line with previous studies (8, 10). However, BMAD z-scores in early-pubertal transgirls increased more during estrogen treatment and were higher after 36 months than the scores reported by Vlot et al after 24 months (8). This might be due to the extra year of estrogen treatment in the current study, although the z-score of BMAD at the femoral neck no longer seemed to increase between 24 and 36 months. In contrast, the BMAD z-scores of the femoral neck in the late-pubertal transgirls were much lower after 36 months in the current study than previously reported (8). This may be due to the lower z-scores at the start of GnRHa treatment (–1.01 vs –0.44) and at the start of estrogen treatment (–1.36 vs –0.36) in the current study compared with the study by Vlot et al.

An important limitation of this study is the lack of an untreated control group. As discussed above, z-scores in transgirls were already well below 0 at the start of treatment, and these might have further decreased even without treatment, as low BMD was also observed in adult transwomen before the start of any treatment (16, 17).

Another issue is which reference population should be used to calculate BMD or BMAD z-scores. In transgirls who started treatment in early puberty, bone architecture may be more similar to that of cisgender females than to cisgender males. A recent study did not find changes in cortical bone geometry in response to estrogen treatment in adult transwomen, but the authors suggested that this might have been different if they had started treatment during puberty (21).

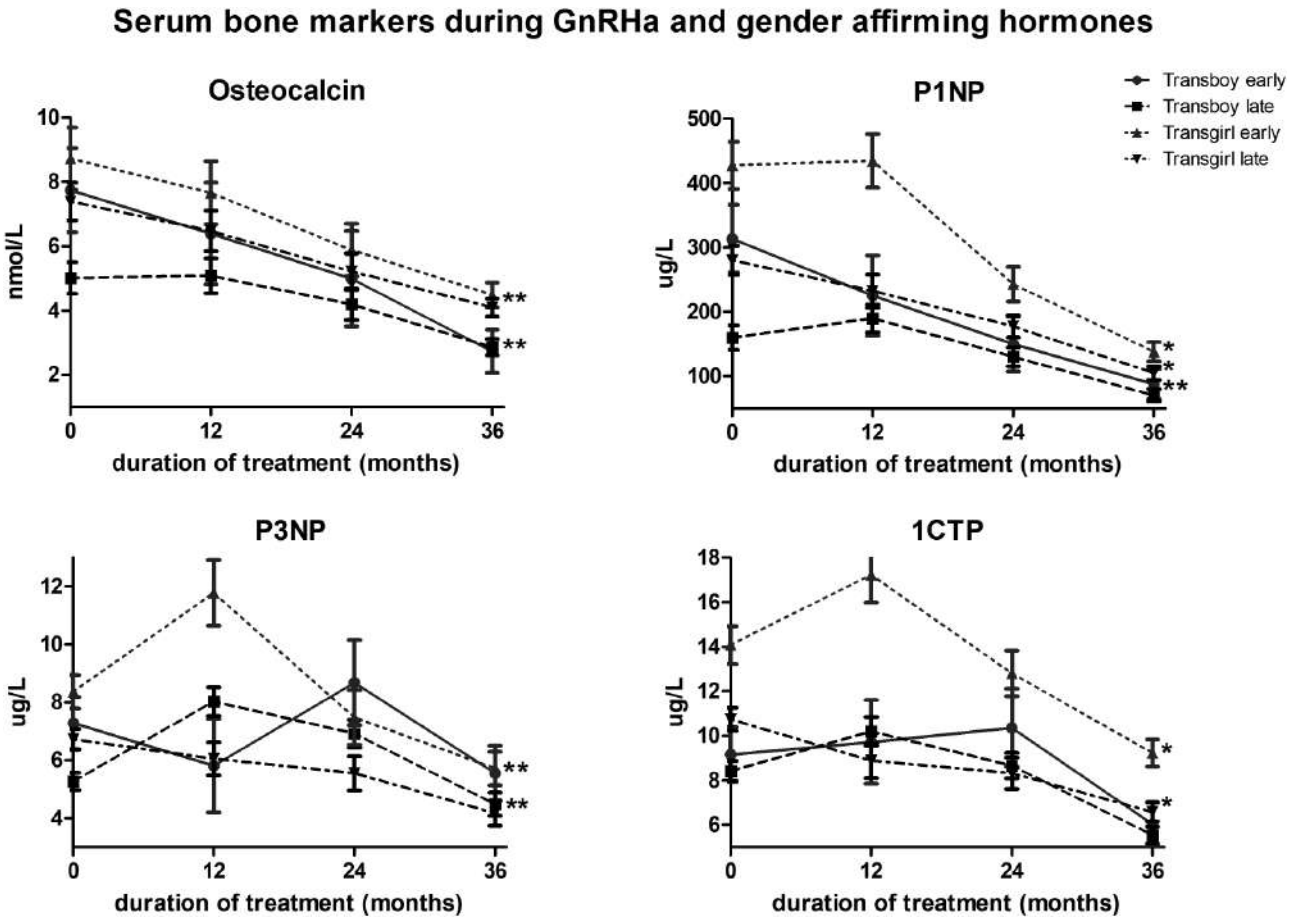

Figure 4. Estimated marginal means and standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

GnRHa are not only used in transgender children, but also in other populations, mainly in children with precocious or early puberty. A recent publication from an international consortium on the use of GnRHa concluded from the available evidence in this group that the treatment was safe with regard to bone mineral density, with attenuated bone mineral accrual reported during treatment but recovery by late adolescence (22). Different findings in children with precocious puberty compared with transgender adolescents may be due to the different timing of GnRHa treatment, the use of gender-affirming hormones, with current estradiol dose possibly insufficient (23), versus endogenous puberty, and due to differences in baseline BMD between the groups.

In transgirls and early-pubertal transboys, all bone markers decreased during the first year of GnRHa treatment while BMD levels remained stable. However, in the late-pubertal transboys bone turnover markers were lower at baseline and did not change. This suggests that the decline of the bone markers during GnRHa treatment may not be due to reduced bone mineral accrual but may rather reflect reduced growth velocity after initiating treatment. The late-pubertal transboys had likely already reached (near) adult height, which could explain the lower and stable levels of bone turnover markers. We previously observed a similar decrease of alkaline phosphatase during GnRHa treatment, but only in those who had not yet completed growth (24). The opposite effect was seen during the first year of treatment with gender-affirming hormones, where bone markers increased in the early pubertal transgirls, who likely had most growth potential. In adults, changes in P1NP were also found to be only weakly correlated to changes in BMD in transwomen and not significantly correlated in transmen (25). A previous study of bone turnover markers in adolescents observed a similar pattern of changes in P1NP and 1CTP to the current study (8). However, changes in osteocalcin were only seen in late-pubertal transboys, possibly due to the small number of subjects in that study with large interindividual differences in the changes of osteocalcin levels (8).

Based on the current study we propose that it is sufficient to perform DXA scans at the start of GnRHa

treatment, every 2 years during GnRHa treatment, at the start of gender-affirming hormone treatment, and then every 2 to 3 years. Adolescents should be counseled on the importance of weight-bearing exercise, an adequate dietary calcium intake, sufficient sunlight exposure to ensure adequate vitamin D levels, or vitamin D supplementation (26). In addition, it is important to ensure an adequate estrogen dose resulting in physiological serum estradiol levels. Routine measurement of bone turnover markers does not seem to be useful for monitoring bone health.

In conclusion, treatment with GnRHa results in a stabilization and maintenance of previously achieved bone mass in the lumbar spine but a small decrease in BMAD of the femoral neck of the nondominant hip. Gender-affirming hormone treatment increases bone accretion and normalizes the age- and sex-specific BMAD z-scores in transboys. Transgirls had lower BMAD z-scores, especially the late-pubertal group, but as z-scores were already lower at baseline, this may be due to other factors than the endocrine treatment, such as lifestyle factors. The consequences of lower BMD for long-term bone health in these individuals remains unclear. Future studies should evaluate peak bone mass in those who started treatment as adolescents and investigate clinically important outcomes such as fracture risk in this population.

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Clinical Trial Information: International Standard Randomized Controlled Trial Number registration no. ISRCTN 81574253 (http://www.controlled-trials.com/isrctn/).

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. 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.
2. 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**:582–90.
3. 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.
4. Waal HAD-vd, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol.* 2006;**155**:S131.
5. Magarey AM, Boulton TJ, Chatterton BE, Schultz C, Nordin BE, Cockington RA. Bone growth from 11 to 17 years: relationship to growth, gender and changes with pubertal status including timing of menarche. *Acta Paediatr.* 1999;**88**(2):139-146.
6. Laurent M, Antonio L, Sinnesael M, et al. Androgens and estrogens in skeletal sexual dimorphism. *Asian J Androl.* 2014;**16**(2):213-222.
7. Olson J, Garofalo R. The peripubertal gender-dysphoric child: puberty suppression and treatment paradigms. *Pediatr Ann.* 2014;**43**(6):e132-e137.
8. 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.
9. 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.
10. 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-E275.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. American Psychiatric Association; 2000.
12. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al.; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;**94**(9):3132-3154.
13. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005;**35**(1):89-99.
14. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: changing insights. *J Sex Med.* 2008;**5**(8):1892-1897.
15. Ward KA, Ashby RL, Roberts SA, Adams JE, Zulf Mughal M. UK reference data for the Hologic QDR Discovery dual-energy x ray absorptiometry scanner in healthy children and young adults aged 6-17 years. *Arch Dis Child.* 2007;**92**(1):53-59.
16. Van Caenegem E, Wierckx K, Taes Y, et al. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab.* 2012;**97**(7):2503-2511.

17. Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. *Horm Behav*. 2007;**52**(3):334-343.
18. 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.
19. Bishop A, Overcash F, McGuire J, Reicks M. Diet and physical activity behaviors among adolescent transgender students: school survey results. *J Adolesc Health*. 2020;**66**(4):484-490.
20. Theisen JG, Sundaram V, Filchak MS, et al. The use of whole exome sequencing in a cohort of transgender individuals to identify rare genetic variants. *Sci Rep*. 2019;**9**(1):20099.
21. Wiepjes CM, Vlot MC, de Blok CJM, Nota NM, de Jongh RT, den Heijer M. Bone geometry and trabecular bone score in transgender people before and after short- and long-term hormonal treatment. *Bone*. 2019;**127**:280-286.
22. Bangalore Krishna K, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;**91**(6):357-372.
23. Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and safety of pubertal induction using 17 -estradiol in transgirls. *J Clin Endocrinol Metab*. 2017;**102**(7):2356-2363.
24. 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.
25. Vlot MC, Wiepjes CM, de Jongh RT, T'Sjoen G, Heijboer AC, den Heijer M. Gender-affirming hormone treatment decreases bone turnover in transwomen and older transmen. *J Bone Miner Res*. 2019;**34**(10):1862-1872.
26. Antoniazzi F, Zamboni G, Bertoldo F, et al. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. *J Clin Endocrinol Metab*. 2003;**88**(3):1096-1101.

WPATH AND USPATH COMMENT ON THE CASS REVIEW

May 17, 2024

The recently published Cass Review is the result of a four-year investigation initiated by the United Kingdom's National Health Service England (NHSE) into the scientific basis of treating transgender youth and the experiences of those involved in transgender care in the UK. It contains 32 recommendations for a reorganization of transgender care for youth in England and Wales. The review took place after concerns arose around the increase in referrals, the evidence base for gender-affirming medical care, and the functioning of the NHS Tavistock Clinic's Gender Identity Development Service (GIDS), the only national care service with a long history of clinical experience and knowledge, which had operated since 1989 and was closed in March 2024. To date there are no new services in operation, and there will be none in the foreseeable future, despite what NHS England or Hillary Cass may claim. WPATH and USPATH are extremely concerned that this has left young transgender and gender diverse (TGD) people and families with little opportunity to obtain transgender care. This is a devastating situation for transgender youth and their families, whose rights are breached as they are being denied medically necessary care. We believe this to be a complete breach of the seven core values enshrined in the NHS Constitution.

Overall, WPATH and USPATH remain deeply concerned about the facts regarding the Cass Review's process and content, as well as its consequences for the provision of care for trans and gender diverse youth. Here are some of the reasons:

1. NHS England, which commissions and finances specialist medical services, including trans health care for youth and adults in England, appointed Hillary Cass in 2020 without any transparent or competitive process. Hillary Cass is a pediatrician with hardly any clinical experience or expertise in providing transgender healthcare for young people. Furthermore, Hillary Cass lacks significant research qualifications or research expertise in transgender health. Yet, the Cass Review purports to make "evidence-based" recommendations based on six systematic reviews carried out by the University of York in the UK, which do not contain any new research that would contradict the recommendations made in professional consensus guidelines of the American Academy of Pediatrics (AAP), the Endocrine Society, and WPATH to name a few.
2. The Cass Review is hailed by some as an "independent" review, referring to the fact that Hillary Cass had negligible prior knowledge or clinical experience of trans and gender diverse youth or indeed transgender medicine and surgery. One senior psychiatrist at a gender identity clinic in England told a national newspaper in the UK that the failure to include those with personal or professional experience "had concerned many within the field." They said: "The terms of reference stated that the

Cass Review 'deliberately does not contain subject matter, experts or people with lived experience of gender services' and Dr. Cass herself was explicitly selected as a senior clinician 'with no prior involvement … in this area.' Essentially, ignorance of gender dysphoria medicine was framed as a virtue. I can think of no comparable medical review of a process where those with experience or expertise of that process were summarily dismissed." WPATH and USPATH agree completely.

3. In contrast to what the Cass Review recommends, WPATH and USPATH firmly stand by the Standards of Care for the Health of Transgender and Gender Diverse People – version 8, which was published in 2022—and based on far more systematic reviews that the Cass Review—in collaboration with The School of Evidence-based Practice Center at Johns Hopkins University and considers that the (research and consensus-based) evidence is such to recommend that providing medical treatment including puberty-blocking medication and hormone therapy is helpful and often life-saving for young TGD people, while withholding such treatment may lead to increased gender dysphoria and adversely affect psychological functioning. Of note, many countries have reacted critically regarding the Cass Review, disagreeing with its unfounded medical opinion to severely limit the use of puberty-blocking medication and hormone therapy for TGD young people. These countries include Canada, the Netherlands, Belgium, Germany, Austria, Switzerland, and many states in the United States. In Germany, a new guideline on adolescent transgender care has been drafted (in collaboration with Austria and Switzerland) and is currently under review by 27 professional societies. As drafted, this guideline does not restrict puberty blockers and is in broad accordance with the WPATH SOC8 recommendations in its adolescent chapter. The Cass Review appears to be an outlier, ignoring more than three decades of clinical experience in this area as well as existing evidence showing the benefits of hormonal interventions on the mental health and quality of life of gender diverse young people (1-9).
4. WPATH and USPATH also have serious concerns regarding the ethics of the provision of puberty-blocking agents for young TGD people in the United Kingdom in the context of a research protocol only. Care and treatment that is consensus- and expert-based occurs in many areas of medicine, including pediatrics. The use of a randomized blinded control group, which would lead to the highest quality of evidence, is ethically not feasible. It is ethically problematic to induce people to participate in a research project as the only way to access a type of care that is evidence based, widely recognised as medically necessary, and often reported as lifesaving. There is no role in modern medicine for such practices, which are not commensurate with providing the highest standard of care for young people, as the Cass Review allegedly advocates for.

Regardless of what Dr. Cass' intentions may or may not have been, the Cass Review process itself intentionally and explicitly excluded any oversight from patients and their families and trans healthcare experts, and its content is not supported by a robust methodology. The Cass Review relies on selective and inconsistent use of evidence, and its recommendations often do not follow from the data presented in the systematic reviews. The Cass Review deprives young trans and gender diverse people of the high-quality care they deserve and causes immense distress and harm to both young patients and their families.

Editor's note: This statement has been adjusted to reflect the fact that the German guideline for adolescent transgender care is still under review.

References

1. de Vries AL, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 2014;134:696-704.
2. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. Lancet Diabetes Endocrinol 2017;5:816-26. doi: 10.1016/S2213-8587(17)30099-2 pmid: 28546095
3. Mahfouda S, Moore JK, Siafarikas A, etal. Gender-affirming hormones and surgery in transgender children and adolescents. Lancet Diabetes Endocrinol 2019;7:484-98. doi: 10.1016/S2213-8587(18)30305-X pmid: 30528161
4. 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:e0261039. doi: 10.1371/journal.pone.0261039 pmid: 35020719
5. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics 2020;145:e20191725. doi: 10.1542/peds.2019-1725 pmid: 31974216
6. 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;66:699-704. doi: 10.1016/j.jadohealth.2019.12.018 pmid: 32273193
7. 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:e20193006. doi: 10.1542/peds.2019-3006 pmid: 32220906
8. Achille C, Taggart T, Eaton NR, etal. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. Int J Pediatr Endocrinol 2020;2020:8. doi: 10.1186/s13633-020-00078-2 pmid: 32368216
9. Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, Rosenthal SM, Tishelman AC, Olson-Kennedy J. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023 Jan 19;388(3):240-250. doi: 10.1056/NEJMoa2206297.

PATHA

PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH AOTEAROA

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Cass Review out of step with high-quality care provided in Aotearoa

By PATHA (Administrator) on 11 Apr 2024 8:05 AM

The Professional Association for Transgender Health Aotearoa (PATHA) is disappointed to see the number of harmful recommendations made by the NHS-commissioned Cass Review, released yesterday in England. This review ignores the consensus of major medical bodies around the world and lacks relevance in an Aotearoa context.

The Cass Review is a report into England's approach to providing gender affirming care through a centralised gender clinic model. The 2022 interim report found this model was not fit for purpose, with wait times for the service extending into years. As a result, the clinic was closed while the NHS determined a better approach to providing this service.

The final Cass Review did not include trans or non-binary experts or clinicians experienced in providing gender affirming care in its decision-making, conclusions, or findings. Instead, a number of people involved in the review and the advisory group previously advocated for bans on gender affirming care in the United States, and have promoted non-affirming 'gender exploratory therapy', which is considered a conversion practice.

It's shocking to see such a significant inquiry into transgender health completely disregard the voices of transgender experts. It would be like reviewing women's health with no women, or Māori health with no Māori involved.

PATHA has shown the benefit of collaborations between transgender community members and clinicians providing gender affirming care. The lived experience and knowledge of our community members and clinicians does not make them biased - it means they're the experts in this care.

The Review commissioned a number of systematic reviews into gender affirming care by the University of York, but seems to have disregarded a significant number of studies that show the benefits of gender affirming care. In one review, 101 out of 103 studies were discarded.

PATHA welcomes further research about the health interventions that support the wellbeing and lives of trans and non-binary people, and of trans communities locally and globally. While we certainly look forward to more longitudinal research, the evidence in support of gender affirming care is clear, and we're disappointed to see this review discard so much robust work from researchers around the world. When multiple observational studies produce similar findings, the cumulative evidence becomes compelling.

The Review's recommendations include restricting access to both social transition and gender affirming hormone therapy, and would require the approval of a national multi-disciplinary team for any gender affirming care to be provided to anyone under 18. Restricting access to social transition is restricting gender expression, a natural part of human diversity. Requiring clinical approval for haircuts and wardrobe changes is intrusive, inappropriate, and a waste of money and time.

We've seen the benefits that increased access to gender affirming care have had on trans communities around Aotearoa. Barriers to care have detrimental impacts on wellbeing, and create additional work for healthcare systems already under stress. Our holistic approach, utilising multi-disciplinary teams, works well for Aotearoa.

In Aotearoa, gender affirming care is available no matter where you live, and has evolved over the last 15 years based on clinical experience, emerging evidence, and updated guidelines. Clinicians around the country, supported by specialists and multidisciplinary teams where needed, work alongside whānau to ensure best practice that is holistic, individualised, and whānau centred, with the best possible outcomes for our rangatahi.

Clinicians working in gender-affirming care welcome the increasing body of evidence about puberty blockers. This is important to help young people and their families make the best decisions about their individualised care.

PATHA is proud to support clinicians and community members working to promote the health and wellbeing of trans and non-binary people around Aotearoa. Our members have contributed to the evidence base in support of gender affirming care, and of trans wellbeing more generally, and will continue to work to improve access and the quality of care around the country.

We've collaborated with AusPATH and other rainbow organisations on this statement released by Equality Australia, and encourage that everyone take good care of themselves, and take time to unplug and check in with those around you. Aroha nui and kia kaha.

About PATHA

The Professional Association for Transgender Health Aotearoa (PATHA) is an interdisciplinary professional organisation working to promote the health, wellbeing, and rights of transgender people. We are a group of professionals who have experience working for transgender health in clinical, academic, community, legal and other settings.

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PATHA

PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH AOTEAROA

Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Af rming Hormone Therapy

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abstract

OBJECTIVES: Our rst 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 rst year of receiving gender-af rming 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-af rming 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: Af rmed 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-af rming hormone therapy in reducing body dissatisfaction. Modest initial improvements in mental health were also evident.

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WHAT S KNOWN ON THIS SUBJECT: Guidelines exist for providing gender-af rming hormone therapy (ie, puberty suppression and masculinizing or feminizing hormone therapy) to transgender youth; however, little research has been conducted on the impact of treatment on body dissatisfaction and mental health and factors that may influence this impact.

WHAT THIS STUDY ADDS: One year of receiving gender-af rming hormone therapy resulted in large reductions in youth body dissatisfaction and modest improvements in mental health. No demographic or treatment-related factors were associated with change over time.

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Two influential longitudinal studies from the Netherlands have helped establish guidelines for providing gender-af rming hormone therapy (ie, puberty suppression and masculinizing or feminizing hormone therapy) to transgender youth with gender dysphoria.[1,2] De Vries et al[3] conducted a prospective study with 70 youth who received puberty suppression (ie, medication to stop the progression of puberty). After 2 years, internalizing, externalizing, and depressive symptoms improved along with global functioning, but there was no improvement in body dissatisfaction or anxiety symptoms. A subset of the same cohort (n = 55) was reassessed after masculinizing or feminizing hormone therapy and gender-af rming surgery (vaginoplasty or mastectomy and hysterectomy), at which point there was a sustained improvement in global functioning and most measures of mental health. Gender dysphoria and body dissatisfaction also improved, and self-reported quality of life was similar to the Dutch population.[4] However, patients were not evaluated after masculinizing or feminizing hormone therapy alone.

In the only other longitudinal study of youth, participants seen in a gender clinic in the United Kingdom (n = 35) demonstrated improvement in clinician assessment of psychosocial functioning after 12 months of receiving puberty suppression.[5] Only 1 cross-sectional study has included a subset of transgender youth (n = 82 of 202). In comparison with those who had not started treatment, individuals who received both puberty suppression and/or masculinizing or feminizing hormone therapy as well as surgery had more favorable body image but not those who received puberty suppression and/or masculinizing or feminizing hormone therapy only.[6] Within this study, youth and adults as well as those receiving puberty suppression and/or masculinizing or feminizing hormone therapy were combined.

The bene ts of gender-af rming treatment are better described in adults. A recent review of 5 longitudinal and 2 cross-sectional studies found that receipt of masculinizing or feminizing hormone therapy alone was associated with improved depression in 5 of 7 studies, improved anxiety in 2 of 2 studies, and better quality of life in 3 of 3 studies.[7] Two studies also found lower rates of body uneasiness in adults who received masculinizing or feminizing hormone therapy alone (ie, dissatisfaction with body parts and negative body-related experiences, such as avoidance and self-monitoring).[8,9]

Understanding the impact of gender-af rming hormone therapy on the mental health of transgender youth is critical given the health disparities documented in this population. Within samples of transgender youth presenting for gender-af rming hormone therapy, estimates of clinically signi cant depressive symptoms or diagnoses have averaged in the range of 30 to 60 ,[10–13] and estimates of clinically signi cant anxiety symptoms or diagnoses have averaged in the range of 20 to 30 .[11,14–16] Lifetime history of suicidal ideation (average range 30 –50),[10,11,16] suicide attempt (average range 15 –30),[10,11,13] and nonsuicidal self-injury (NSSI) (average range 20 –40)[12,13,16] also appear common.

There is also some evidence that rates of mental health concerns may vary by gender, but no clear pattern has emerged.[11,14,15,17] Two studies have found higher levels of body dissatisfaction among af rmed females (ie, individuals assigned male at birth who identify as female) in comparison with af rmed males (ie, individuals assigned female at birth who identify as male).[6,18] Changes associated with puberty, as reflected in age and/or Tanner stage (ie, stage of puberty), may exacerbate body dissatisfaction and mental health concerns. Fewer studies have examined differences by age; however, one study found greater symptoms of depression but not anxiety among older adolescents,[16] and one study found higher levels of body dissatisfaction.[4] None have speci cally examined the impact of Tanner stage.

Our rst aim in this study was to explore how transgender youth baseline body dissatisfaction, depression, and anxiety symptoms vary on the basis of their gender, age at initial assessment, and Tanner stage at rst medical visit. Consistent with our earlier article examining differences in mental health functioning using the Child Behavior Checklist and Youth Self-Report,[14] we hypothesized that af rmed males will report greater symptoms of depression and anxiety. We also hypothesized that older age and greater Tanner stage will be associated with higher ratings of body dissatisfaction and more symptoms of depression and anxiety.

Our second aim was to examine how transgender youth body dissatisfaction, depression, and anxiety symptoms change over the rst year of receiving gender-af rming hormone therapy. We anticipated improvements in each of these domains but did not have any a priori hypotheses regarding which domains would demonstrate the greatest improvements.

Our third aim was to explore how any changes over time vary by af rmed gender, Tanner stage, age, type of treatment, months on masculinizing or feminizing hormone therapy, mental health treatment received, and whether chest (ie, "top") surgery was also obtained (among those assigned female at birth). We hypothesized that older age, greater Tanner stage,

receipt of puberty suppression only, fewer months on masculinizing or feminizing hormone therapy, and lack of chest surgery will be associated with fewer changes over time. Lastly, for descriptive purposes, we report information on lifetime and follow-up rates of suicidal ideation, suicide attempts, NSSI, and mental health treatment.

METHODS

Participants and Procedure

Participants are youth who received gender-af rming hormone therapy with a multidisciplinary program in Dallas, Texas. 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 (this letter is no longer required). Approximately 34 of families did not follow-up after the phone intake. Initial assessments occurred between August 2014 and March 2018, with most occurring in 2017 (41) or 2016 (37). At home before this visit, participants completed self-report measures of depression, anxiety, and body dissatisfaction. During the visit, clinicians also completed a report of depressive symptoms and collected information regarding lifetime and recent suicidal ideation, suicide attempts, and NSSI as well as current participation in therapy and support groups and use of psychiatric medication(s).

After the assessment, participants were discussed by the multidisciplinary team of providers from psychology, social work, pediatric endocrinology, pediatric and adolescent gynecology, and adolescent medicine. The Endocrine Society Clinical Practice Guidelines[2] guided the initiation of hormone therapy. Chest surgery was not performed within the program, but participants were provided with referrals when requested.

Approximately 1 year after this initial assessment (range: 11–18 months), 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.

Survey and clinician data were entered into a research database for analysis along with demographic and treatment-related information (ie, Tanner stage at rst medical visit, treatment start and end dates, and chest surgery date extracted from physicians notes). All participants provided consent, or assent with parent consent, to allow this information to be used for research. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center.

Measures

Participants were asked to self-report their gender identity (all ages) and sexual orientation (age 12 and older). These responses were recorded verbatim by the clinician and entered into the research database. Gender identities were coded into the following categories: (1) male, boy, or man; (2) male spectrum (eg, “trans masculine” or “masculine nonbinary”); (3) female, girl, or woman; (4) female spectrum (eg, “mostly female, slightly nonbinary”); and (5) nonbinary (eg, “agender” or “part girl, part boy”).

To assess body dissatisfaction, participants aged 12 years and older rated their degree of dissatisfaction with 29 areas of the body using the Body Image Scale (BIS).[19] Participants of all ages completed the Screen for Child Anxiety Related Emotional Disorders (SCARED), which produces a total score as well as subscale scores for panic-related, social, separation-related, generalized, and school avoidance–related anxiety symptoms,[20] as well as the Quick Inventory of Depressive Symptoms (QIDS)[21] to measure symptoms of depression that reflect the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* criteria for major depressive disorder.[22] The QIDS 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. When the percentage of missing values for each total score and subscale score was 15 , missing values were imputed by using the mean of nonmissing values.

Analyses

To examine baseline differences in depression (QIDS self and clinician), anxiety (SCARED), and body dissatisfaction (BIS), bivariate correlation coef cients were rst examined by using Pearson s r for age, Spearman s for Tanner stage, and point biserial for gender. Variables with signi cant correlations were then simultaneously entered into a linear regression for each outcome, and Cohen s f^2 was calculated as a measure of effect size (0.1 = small, 0.25 = moderate, and 0.4 = large).[23]

To examine change over time, QIDS (self and clinician), SCARED, and BIS scores were rst 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 signi cant. Cohen s *d* was used as a measure of effect size (0.2 = small, 0.5 = moderate, and 0.8 = large).[23] Changes

in clinical groupings on the QIDS were also examined by using the Wilcoxon rank test. For both baseline and longitudinal analyses, we planned to rst examine the SCARED total score then test for differences in subscale scores only if this change was signi cant.

To test for associations between change scores and demographic and treatment characteristics, change scores were calculated by subtracting baseline scores from follow-up scores for variables that exhibited a signi cant change over time. Bivariate correlation coef cients were then examined by using Pearson s r for age and months on feminizing or masculinizing hormone therapy, Spearman s for Tanner stage and therapy frequency, and point biserial for gender, treatment type, psychiatric medication use, support group participation, and chest surgery receipt (for those assigned female at birth). We planned to include any variables with signi cant correlations in a linear regression. *P* .01 was signi cant for all statistical tests to help account for the overall number of tests. Con dence intervals (CIs) are reported at the 95 level.

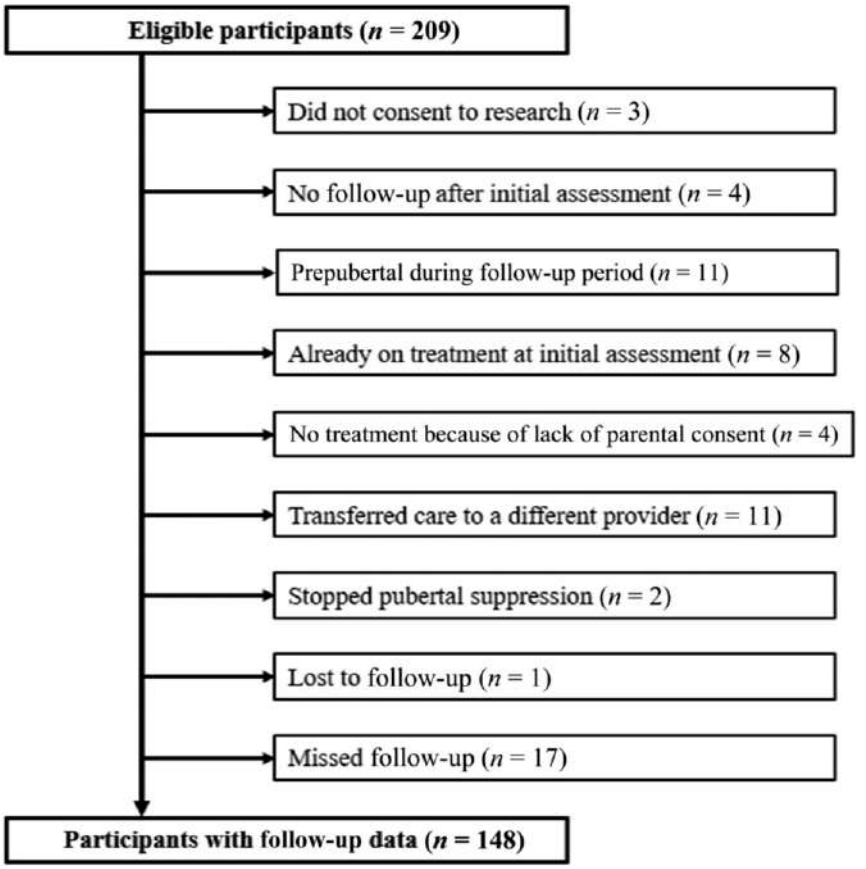

FIGURE
Flow diagram.

RESULTS

Figure 1 presents a flow diagram of participants who were due for follow-up (≥18 months since initial assessment), participants with follow-up data, and the reasons why follow-up data were not available or excluded. The mean number of months between initial assessment and reassessments was 14.9 (SD 2.1). Table 1 presents demographic information on participants. At the initial assessment, patients ranged in age from 9 to 18 years (mean 15.4; SD 2.0). All but 1 participant met *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* criteria for gender dysphoria. This participant subsequently met criteria at a follow-up visit and was started on treatment. 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). For participants who were on masculinizing or feminizing hormone therapy, the mean length of time receiving treatment before follow-up was 10.9 months (range 1–18; SD 3.3). During the follow-up period, 2 participants stopped puberty suppression without starting masculinizing or feminizing hormone therapy, and no participants stopped masculinizing or feminizing hormone therapy. Fifteen af rmed males obtained chest surgery at an average age of 17.1 years (range 15.2–18.7; SD 1.2) and at an average of 9.2 months from baseline (range 3.0–16.0; SD 3.3).

Table 2 presents means, SDs, and ranges for QIDS, SCARED, and BIS scores at initial assessment and follow-up for the full sample as well as by gender and treatment type. At baseline, af rmed males had greater clinician-reported depressive symptoms (CI −3.76 to −0.81), self-reported depressive symptoms (CI −4.46 to −0.79), total anxiety symptoms (CI −14.94 to −3.99), panic symptoms (CI −5.88 to −1.78), and school avoidance symptoms (CI −1.81, to −0.36) in comparison with af rmed females. However, Cohen s f^2 effect sizes were all in the small range (0.07, 0.06, 0.09, 0.10, and 0.07, respectively). No differences were found by age or Tanner stage.

Within the full sample, a signi cant decrease in body dissatisfaction (CI

TABLE Participant Demographics

	n ( )
Gender identity	
Male, boy, or guy	81 (55)
Male spectrum	9 (6)
Female, girl, or woman	52 (35)
Female spectrum	2 (1)
Something else[a]	3 (2)
Assigned sex	
Male	55 (37)
Female	94 (63)
Sexual orientation[b]	
Pansexual	25 (20)
Straight	24 (19)
Bisexual	15 (12)
Gay	12 (10)
Unsure	12 (10)
No label	11 (9)
Asexual	10 (8)
Something else	10 (8)
Lesbian	6 (5)
Race	
White	137 (95)
African American	3 (2)
Multiracial	3 (2)
American Indian	1 (1)
Ethnicity	
Hispanic	24 (17)
Non-Hispanic	120 (83)
Tanner stage	
I	3 (2)
II	6 (4)
III	5 (4)
IV	32 (23)
V	94 (67)
Treatment type[c]	
Puberty suppression only	25 (17)
Masculinizing or femininizing therapy only	93 (63)
Both treatments	30 (20)

[a] Excluded from gender analyses.

[b] Age 12 and older.

[c] Masculinizing or feminizing therapy only and both treatments were collapsed for analysis by treatment type.

14.74 to 21.90), self-reported depressive symptoms (CI 1.24 to 2.97), and total anxiety symptoms (CI 1.05 to 6.70) was observed during the follow-up period. Decreases in generalized, separation, and school-related anxiety symptoms were signi cant at the *P* .05 level but not the *P* .01 level. No change in clinician report of depressive symptoms was found. Cohen s *d* effect sizes were large for change in BIS scores (1.04), small to moderate for change in QIDS self-report scores (0.44), and small for change in SCARED total scores (0.27). Table 3 reports the percentage of the sample that fell into each clinical category on the QIDS at initial assessment and follow-up. A signi cant change was also found in self-reported depressive symptom categories (*P* .001) but not clinician-reported categories. No correlations were found between change scores and demographic and treatment-related characteristics. Although change scores were generally higher for participants who received chest surgery, no correlations were signi cant.

Table 4 presents descriptive data on mental health treatment, and Table 5 presents data on suicidal ideation, suicide attempt, and NSSI. During the follow-up period, the distribution of therapy frequency was as follows: none (16), less than every 3 months (15), every 2 to 3 months (12), monthly (22), every other week (21), and weekly (14). Of those who experienced suicidal ideation during the follow-up period, 94 had a lifetime history. These gures were 67 for suicide attempt and 87 for NSSI.

DISCUSSION

Youth reported large improvements in body dissatisfaction during the 1-year follow-up period. The amount of improvement was not related to treatment type. These ndings are consistent with a handful of studies that have documented improvements in body dissatisfaction within samples of adults receiving feminizing or masculinizing hormone therapy[8,9] but contrast with the 2 existing studies of youth. Within the longitudinal cohort from Amsterdam, puberty suppression alone was not associated with improvements in body dissatisfaction,[3] and within a cross-sectional study with a mixed sample of youth and adults, puberty suppression and/or feminizing or masculinizing hormone therapy was not associated with more favorable body image.[6] In contrast to the Amsterdam sample, youth in the current study were younger when starting puberty suppression (age: mean 12.5 and range 9.8–14.9 versus mean 13.7 and range 11.1–17.0).

Age, puberty stage, length of time receiving feminizing or masculinizing hormone therapy, and receipt of chest surgery were also not associated with amount of improvement. However, the sample size of participants receiving puberty suppression only and chest surgery were small, and variations in months on feminizing or masculinizing hormone therapy may not have been meaningful enough in the relatively short follow-up period.

TABLE 2 Body Dissatisfaction, Depression, and Anxiety Symptoms at Baseline and Follow-up

	n	Range[a]	Baseline, Mean (SD)	Follow-up, Mean (SD)
Body dissatisfaction (BIS)		0–116		
Full sample[b]	96		69.9 (15.6)	51.7 (18.4)
Af rmed males	66		71.1 (13.4)	52.9 (16.8)
Af rmed females	30		67.5 (19.5)	49.0 (21.6)
Puberty suppression	10		64.1 (18.2)	53.8 (20.1)
Feminine or masculine hormone therapy	86		70.7 (15.2)	51.4 (18.3)
Depressive symptoms (QIDS), self report[c]		0–27		
Full sample[b]	118		9.4 (5.2)	7.3 (4.6)
Af rmed males	76		10.4 (5.0)	7.5 (4.5)
Af rmed females	40		7.5 (4.9)	6.6 (4.4)
Puberty suppression	13		8.2 (6.1)	7.0 (5.6)
Feminine or masculine hormone therapy	105		9.6 (5.0)	7.4 (4.5)
Depressive symptoms (QIDS), clinician report[c]		0–27		
Full sample	125		5.8 (4.2)	5.9 (3.9)
Af rmed males	78		6.7 (4.4)	6.2 (4.1)
Af rmed females	45		4.2 (3.2)	5.4 (3.4)
Puberty suppression	19		5.3 (4.9)	5.5 (4.8)
Feminine or masculine hormone therapy	106		5.9 (4.1)	6.0 (3.8)
Anxiety symptoms (SCARED), total score[c]		0–82		
Full sample[d]	102		32.4 (16.3)	28.6 (16.1)
Af rmed males	65		35.4 (16.5)	29.8 (15.5)
Af rmed females	33		26.4 (14.2)	24.3 (15.4)
Puberty suppression	22		31.8 (16.6)	29.3 (17.1)
Feminine or masculine hormone therapy	80		32.6 (16.3)	28.4 (15.9)
Panic symptoms (SCARED)[c]		0–26		
Full sample	104		8.2 (6.3)	7.1 (6.3)
Af rmed males	66		9.3 (6.5)	7.9 (6.5)
Af rmed females	34		5.7 (4.9)	5.1 (4.9)
Puberty suppression	22		8.7 (6.5)	7.2 (5.7)
Feminine or masculine hormone therapy	82		8.1 (6.3)	7.1 (6.5)
Generalized anxiety symptoms (SCARED)		0–18		
Full sample	104		9.7 (5.1)	8.7 (5.1)
Af rmed males	66		10.4 (5.0)	9.0 (5.1)
Af rmed females	34		8.6 (5.1)	8.0 (5.1)
Puberty suppression	22		8.5 (5.2)	8.2 (5.4)
Feminine or masculine hormone therapy	82		10.0 (5.1)	8.8 (5.0)
Social anxiety symptoms (SCARED)		0–14		
Full sample	104		8.0 (4.1)	7.6 (4.3)
Af rmed males	66		8.5 (4.0)	7.8 (4.1)
Af rmed females	34		7.1 (3.9)	6.8 (4.4)
Puberty suppression	22		6.3 (3.6)	7.3 (4.7)
Feminine or masculine hormone therapy	82		8.5 (4.1)	7.7 (4.2)
Separation anxiety symptoms (SCARED)[e]		0–16		
Full sample	103		4.0 (3.4)	3.3 (2.7)
Af rmed males	65		4.2 (3.4)	3.4 (2.6)
Af rmed females	34		3.4 (3.3)	2.7 (2.3)
Puberty suppression	22		5.8 (4.0)	4.2 (3.1)
Feminine or masculine hormone therapy	81		3.5 (3.0)	3.1 (2.5)
School avoidance symptoms (SCARED)[c]		0–8		
Full sample	102		2.6 (2.2)	2.0 (2.1)
Af rmed males	65		2.9 (2.3)	2.0 (2.3)
Af rmed females	33		1.8 (1.7)	1.9 (2.1)
Puberty suppression	22		2.6 (2.7)	2.4 (2.4)
Feminine or masculine hormone therapy	80		2.6 (2.1)	2.0 (2.0)

[a] Absolute range.

[b] Signi cant change from initial assessment to follow-up (P .001).

[c] Signi cant difference in baseline scores by gender (P .01).

[d] Signi cant change from initial assessment to follow-up (P .01).

[e] Signi cant difference in baseline scores by age (P .01).

TABLE 3 Depressive Symptoms (QIDS) Scoring Ranges

	Range	Self-Report[a]		Clinician Report	
		Baseline, *N* ( )	Follow-up, *N* ( )	Baseline, *N* ( )	Follow-up, *N* ( )
Not elevated	0–5	33 (25)	51 (40)	73 (53)	67 (49)
Mild	6–10	46 (35)	48 (37)	44 (32)	49 (36)
Moderate	11–15	29 (22)	22 (17)	15 (11)	16 (12)
Severe	16–27	24 (18)	8 (6)	5 (4)	4 (3)

[a] Signi cant change from initial assessment to follow-up (*P* .001).

Most participants (90) were also in advanced stages of puberty (Tanner stage IV or V) when presenting for care. Limitations associated with collecting data within a busy clinical setting with multiple providers also resulted in missing data. Nonetheless, results suggest that youth receiving gender-af rming hormone therapy experience meaningful short-term improvements in body dissatisfaction, and no participants discontinued feminizing or masculinizing hormone therapy. These results provide additional support for the incorporation of these treatments into the standards of care for transgender youth experiencing gender dysphoria.[1,2]

Youth also reported modest improvements in mental health functioning during the follow-up period. These results are consistent with the existing longitudinal studies of youth.[3–5] Several factors may help explain why improvements were not greater than what was observed. Although physical changes associated with feminizing or masculinizing hormone therapy often start within the rst 3 months, changes continue over the course of several years. Furthermore, environmental stressors associated with one s transgender status may not improve after hormone therapy and could potentially worsen should they increase the youth s visibility as a transgender person. Research has consistently documented higher rates of bullying among transgender youth in comparison with nontransgender youth.[24,25] Within the current study, rates of school avoidance–related anxiety did not improve over the follow-up period.

The larger political context is also important to consider. Within Texas, where the current study was conducted, a well-publicized "bathroom bill" was introduced during the study period that prohibited transgender people from using a restroom that was different from the sex on their birth certi cate, although the bill ultimately failed to pass.[26] As a whole, the mental health functioning of youth from the present clinic as well as youth from a handful of other US- and European-based clinics appears poorer than the mental health functioning of youth from the Amsterdam clinic.[11,14,17] Previous studies have attributed this difference to Amsterdam s social and political climate, which is known to be more supportive of the lesbian, gay, bisexual, and transgender population.[17]

TABLE 4 Mental Health Treatment

	At Initial Assessment, *n* ( )	Follow-up Period, *n* ( )
Psychiatric medication	67 (47)	80 (61)
Therapist or counselor	144 (97)	114 (84)
Support group[a]	60 (43)	45 (35)

[a] Participation by parents and/or youth (eg, transgender family support organization; lesbian, gay, bisexual, and transgender youth center; or school-based Gay-Straight Alliance).

Consistent with our study examining baseline differences in mental health functioning as measured by the Child Behavior Checklist and Youth Self-Report,[14] af rmed males reported greater symptoms of depression and several forms of anxiety in comparison with af rmed females. However, the effect size of these differences was smaller within the current study in comparison with the former. Differences in measurement approach may help explain the mixed ndings regarding gender differences in mental health functioning across youth clinics.[11,15,17] Although some research suggests that nonclinic samples of af rmed male youth report more experiences of bullying,[24] af rmed females are thought to experience greater stigma regarding expression of femininity. Consistent with the current sample, the sex ratio of youth presenting to clinics also appears to be shifting from more af rmed females to more af rmed males presenting for care.[27] Although causes of this shift are largely unknown, they may be associated with other shifts in clinical presentations (eg, mental health and psychosocial functioning).

CONCLUSIONS

The current study is the largest longitudinal study of youth receiving gender-af rming hormone therapy to date and documents important improvements in body dissatisfaction over the rst year of treatment. Continued longitudinal study of this

TABLE 5 Suicidal Ideation, Suicide Attempt, and NSSI

	Lifetime, *n* ( )	1–3 mo Before Initial Assessment,[a] *n* ( )	Follow-up Period, *n* ( )
Passive ideation	105 (81)	33 (25)	51 (38)
Suicide attempt	20 (15)	3 (2)	6 (5)
NSSI	68 (52)	13 (10)	23 (17)

[a] One month for passive ideation and 3 months for NSSI and suicide attempt(s).

population will increase the eld s understanding of the bene ts of gender-af rming hormone therapy and assist providers in better anticipating needs. Follow-up periods of several years or more will help document the full impact of the physical changes with feminizing or masculinizing hormone therapy, and larger sample sizes will improve the ability to examine the speci c impacts of treatment type and chest surgery. Greater consideration of intersectionality and sociocultural context will further strengthen these efforts.

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ABBREVIATIONS

BIS: Body Image Scale
CI: con dence interval
NSSI: nonsuicidal self-injury
QIDS: Quick Inventory of Depressive Symptoms
SCARED: Screen for Child Anxiety Related Emotional Disorders

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REFERENCES

1. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;13(4):165–232
2. 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
3. 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
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
5. 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
6. 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
7. Rowniak S, Bolt L, Shari C. Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: a quantitative systematic review. *JBI Database Syst Rev Implement Rep*. 2019;17(9):1826–1854
8. Turan Ş, 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
9. 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
10. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J Adolesc Health*. 2015;57(4):374–380
11. 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
12. 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

13. Peterson CM, Matthews A, Copps-Smith E, Conard LA. Suicidality, self harm, and body dissatisfaction in transgender adolescents and emerging adults with gender dysphoria. *Suicide Life Threat Behav*. 2017;47(4):475–482
14. Kuper LE, Mathews S, Lau M. Baseline mental health and psychosocial functioning of transgender adolescents seeking gender-af rming hormone therapy. *J Dev Behav Pediatr*. 2019; 40(8):589–596
15. 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
16. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated dif culties. *Clin Child Psychol Psychiatry*. 2016;21(1):108–118
17. de Graaf NM, Cohen-Kettenis PT, Carmichael P, et al. Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: a clinical comparison study between four clinics. *Eur Child Adolesc Psychiatry*. 2018;27(7):909–919
18. 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
19. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975;4(6):639–656
20. 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
21. 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
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. Mahwah, NJ: Lawrence Erlbaum Associates; 1988
24. Eisenberg ME, Gower AL, McMorris BJ, Rider GN, Shea G, Coleman E. Risk and protective factors in the lives of transgender/gender nonconforming adolescents. *J Adolesc Health*. 2017; 61(4):521–526
25. 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
26. Wikipedia. Bathroom bill. Available at: https://en.wikipedia.org/wiki/Bathroom_bill. Accessed August 15, 2019
27. Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med*. 2015; 12(3):756–763

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Invited Commentary | Pediatrics

Pubertal Blockade and Subsequent Gender-Affirming Therapy

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For youth who identify as transgender or are unsure and wish to explore possibilities before the development of permanent secondary sex characteristics, use of a gonadotropin-releasing hormone analogue (GnRHa) is a key medical option. Sometimes colloquially called "puberty blockers," they have been used safely for decades in children with precocious puberty[1] and endometriosis,[2] among other medical indications. Multiple professional societies now endorse pubertal blockade for youth with gender dysphoria.[3,4] Recently, the use of GnRHa has received attention because of legislated concerns regarding the medical and surgical treatment of transgender youth, including criminalizing the provision of this care in some states.[5] Without evidence, the assumption has been made that GnRHa treatment leads to increased ultimate use of gender-affirming therapy (GAT) in transgender youth and that prescription of a GnRHa inappropriately advances the decision to start GAT. The article by Nos et al[6] provides data to the contrary—that this therapy can be offered both for mental health and cosmetic benefits without the concern of increasing the subsequent use of GAT.

An understanding of the medical management of a transgender child or adolescent is needed to appreciate the issues at hand.[3,4,7] A GnRHa is more potent than native GnRH and produces initial stimulation of pituitary gonadotrophs, with increased secretion of follicle-stimulating hormone, luteinizing hormone, and gonadal hormones, followed by downregulation of the pituitary-gonadal axis. As sex steroid secretion is inhibited, the development of pubertal changes ceases. Pubertal blockade with a GnRHa buys time for a child or adolescent, pausing puberty and allowing for the exploration of gender identity. Initiated early in puberty, the GnRHa delays the development of irreversible pubertal changes and, in some cases, eliminates the need for subsequent surgery. GnRHa therapy is reversable; discontinuation leads to prompt resumption of the pituitary-gonadal axis. Although pubertal blockade and GAT are often prescribed as complementary approaches, they are separate phases in transgender treatment.[3]

Through a retrospective cohort study of billing and pharmacy records, Nos and colleagues[6] explored the timely question of whether GnRHa use was associated with subsequent use of GAT among transgender and gender-diverse adolescents. They reviewed data between 2009 and 2018 from the US Military Healthcare System. Participants had at least 2 transgender-related encounters, with the first occurring between ages 10 and 17 years, and at least 1 encounter after the participant's 14th birthday (the earliest a clinician would start GAT according to current guidelines).[3,4,7] The sample included 434 adolescents, with 71.9% assigned female at birth and 69.1% having an enlisted insurance sponsor. Younger patients (aged 10-13 years) were more likely to start GnRHa therapy than older (aged 14-17 years) patients: 57.1% vs 10.1%. Patients who were assigned male at birth were more likely to receive GnRHa than those assigned female but were not more likely to be prescribed gender-affirming hormones. In fact, patients who were prescribed GnRHa were less likely to start GAT within 6 years of the first encounter than those who were not (hazard ratio, 0.52; 95% CI, 0.37-0.71). For clinicians, the salient point is that the prescription of a GnRHa did not imply the ensured subsequent use of GAT. The findings suggest that clinicians can offer GnRHa therapy without the concern of influencing the future use of GAT. The decision to initiate GnRHa therapy represents an independent therapeutic decision for a clinician, ideally working in concert with a multidisciplinary team of both medical and mental health clinicians.[5]

Limitations of the study of Nos and colleagues[6] merit discussion. They included younger children compared with earlier studies, which is a strength of the study, but as younger age was associated with higher GnRHa discontinuation rates, this could explain the finding. However, overall,

few patients discontinued treatment. Data were also extracted from an administrative database that did not afford information on the reasons why a clinician initiated therapy or not, and why patients chose to continue or discontinue the treatment. Patients could have obtained prescriptions outside of the Military Healthcare System that were not captured. However, the high costs out of pocket or through private insurance make this possibility unlikely. Lack of official approval for GAT coverage before 2016 may have influenced the decisions of patients or clinicians. Finally, there may be inherent biases among military medical personnel regarding gender identity and potential reluctance to provide treatment. The reasons could be personal ones or related to a lack of expertise. Replication of these results in a different study setting will be important to expand the generalizability of the current findings.

A question that arises in the course of transgender care is whether GnRHa therapy has long-term adverse medical consequences, including effects on bone health. More than one-half of an individual's bone density is acquired during adolescence, and transgender youth assigned male at birth are known to be at higher risk for low bone density even before GnRHa therapy.[7] Understanding whether GnRHa use is associated with fracture risk will be the critical long-term question that must be answered in future studies. In pediatrics, we are often left needing to weigh risks vs benefits, with limited available evidence, and needing to prescribe medications off-label. For the adolescent who goes on to receive GAT, theoretically and anecdotally, reintroduction of sex steroids appears to mediate skeletal gains, especially for transgender male individuals. In considering bone health and other health outcomes, optimizing bone density must be balanced with the known benefits of GnRHa for gender dysphoria, including decreased suicidal ideation.[6] Concerns about skeletal losses become less significant in an adolescent with active suicidal ideations. Although the significance of the risks may be unclear, there is strong evidence regarding the benefits of GnRHa in transgender youth: it can be a life-changing and lifesaving treatment for a vulnerable population who is at high risk for anxiety, depression, and suicide.[4,5,7]

The treatment decisions for transgender youth can be complex, with many factors that need to be considered. The novel findings provided by the study of Nos and colleagues[6] add to the growing body of work demonstrating that GnRHa therapy is a safe and necessary component of transgender care, especially for children or adolescents with gender dysphoria. Their results emphasize that use of GnRHa and subsequent GAT are different phases of treatment, and their use should be guided by independent decisions that a clinician makes separately. From a cosmetic standpoint, it is much easier to treat a patient if pubertal changes have only just begun to develop, and gender dysphoria subsides as the worry of continued development of secondary sex characteristics comes to a halt. We hope that an enhanced understanding of transgender medical management, including the separate phases of therapy, and how a GnRHa works therapeutically, will help to dispel myths. The study by Nos and colleagues[6] is hopefully one step forward in that direction. One phase of transgender treatment does not and should not dictate the next phase, thereby enabling clinicians to individualize care. Perhaps, even moving away from the term "puberty blocker" and instead describing mechanistically and clinically how these agents work will help return the focus of gender care to what matters most: the health and wellness of the child or adolescent.

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REFERENCES

1. Magiakou MA, Manousaki D, Papadaki M, et al. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab*. 2010;95(1):109-117. doi:10.1210/jc.2009-0793

2. Gallagher JS, Missmer SA, Hornstein MD, Laufer MR, Gordon CM, DiVasta AD. Long-term effects of gonadotropin-releasing hormone agonists and add-back in adolescent endometriosis. *J Pediatr Adolesc Gynecol*. 2018;31(4):376-381. doi:10.1016/j.jpag.2018.03.004

3. 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

4. Rafferty J; Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*. 2018;142(4):e20182162. doi:10.1542/peds.2018-2162

5. Kremen J, Williams C, Barrera EP, et al; Gender Multispecialty Service (GeMS) Team. Addressing legislation that restricts access to care for transgender youth. *Pediatrics*. 2021;147(5):e2021049940. doi:10.1542/peds.2021-049940

6. 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

7. Bachrach LK, Gordon CM. Bone health among transgender youth: what is a clinician to do? *Pediatrics*. 2021;148(4):e2021051137. doi:10.1542/peds.2021-051137

Child and Adolescent Mental Health

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Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature

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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.

Key Practitioner Message

What is known?

- Increasing numbers of early adolescents who are transgender or gender diverse (TGD) and seeking professional help.
- Pubertal development may lead to (a) greater anxiety about sexual identity and (b) suicidal thoughts among TGD.
- Professional organizations, such as the Endocrine Society and the World Professional Association for Transgender Health (WPATH), have recommended the use of puberty-blocking hormones to arrest pubertal development, thus allowing early adolescents and their families more time to consider the possible outcomes of gender reassignment.

What is new?

- This article is a report of a critical and systematic review of literature about the use of puberty-blocking hormones among TGD, the positive, and the negative outcomes associated with their use.
- The findings of this systematic review can guide healthcare professionals in their discussions with TGD youth and their families as they consider the risks and benefits of puberty suppression.

What is significant for clinical practice?

- A summary of current research on the use of puberty-blocking hormones suggests that clinicians follow the guidelines offered by the Endocrine Society and WPATH to enhance the positive outcomes associated with use of these medications.
- Clinicians and researchers should work together to conduct well-designed and rigorous longitudinal and mixed methods studies of TGD youth using GnRHa.

Keywords: Transgender; adolescent; puberty blockers; critical review

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Introduction

Recently, there has been an increase in the number of parents seeking medical advice and care for their early adolescent children who are transgender or gender diverse [TGD] (Bonifacio & Rosenthal, 2015; Turban, 2017). A study of a representative sample of middle school youth in San Francisco using the Youth Risk Behavior Survey (YRBS) showed that 1.3% self-identified as transgender (Shields et al., 2013); in the 2017, YRBS data collected from a nationally representative sample of high school students ($N = 131,901$), 1.8% responded 'Yes, I am transgender', and another 1.6% responded, 'I am not sure if I am transgender' (Johns et al., 2019, p. 68). Compared to their cisgender peers, these gender diverse youth bear a disproportionate burden for mental health problems including substance use and suicide attempt (Lowry et al., 2018).

Hormonal treatment, including the use of puberty suppressing drugs, provides a potentially life-saving solution for these patients, yet for this specific population of patients, the long-term consequences of these drugs are relatively unknown (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2015). For children and adolescents who experience gender dysphoria (GD), the possibility of receiving this treatment provides hope; however, the lack of longitudinal evidence may lead to barriers in accessing and receiving treatment. Two groups, the World Professional Association for Transgender Health (WPATH, s2011) and the global Endocrine Society in the United States (Hembree et al., 2009, 2017), have provided consensus expert guidelines for the use of puberty-blocking agents in children and early adolescents with GD. The use of these medications, in many early pubertal children, is an important component of gender-affirming care (Edwards-Leeper, Leibowitz, & Sangganjanavanich, 2016). These consensus guidelines have been critical in supporting the work of medical professionals who are balancing clinical judgment and evidence-based research in the care of these patients.

In a descriptive study of the physiological and psychological characteristics of 101 transgender youth between the ages of 12 and 24 years, Olson, Schrager, Belzer, Simons, and Clark (2015) found that these youth were aware of their gender incongruence at a mean age of 8.3 ± 4.5 years, over one-third experienced symptoms of clinical depression, and over half reported having suicidal thoughts at least once and about one in three had made one or more suicide attempts. Liu and Mustanski (2012) followed a community sample of 246 LGBT youth between the ages of 16 and 20 years prospectively and found that previous victimization predicted both self-harm and suicidal ideation. Clearly, the risk of adverse mental and physical outcomes among this population of youth is high. Thus, the need to find a way to prevent such dire consequences is equally high.

Researchers in the Netherlands conducted a qualitative study of 13 early adolescents (five trans girls and eight trans boys) and explored the perceptions of these adolescents (average age of 16 years 11 months) and the professional teams working with them about the use of puberty suppression in the form of gonadotropin-releasing hormone agonists (GnRHa) (Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2016). Themes derived from interviews with these adolescents were that relative to using GnRHa for puberty suppression, (a) it is difficult to determine the appropriate age for starting the use of these hormones, (b) long-term effects of using suppression are unknown, and (c) both stereotypes and greater media attention create a social context that can be positive or negative. These themes were compared with data collected previously from professionals working with TGD youth and results in that study revealed that professionals worried more about long-term effects than did the youth, yet the youth worried more about the appropriate age for starting puberty suppression.

The advantages of using puberty suppression in children and adolescents with gender dysphoria have been identified as improving some psychological functioning such as decreased depression and improved global functioning. Identified disadvantages were unpleasant side effects such as hot flashes in AFAB youth treated later in puberty (e.g., Tanner stages 4–5), decreased growth velocity, and increased body mass index (Chew, Anderson, Williams, May, & Pang, 2018). In addition, bone turnover and bone mineral density have been shown to decrease with use of GnRHa, particularly in young transwomen (Vlot et al., 2017). A significant barrier to use of puberty suppressing medications is the high cost of the medications with insurance coverage for treatment of GD in children and early adolescents being highly variable and, in some cases, specific insurance plan exclusions (Stevens, Gomez-Lobo, & Pine-Twaddel, 2015).

The use of puberty suppressing drugs (e.g., gonadotropin-releasing hormone agonists or GnRHa) has long been viewed as the standard of care for children with central precocious puberty (Lee et al., 2014) and adverse physical and psychological effects have been rare (Krishna et al., 2019; Yu, Yang, & Hwang, 2019). GnRHa have also been used in adolescent females with endometriosis with mixed results (DiVasta & Laufer, 2013; Gallagher et al., 2018). Although these uses are beyond the scope of this review, it is important to acknowledge that risks and benefits among these disparate populations could differ.

Purpose

Despite the increase in demand for more healthcare services for TGD youth, research is still in its relative infancy. The purpose of this critical review is to present the current state of research on the use of puberty-blocking hormones in prepubescent TGD children/early adolescents.

Method

As authors of this review, we followed a seven-step method for critical reviews of the literature described by Cooper (2017). The seven steps are as follows: (a) formulate the problem; (b) search the literature; (c) gather information/data from the published studies; (d) evaluate the quality of the studies found; (e) analyze and integrate outcomes of the studies; (f) interpret the evidence found; and (g) present the results. Because there were no human subjects involved, we did not request institutional review board approval. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) as a guideline for reporting our process and displaying our decision

points as shown in Figure 1 (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

Problem identification

The problem addressed in this review was identified in the introduction as a lack of knowledge about (a) the criteria for using puberty-blocking drugs; (b) the known risks associated with use of these drugs; and (c) the benefits of using such drugs with early adolescents. We specifically sought to answer the following questions relative to TGD early adolescents:

1 What prerequisite criteria (e.g., diagnosis of gender dysphoria; Tanner stage of sexual maturation) are being met before physicians administer gonadotropic-releasing hormone agonists (GnRHa)?

2 What specific drugs are used to suppress puberty in early adolescents?

3 What are the known risks and adverse outcomes of using GnRHa in early adolescents?

4 What have been the positive outcomes of using puberty suppression drugs in early adolescents?

Inclusion/exclusion criteria and literature search

Inclusion/Exclusion Criteria: Our inclusion criteria were that articles had to be either qualitative or quantitative research papers, written in English with a focus on the use of puberty-blocking drugs/hormones in early adolescents (e.g., ages 10–14) who self-identified as transgender or who had a medical diagnosis of gender dysphoria. The researchers had to identify risks and/or benefits associated with the use of these medications. Our exclusion criteria were editorials, letters to the editor, systematic reviews, and opinion pieces.

We consulted a health sciences librarian skilled in searching the literature on healthcare topics. She performed the search using four relevant and accessible databases: LGBT Life, PsycINFO, PubMed, and Web of Science. Search strategies were composed for each database, using subject headings and keywords to recover articles on transgender persons and puberty

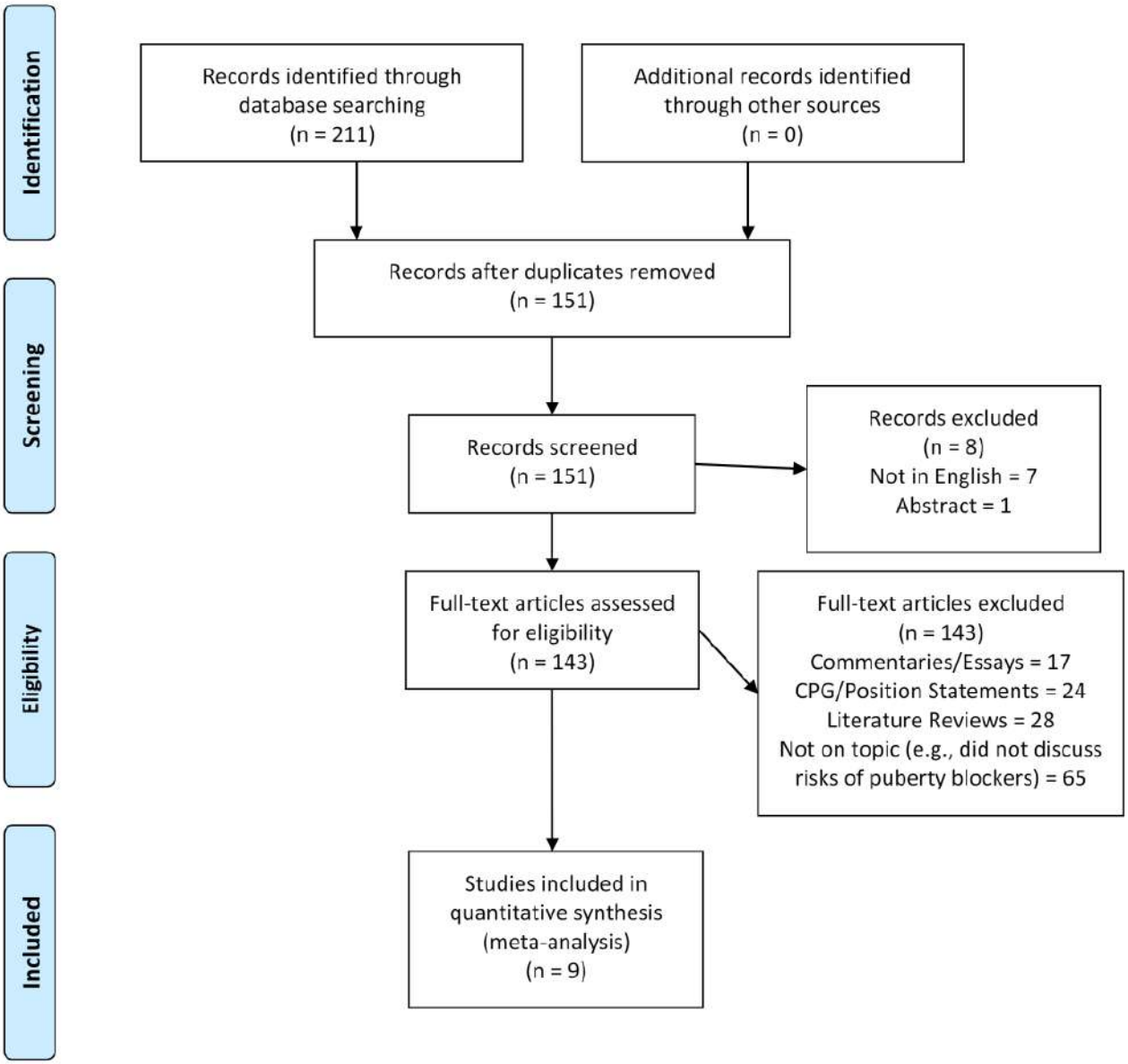

Figure 1. PRISMA flow diagram. CPG, Clinical Practice Guidelines [Colour figure can be viewed at wileyonlinelibrary.com]

blockers, puberty suppressors, or puberty inhibitors. Table 1 details the search terms for each database.

Our search resulted in a sample of $N = 211$ (Figure 1). We first removed duplicates, then divided the identified articles evenly among the first three authors. Using a screening checklist designed specifically for this review, we examined the abstract and the entire published paper to answer the following questions:

1 Was the paper written in English?
2 Was the focus of the paper on transgender youth/children or prepubescent children/early adolescents with gender dysphoria?
3 Did the article focus on the use of puberty-blocking drugs/hormones such as gonadotropin-releasing hormone analog (GnHRa)?
4 Did the authors identify risks and/or benefits associated with the use of these hormones?
5 Did the study use a qualitative or quantitative research design?
6 Was the paper a systematic or integrative literature review?

All papers for which the first five questions were answered affirmatively and the last question was not, were retained for full review.

Data extraction

After screening the articles, we developed a data extraction tool that included the name of the first author and date of the publication, the purpose of the study, a description of the sample (e.g., number and age of participants), prerequisites identified prior to use of puberty-blocking drugs, the names or types of drugs used, the youth's Tanner stage at the time the drugs were first administered, identified risks or adverse outcomes, positive outcomes, and our quality assessment value (see details below, in Step Four). We then extracted data from each article included to describe our sample and to address our research questions.

Evaluation of quality of studies

To determine the quality of each paper, two authors independently completed a checklist for each of the studies, compared their ratings and discussed differences until coming to consensus. We used one of three checklists, depending on the type of study design, to evaluate the quality of the information found in our literature sample and to report any type of bias found in the process. The three checklists were specific for evaluating the quality of retrospective chart reviews (Vassar & Holzmann, 2013), Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional and observational studies, and the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018). In assessing the quality of retrospective chart reviews, we created a checklist with the 10 questions specified by Vassar and Holzmann (2013) and arbitrarily created ratings of *poor* (1–3 yes answers), *fair* (4–6 yes answers), and *good* (7–10 yes answers). In using the JBI checklists, we computed a percentage of met criteria to determine quality and followed the same rating categories of *poor*, *fair*, and *good*. For all checklists used, if all criteria were met, the study was given a rating of *excellent*.

Analysis of outcomes and interpretation of evidence

Data analyzed for the nine articles included in this review were derived from retrospective chart reviews, case reports, a cross-sectional study, and prospective, observational studies. Thus, no statistical analysis nor meta-analysis could be done. Rather, data derived to answer our research questions are presented in the next step showing our results.

Table 1. Terms used to search four databases related to use of puberty blockers for early adolescents

Step	Term(s)
Database: LGBT Life	
1	puberty
2	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
3	1 AND 2
Database: PsycINFO	
1	transgender OR gender nonconforming OR nonbinary
2	puberty
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	1 AND 4
Database: PubMed	
1	('Transgender Persons'[Mesh] OR transgender [Title/Abstract] OR gender [2:17PMitle/Abstract][9:27 AMitle/Abstract] OR nonbinary[Title/Abstract]
2	puberty[Title/Abstract] OR prepuberty[Title/Abstract] OR prepubertal [Title/Abstract] OR prepubescent[Title/Abstract] OR prepubescence[Title/Abstract]
3	blocker[Title/Abstract] OR blockers[Title/Abstract] OR suppressor[Title/Abstract] OR suppressors[Title/Abstract] OR inhibitor [Title/Abstract] OR inhibitors[Title/Abstract] OR hormone suppressor[Title/Abstract]
4	bicalutamide[Title/Abstract] AND anastrozole [Title/Abstract]
5	3 OR 4
6	2 AND 5
7	'Gonadotropin-Releasing Hormone'[Mesh] OR gonadotropin- Releasing hormone[Title/Abstract] OR GnRH[Title/Abstract] OR histrelin[Title/Abstract] OR leuprorelin[Title/Abstract]
8	6 OR 7
9	1 AND 8
Database: Web of Science	
1	transgender OR gender nonconforming OR gender nonconforming OR nonbinary
2	puberty OR prepuberty OR prepuberty OR pubescent OR pubescence
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	gonadotropin-releasing hormone OR GnRH or histrelin OR leuprorelin
6	bicalutamide OR anastrozole
7	5 OR 6
8	4 OR 7
9	1 AND 8

Results

Our searches yielded a total of 151 unique articles (after all duplicates were removed) related to the search terms. Details of the nine articles retained for review are in Table 2; all were published recently, between 2011 and 2020. Of these, four articles were retrospective chart reviews, two were case reports, one was cross-sectional, one was a prospective study to evaluate the efficacy and safety of using a GnRHa (triptorelin) drug over time in transgender adolescents (Schagen, Cohen-Kettenis, Delemarre-van de Waal, & Hannema, 2016). Sample sizes in these studies ranged from 1 to 192. The samples were 9–35 years of age and included a total of 296 transgender females, assigned male at birth (AMAB) and 404 transgender males, assigned female at birth (AFAB) and 2 who were undecided patients assigned male at birth ($N = 702$). Race/ethnicity was not reported in 6/9 (66.7%) of the studies reviewed. In the other three studies, the vast majority of the samples (96%, 83.5%, and 68.5% respectively) were Caucasian/White.

Prerequisite criteria

The prerequisite criteria that were met before physicians administered GnRHa drugs to early adolescents were not reported in four of the studies (Klaver et al., 2018; Nahata, Quinn, Caltabellotta, & Tishelman, 2017; Turban, King, Carswell, & Keuroghlian, 2020; de Vries, 2011). Other criteria mentioned were as follows: (a) being screened by a mental health professional who made a diagnosis of gender dysphoria (Khatchadourian, Amed, & Metzer, 2014; Vlot et al., 2017); and (b) diagnosis of gender identity disorder or lifelong extreme gender dysphoria and living in a supportive environment (Cohen-Kettenis, Schagen, Steensma, DeVries, & Delemarre-van de Waal, 2011; Schagen et al., 2016); and (c) gender dysphoria and gender incongruence (Schneider et al., 2017).

Drugs used to suppress puberty

The GnRH analogue drug named to suppress puberty in children in four of the reviewed studies was triptorelin

Table 2. Articles in a critical review of literature on use of puberty blockers in prepubescent child

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
Cohen-Kettenis et al. (2011)	Case report to describe a 22-year follow-up of FtM treated with GnRH analogs at age 13.	$N = 1$ AFAB; age 35 years. Race/ethnicity not reported.	States 'fulfilled the current criteria for GnRH analog treatment eligibility' (p. 844). Does not explicitly list what these were. Diagnosis of gender identity disorder at age 16 (p. 843).	B3; P3	Triptorelin at age 13.7 years 3.75 mg q 4 weeks IM. Age 18.6 stopped triptorelin and initiated testosterone-ester mixture.	None reported directly for GnRHa use. At age 35 FSH and LH were elevated owing to gonadectomy	At age 35, all anthropomorphic measurements were within normal limits (50th percentile ± 2 *SD*); fasting labs within normal limits. Patient is 'still convinced that his choice to live as a man was the right one' (p. 846).
De Vries et al. (2011)	Prospective follow-up to compare GD and psychological functioning before and after puberty suppression.	$N = 70$ Mean age = 13.6 (1.8) years Race/ethnicity N\not reported	Not provided in this paper.	Not provided in this paper.	GnRHa, but no drug name given.	AFAB had more anxiety and anger and had more problem behaviors than AMAB. GD was not significantly changed over time.	Both AFAB and AMAB showed significant fewer emotional and behavior problems over time. Both also reported decreases in depressive symptoms and increases in global functioning.
Khatchadourian et al. (2014)	Retrospective chart review; describe patient characteristics, treatment, & response	$N = 84$: 45 AFAB; 37 AMAB 2 undecided natal males Ages 11.4–19.8 years. Race/ethnicity not reported.	Screened by mental health professional. Tanner 2 or +. Diagnosis of gender dysphoria by Utrecht Scale or other scales.	Tanner stage 2	GnRHa 14/15 FtM transitioned to testosterone (7 continued GnRHa, 7 discont. GnRHa). GnRHa to 11 MtF (5 rec'd estrogen and 1		13 months = not pursue change. Drug name not provided.

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
					of these DC'd GnRHa; 1 stopped due to emotional lability; 1 stopped due to heavy smoking. One MtF stopped GnRHa after		
One stopped GnRHa due to mood swings & emotional lability.	Need long-term follow-up studies. FtM patients who undergo mastectomy have more favorable post-op outcomes. Should be told about fertility preservation.						
Klaver et al. (2018)	Retrospective design. Examine how body shape and composition change during treatment with GnRHa	*N* = 192: 71 AMAB 121 AFAB Age 22 years. 3 Asian, 3 Black American, 184 Caucasian (96%)	Diagnosis of gender dysphoria.	Breast stage 2 for girls (age 14.5). Gonad stage 3 for boys (age 15.3)	Sub-q GnRHa 3.75 for 4 weeks. No drug name provided. Added cross-sex hormones at age 16.	Greater changes in body composition (> fat in MtF and < fat in FtM compared to cisgender).	Earlier treatment associated with closer resemblance to desired sex
Nahata et al. (2017)	Retrospective medical record review to examine mental health diagnoses, self-injurious behaviors, school victimization, and rates of insurance for hormone therapy.	*N* = 79: *n* = 28 AMAB *n* = 51 AFAB Ages 9–18 years 83.5% White 6.3% Black 6.3% biracial 2.5% American Indian 1.3% Hispanic	Diagnosis of gender dysphoria and 'readiness' for hormone treatment by psychiatrist (p. 189)	Beginning at Tanner 2–3	27 received GnRHa but no drug name was given.	Cost of GnRHa = up to $25k per year. Only 8 of 27 had insurance coverage	Not reported
Schagen et al. (2016)	Prospective observational study to evaluate efficacy and safety of GnRHa (triptorelin)	*N* = 116: 49 AMAB 67 AFAB Ages 11.1–18.6 years. Race/ethnicity not reported.	Diagnosis of gender identity disorder, lifelong extreme gender dysphoria, psychologically stable, living in supportive environments.	Median Tanner stage at initiation MtF- 4 FtM -	3.75 mg IM Triptorelin (GnRHa) every 4 weeks after initial at 0, 2, 4 week dosing	Decreased alkaline phosphatase - probably related to slowed growth velocity; decrease in lean body mass % and increase in fat %; decreased height velocity.	All subjects had suppressed gonadotropin and sex steroids; testicular volume decreased in MtF and menses ceased in FtM. No sustained creatinine or LFT abnormalities
Schneider et al. (2017)	Longitudinal case report of	*N* = 1 Age 11,	Diagnosis of gender	Tanner stage 2		Global IQ decreased	

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
	effects of puberty suppression on brain white matter.	FMAB. Race/ethnicity not reported.	dysphoria and gender incongruence.		Leuprorelin 3.75 mg. IM/ every 28 days	slightly, some difficulty in math and exact sciences.	Improvement in affective and social life.
Turban et al. (2020)	Cross-sectional survey to relate access to puberty blockers in adolescence and mental health outcomes in adulthood.	*N* = 89 who received puberty blockers between ages 9 and 16. From national Transgender Survey.	Not provided in this paper.	Not provided in this paper.	Not provided in this paper.	None noted	Decreased lifetime suicidal ideation and past-month psychological distress and binge drinking. Reduced lifetime illicit drug use.
Vlot et al. (2017)	Retrospective study of bone turnover markers and bone density in adolescents receiving GnRHa and later HRT	*N* = 70: 28 AMAB 42 AFAB Ages 11.5–18.6. Race/ethnicity not reported.	Diagnosis of gender dysphoria	FtM - start at T2+; MtF - start testicle volume at least 6–8 ml or when T2-3	Triptorelin 3.75 mg subcutaneously every 4 weeks At 16 yo - testosterone or estradiol added.	Decrease in bone turnover markers ICTP and P1NP, also coincides with decrease in BMAD Z scores primarily in lumbar spine (most hormone sensitive); even after HRT started, in most, pretreatment Z scores were not reached even after 24 months on HRT	Some recovery of BMAD Z scores after HRT started

Abbreviations: AFAB, males, assigned female at birth; AMAB, females, assigned male at birth; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist.

(Cohen-Kettenis et al., 2011; Schagen et al., 2016; Vlot et al., 2017) and leuprorelin (Schneider et al., 2017). The other five studies just used the term GnRHa but provided no specific drug name. Gender-affirming drugs such as testosterone and estradiol were mentioned in some studies as added later in the treatment protocols.

Risks/adverse outcomes

Known risks and adverse outcomes of using GnRHa in children included mood swings and emotional lability (Khatchadourian et al., 2014). Klaver et al. (2018) reported different changes in body composition between patients AMAB and patients AFAB after treatment; persons AMAB had increased fat whereas AFAB persons had decreased fat compared to cisgender peers. Nahata et al. (2017) reported the cost of using GnRHa as an adverse byproduct of this treatment in addition to the lack of insurance coverage. Other adverse risks associated with use of these hormones included slow growth, decrease in lean body mass, increased fat, and decreased height velocity (Schagen et al., 2016); and decrease in bone turnover markers (Vlot et al., 2017).

Positive outcomes associated with GnRHa

Positive outcomes associated with using GnRHa drugs with adolescents included anthropomorphic measurements returning to normal limits in adulthood (Cohen-Kettenis et al. 2011); and better outcomes for patients assigned female at birth who also underwent mastectomy (Khatchadourian et al., 2014). Schagen et al. (2016) reported positive changes in secondary sexual characteristics along with the lack of sustained creatinine or LFT abnormalities. Schneider et al. (2017) reported the individual's improvement in affective and social life. Similarly, de Vries et al. (2011) found significant improvements in general functioning, decreases in depressive symptoms, and decreases in emotional and behavioral problems. One study reported no positive outcomes (Nahata et al., 2017). Importantly, when

compared to youth who did not receive pubertal suppression, those who did showed lower lifetime rates of suicidal ideation (Turban et al., 2020).

Quality

Table 3 is a summary of the quality checklists used to determine quality in the four studies that were retrospective chart reviews. In sum, three of the studies were deemed of fair quality with relatively high risk for bias. These studies had quality scores that were 4 and 5 criteria out of 10 that were met; one study was assessed as good with a score of 7 out of 10 criteria met. The risk of bias in the studies with fair quality was owing to such things as not reporting how data abstractors were trained and monitored, lack of standardized abstraction forms, and lack of procedural manual or description of data abstraction process in the study. None of the studies reviewed here reported having pilot tested the data collection method or tools. All of these studies met the criterion for addressing ethical and legal concerns.

The prospective studies by de Vries et al. (2011), and Schagen et al. (2016), plus the cross-sectional study by Turban et al. (2020), which were assessed using the JBI checklist, earned 'good' ratings as shown in Table 4. The study by Cohen-Kettenis et al. (2011) was a single case study, for which we used the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018), was rated excellent, having met all eight criteria (100%). We also used the JBI Critical Appraisal Checklist for Case Reports for the other single case study by Schneider et al. (2017) and rated it good, with 7 of 8 criteria met (87.5%). The checklists for these two case reports are in Table 5.

Discussion

The studies identified and reviewed here are current with publication dates ranging from 2011 to 2020. As adolescents, their families, and healthcare providers seek more guidance about using GnRHa drugs to suppress puberty, the findings from this critical review are timely, unique, and useful. Given the relatively short amount of time that GnRHa drugs have been used for patients with GD, it is not unexpected that we found no longitudinal empirical studies to guide practice in this expanding population, although studies are currently underway (Olson-Kennedy et al., 2019). At present, the lack of longitudinal data remains a gap in the literature. From an exhaustive search of four databases, however, we were able to answer our four research questions with data from a total sample of $N = 702$ youth described in a mere nine published articles. The samples ranged not only in size (1–192) but also in age (9–35). Although race/ethnicity was reported in <67% of the studies, where it was, the vast majority of participants were Caucasian or White. Clearly, more studies are needed to address the needs of this diverse and expanding population.

Being screened by a mental health professional to establish a diagnosis of gender dysphoria (GD) or gender

Table 3. Vassar & Holzmann's quality checklist for retrospective chart reviews of articles in critical review of puberty-blocking drugs (by first author)

Quality Question	Khatchadourian	Klaver	Nahata	Vlot
1. Are there well-defined and clearly articulated research questions?[a]	Aim to describe cohort in hospital Yes = 1	Aim to examine changes and compare Yes = 1	Goals to examine prevalence of mental health diagnoses and insurance coverage. Yes = 1	Objective to investigate course of three bone turnover markers during Rx. Yes = 1
2. Is there clear evidence of an a priori sampling plan?	No = 0	Yes = 1	Yes = 1	Yes = 1
3. Were the variables operationalized adequately?	(e.g., age at first visit, natal sex, Tanner at first visit). Yes = 1	Yes = 1	Yes = 1	Yes = 1
4. Were data abstractors trained and monitored throughout the study?	No = 0	No/not stated = 0	Yes = 1	No = 0
5. Was a standardized abstraction form used?	No/uncertain = 0	No/not stated = 0	Yes = 1	No = 0
6. Was there a procedural manual or description for data abstraction?	No/uncertain = 0	No/not stated = 0	No = 0	No = 0
7. Were there explicit inclusion and exclusion criteria?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
8. Were interrater/intrarater reliability addressed?	No = 0	No = 0	No = 0	No = 0
9. Was there a pilot test of the data collection and analysis?	No/uncertain = 0	No = 0	No = 0	No = 0
10. Were ethical and legal considerations addressed?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
OVERALL ASSESSMENT	Fair: 4/10	Fair: 5/10	Good: 7/10	Fair: 5/10

[a]If there was a clear aim, objective, or goals for the study, and research questions could be inferred, we rated this criterion as 'yes'.

Table 4. Joanna Briggs Institute's critical appraisal checklist for cross-sectional and prospective observational studies

	de Vries et al. (2011)	Schagen et al. (2016)	Turban et al. (2020)
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y
2. Were the study subjects and the setting described in detail?	Y	Y	NA
3. Was the exposure measured in a valid and reliable way?	U	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y
5. Were confounding factors identified?	N	U	Y
6. Were strategies to deal with confounding factors stated?	N	U	Y
7. Were the outcomes measured in a valid and reliable way?	Y	Y	U
8. Was appropriate statistical analysis used?	Y	Y	Y
TOTAL PERCENTS	62.5%	75%	85.7%%

Legend: Y = yes; N = no; U = unclear; NA = not applicable. Denominator does not include items judged 'NA'.

Table 5. Joanna Briggs institute's critical appraisal checklist for case report reports

Criteria	Cohen-Kettenis et al. (2011)	Schneider et al. (2017)
1. Were patient's demographic characteristics clearly described and presented?	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
6. Was the postintervention clinical condition clearly described?	Yes	No
7. Were adverse events (harms) or unanticipated events identified and described	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes
TOTAL criteria met	8/8 = 100%	7/8 = 87.5%

identity disorder (GID) was found as a prerequisite to using puberty-blocking drugs in half of the studies. The studies that included older samples, meaning that diagnostic prerequisites were met prior to publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), reported using a diagnosis of gender identity disorder (GID) rather than GD. Authors of all the studies reviewed here noted that this diagnosis was an essential starting point before considering the use of puberty suppressors. All studies in this sample also included not initiating puberty suppressing drugs prior to the onset of puberty. These recommendations are consistent with guidelines published by WPATH (2011) and the Endocrine Society (2017), which note that hormonal therapies should not be instituted prior to the onset of puberty. They are also consistent with a gender-affirming conceptualization of care based on the premise that society upholds diversity in gender development and expression (Edwards-Leeper et al., 2016, p 165).

There was general agreement that gonadotropin-releasing hormone analogue (GnRHa) drugs are preferred for puberty suppression. Five of the papers reviewed here described the use of triptorelin or leuprorelin (off-label), followed by sex-affirming hormones. The other four papers did not give the name of the drugs used, but the authors wrote that GnRHa drugs were administered. These procedures follow the 'Dutch protocol' outlined by Delemarre-van de Waal and Cohen-Kettenis (2006) in which 3.75 mg. of triptorelin is given every four weeks intramuscularly or subcutaneously when adolescents have reached Tanner stages 2–3 and have been diagnosed with gender dysphoria (previously gender identity disorder).

As for positive outcomes, improved psychological health was identified in this review (Turban et al., 2020; de Vries et al., 2011). The most recent study by Turban et al. (2020) was the first to demonstrate that access to pubertal suppression during adolescence was associated with decreased lifetime suicidality among transgender adults. In a prospective, longitudinal investigation, de Vries et al. (2011) reported improvements in general functioning as well as decreases in depressive symptoms and emotional and behavioral problems. The findings of these two studies are further supported by a recent longitudinal investigation that found youth aged 9–25 years who engaged in gender-affirming endocrine treatment (i.e., puberty suppression or cross-sex hormones) demonstrated improved mental health over time (Achille et al., 2020). The chance to have more time to consider medical transition was helpful to the young person in one of the case study reports (Cohen-Kettenis et al., 2011). Despite these psychosocial improvements, most of the studies reviewed here focused on biological outcomes rather than psychosocial ones. Although the biological outcomes that affirm the patient's gender are critical to the success of using puberty-blocking drugs, a more holistic view including psychosocial outcomes are equally important to ensure all needs of patients are being met. Such a holistic view highlights both the physical and mental health implications of access to puberty suppression. As the Endocrine Society (2017) indicate, transgender individuals in puberty should be cared for by a multi-disciplinary team that can address both mental and physical health concerns simultaneously.

As other studies have shown, risks and adverse outcomes described in these studies included emotional lability, changes in body composition (e.g., fat deposits),

decreased height velocity, decreased bone turnover, decreased bone mineral density, high cost of these drugs, and inadequate insurance coverage. These findings raise issues with important policy implications and beg for further study.

We need more studies that address the potential positive and negative outcomes related to the use of puberty-blocker therapies not only as they affect the individual but also as they affect the family. Families with health insurance policies that do not support all the services described in the WPATH standards of care for transgender adolescents may suffer financial hardships that could be prevented with additional research demonstrating long-term benefits of this treatment (Padula & Baker, 2017). Families may also need counseling and support groups to deal with issues such as stigma, uncertainty about the future (Gray, Sweeney, Randazzo, & Levitt, 2016), grief and family conflict as youth begin to consider seriously pursuing puberty suppression (Ashley, 2019). Research confirms that TGD youth who lack family and other forms of social support bear a heavy burden of psychological distress (McConnell, Birkett, & Mustanski, 2016).

The quality of the studies reviewed was modest but promising. In all the studies reviewed, the primary risk for bias was selection of the samples, but this may be unavoidable given that the population in each case is already self-selected. Nearly half (44%) of the studies reviewed were retrospective chart reviews and only one of these was rated as 'good', which meant that it had a relatively low risk for bias compared to the others. Because the other three studies omitted important criteria for retrospective chart reviews, they reflected fairly large risks for bias, particularly concerning the inexact methods by which data were extracted from the patients' records. Although the remaining studies were deemed 'good' or 'excellent' in terms of meeting more criteria for their respective study designs, these designs provided low-level evidence: case reports, prospective observational, and cross-sectional studies. Case studies are considered to be the weakest of designs or lowest form of evidence, containing threats to internal validity including history, maturation, and mortality (Campbell & Stanley, 1963; Cochrane, n.d.). These findings suggest the need for additional studies to be conducted using more rigorous designs with fewer threats to internal validity.

The findings from this review support the position taken by Reisner et al. (2016) that we need more longitudinal studies on youth who have taken puberty-blocking drugs in adolescence. Such studies as well as studies using mixed methods designs could document both biological and psychosocial changes over time and are able to provide a more holistic and comprehensive view of how the use of such agents affects the lives of individuals as they explore this critical time of development. Moreover, qualitative studies are needed to document the first-person experiences of TGD youth, as Vrouenraets et al. (2016) have also suggested.

Additional research can lend more strength to current clinical guidelines and assist clinicians in caring for these patients and their families especially as questions arise during treatment. Underscoring the need for ongoing research, access to puberty blockers, and the potential benefits that they provide, is not universal and varies greatly by geography, insurance status, healthcare provider availability among other factors (Kimberly et al., 2018). An increase in high-quality longitudinal data should lend additional support to what healthcare providers are witnessing clinically: improvements in short- and long-term health outcomes of these very vulnerable youth. With additional research should come increased access to these treatment modalities and improvements in mental health outcomes.

Limitations

This study was limited to a review of papers published in English, thus we may have missed important findings published in other languages and other countries. This study was also limited to only four databases. Other databases may have included studies that we missed. Our specific research questions also may have limited our inclusion criteria. Despite these limitations, the findings are strengthened by our adherence to a critical and systematic review process, including the extensive search assistance from an experienced science librarian (last author), and the relatively large number of total participants in the nine studies reviewed.

Implications

The implications for multidisciplinary teams of healthcare professionals working with this population are that this body of research supports the use of puberty suppression in early adolescents who are carefully screened for gender dysphoria and who have reached an early stage of pubertal development.

Conclusion

Despite a recent increase in the number of TGD youth seeking healthcare services for their gender dysphoria, there exists a relatively small amount of research regarding the positive and negative short- and long-term effects of using GnRHa drugs to suppress puberty and to allow more time for gender identity exploration. The need for additional well-designed longitudinal and mixed methods studies is critical to support and even improve current practice for this very vulnerable population. Although large long-term studies with diverse and multicultural populations have not been done, the evidence to date supports the finding of few serious adverse outcomes and several potential positive outcomes. This literature suggests the need for TGD youth to be cared for in a manner that not only affirms their gender identities but that also minimizes the negative physical and psychosocial outcomes that could be associated with pubertal development.

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Ethical approval

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References

Achille, C., Taggart, T., Eaton, N.R., Osipoff, J., Tafuri, K., Lane, A., & Wilson, T.A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. *International Journal of Pediatric Endocrinology, 8*. https://doi.org/10.1186/s13633-020-00078-2

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th edn). Arlington, VA: American Psychiatric Publishing.

Ashley, F. (2019). Puberty blockers are necessary, but they don't prevent homelessness: Caring for transgender youth by supporting unsupportive parents. *The American Journal of Bioethics, 19*, 87–89.

Bonifacio, H.J., & Rosenthal, S.M. (2015). Gender variance and dysphoria in children and adolescents. *Pediatric Clinics of North America, 62*, 1001–1016.

Campbell, D.T., & Stanley, J.C. (1963). *Experimental and quasi-experimental designs for research*. Boston: Houghton Mifflin Company.

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics, 14*, e2017374.

Cochrane Consumer Network (n.d.) Levels of evidence. Available from: https://consumers.cochrane.org/levels-evidence

Cohen-Kettenis, P.T., Schagen, S.E.E., Steensma, T.D., DeVries, A.L.C., & Delemarre-van de Waal, H.A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22 -year follow-up. *Archives of Sexual Behavior, 40*, 843–847.

Cooper, H. (2017). *Research synthesis and meta-analysis: A step-by-step approach* (5th edn). Los Angeles: Sage.

de Vries, A.L.C., Steensma, T.D., Doreleijers, T.A.H., & Cohen-Kettenis, P.T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *Journal of Sexual Medicine, 8*, 2276–2283.

Delemarre-van de Waal, H.A., & Cohen-Kettenis, P.T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology, 155*, S131–S137.

DiVasta, A., & Laufer, M.R. (2013). The use of gonadotropin releasing hormone analogues in adolescent and young patients with endometriosis. *Current Opinion in Obstetrics and Gynecology, 25*, 287–292.

Drummond, K.D., Bradley, S.J., Peterson-Badali, M., & Zucker, K.J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology, 44*, 34–45.

Edwards-Leeper, L., Leibowitz, S., & Sangganjanavanich, V.F. (2016). Affirmative practice with transgender and gender nonconforming youth: Expanding the model. *Psychology of Sexual Orientation and Gender Diversity, 3*, 165–172.

Endocrine Society (2017). Guidelines and clinical practice. Available from: practice/clinical-practice-guidelines/gender-dysphoria-gender-https://www.endocrine.org/guidelines-and-clinical-incongruence [last accessed 25 June 2019].

Gallagher, J.S., Missmer, S.A., Hornstein, M.D., Laufer, M.R., Gordon, C.M., & DiVasta, A.D. (2018). Long-term effects of gonadotropin-releasing agonists and add-back in adolescent endometriosis. *Journal of Pediatric and Adolescent Gynecology, 31*, 376–381.

Gray, S.A.O., Sweeney, K.K., Randazzo, R., & Levitt, H.M. (2016). "Am I doing the right thing?": Pathways to parenting a gender variant child. *Family Process, 55*, 123–138.

Hembree, W.C., Cohen-Kettenis, P., Delemarre-van de Waal, H.A., Gooren, L.J., Meyer, W.J., Spack, N.P., … & Montori, V.M. (2009). Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology, and Metabolism, 94*, 3132–3154.

Hembree, W.C., Cohen-Kettenis, P.T., Gooren, L., Hannema, S.E., Meyer, W.J., Murad, M.H., … & T'Sjoen, G.G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism, 102*, 3869–3903.

Joanna Briggs Institute (2018). Critical appraisal tools. The University of Adelaide. Available from. http://joannabriggs.org/research/critical-appraisal-tools.html [last accessed 5 May 2019].

Johns, M.A., Lowry, R., Andrzejewski, J., Barrios, L.D., Demissie, Z., McManus, T., … & Underwood, J.M. (2019). Transgender identitiy and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students—19 states and large urban school districts, 2017. *Morbidity and Mortality Weekly Report, 68*, 67–71.

Khatchadourian, K., Amed, S., & Metzer, D.L. (2014). Clinical management of youth with gender dysphoria in Vancouver. *The Journal of Pediatrics, 164*, 906–911.

Kimberly, L.L., Folkers, K.M., Friesen, P., Sultan, D., Quinn, G.P., Bateman-House, A., … & Salas-Humara, C. (2018). Ethical issues in gender-affirming care for youth. *Pediatrics, 142*, e20181537.

Klaver, M., de Mutsert, R., Wiepjes, C.M., Twisk, J.W.R., den Heijer, M., Rotteveel, J., & Klink, D.T. (2018). Early hormonal treatment affects body composition and body shape in young transgender adolescents. *Journal of Sexual Medicine, 15*, 251–260.

Krishna, K.B., Fuqua, J.S., Rogol, A.D., Klein, K.O., Popovic, J., Houk, C.P., … & Lee, P.A. (2019). Use of gonadotropin-releasing ormone analogs in children: Update by an international consortium. *Hormone Research in Paediatrics, 91*, 357–372.

Lee, J.W., Kim, H.J., Choe, Y.M., Kang, H.S., Kim, S.I., Jun, Y.H., & Lee, J.E. (2014). Significant adverse reactions to long-acting gonadotropin-releasing hormone agonists for the treatment of central precocious puberty and early onset puberty. *Annual Pediatric Endorinology Metabolism, 19*, 135–140.

Liu, R.T., & Mustanski, B. (2012). Suicidal ideation and self-harm in lesbian, gay, bisexual, and transgender youth. *American Journal of Preventive Medicine, 42*, 221–228.

Lowry, R., Johns, M.M., Gordon, A.R., Austin, B., Robin, L.E., & Kann, L.K. (2018). Nonconforming gender expression and associated mental distress and substance use among high school students. *JAMA Pediatrics, 172*, 1020–1028.

McConnell, E., Birkett, M., & Mustanski, B. (2016). Families matter: Social support and mental health trajectories among lesbian, gay, bisexual, and transgender youth. *Journal of Adolescent Health, 59*, 674–680.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & the PRISMA Group (2009). Reprint—Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *Physical Therapy, 89*, 873–880.

Nahata, L., Quinn, G.P., Caltabellotta, N.M., & Tishelman, A.C. (2017). Mental health concerns and insurance among transgender adolescents. *LGBT Health, 4*, 188–193.

Olson, J., Schrager, S.M., Belzer, M., Simons, L.K., & Clark, L.F. (2015). Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *Journal of Adolescent Health, 57*, 374–380.

Olson-Kennedy, J., Chan, Y.-M., Garofalo, R., Spack, N., Chen, D., Clark, L., … & Rosenthal, S. (2019). Impact of early medical treatment for transgender youth: Protocol for the longitudinal, observational trans youth care study. *JMIR Research Protocols, 8*, e14434.

Padula, W.V., & Baker, K. (2017). Coverage for gender-affirming care: Making health insurance work for transgender Americans. *LGBT Health, 4*(4), 244–247.

Reisner, S.L., Deutsch, M.B., Bhasin, S., Bockting, W., Brown, G.R., Feldman, J., … & Goodman, M. (2016). Advancing methods for US transgender health research. *Current Opinion in Endocrinology Diabetes Obesity, 23*, 198–207.

Schagen, S.E.E., Cohen-Kettenis, P.T., Delemarre-van de Waal, H.A., & Hannema, S.E. (2016). Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress

puberty in gender dysphoric adolescents. *The Journal of Sexual Medicine, 13*, 1125–1132.

Schneider, M.A., Spritzer, P.M., Soll, B.M.B., Fontanari, A.M.V., Carneiro, M., Tovar-Moll, F., … & Lobato, M.I.R. (2017). Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression. *Frontiers in Human Neuroscience, 11*, 528.

Shields, J.P., Cohen, R., Glassman, J.R., Whitaker, K., Franks, H., & Bertolini, I. (2013). Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *Journal of Adolescent Health, 42*, 248–250. https://doi.org/10.1016/j.jadohealth.2012.06.016

Stevens, J., Gomez-Lobo, V., & Pine-Twaddell, E. (2015). Insurance coverage of puberty blocker therapies for transgender youth. *Pediatrics, 136*, 1029–1031.

Turban, J.L. (2017). Transgender youth: The building evidence base for early social transition. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*, 101–102.

Turban, J.L., King, D., Carswell, J.M., & Keuroghlian, A.S. (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics, 145*, e20191725.

Vassar, M., & Holzmann, M. (2013). The retrospective chart review: Important methodological considerations. *Journal of Educational Evaluation for Health Professions, 10*, 1–7.

Vlot, M.C., Klink, D., den Heijer, M., Blankenstein, M.A., Rotteveel, J., & Heijboer, A. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone, 95*, 11–19.

Vrouenraets, L.J.J.J., Fredriks, A.M., Hannema, S.E., Cohen-Kettenis, P.T., & DeVries, M.C. (2015). Early medical treatment of children and adolescents with gender dysphoria: An empirical ethical study. *Journal of Adolescent Health, 57*, 367–373.

Vrouenraets, L.J.J.J., Fredriks, A.M., Hannema, S.E., Cohen-Kettenis, P.T., & DeVries, M.C. (2016). Perceptions of sex, gender, and puberty suppression: A qualitative analysis of transgender youth. *Archives of Sexual Behavior, 45*, 1697–1703.

World Professional Association for Transgender Health (2011). Standards of care for the health of transsexual, transgender, and gender nonconforming people (7th version). Available from: https://www.wpath.org/media/cms/Documents/Web%20Transfer/SOC/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf [last accessed 10 December 2020].

Yu, R., Yang, S., & Hwang, T. (2019). Psychological effects of gonadotropin-releasing hormone agonist treatment in girls with central precocious puberty. *Journal of Pediatric Endocrinology and Metablism, 32*, 1071–1075.

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COMMENT

A comment from SIGIS, SIE and SIAMS: "Puberty blockers in transgender adolescents—a matter of growing evidence and not of ideology"

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The Italian Society of Gender, Identity and Health (SIGIS), together with the Italian Society of Endocrinology (SIE) and the Italian Society of Andrology and Sexual Medicine (SIAMS), supports the use of gonadotropin-releasing hormone agonist (GnRHa) to temporary suspend puberty in accurately evaluated transgender and gender diverse (TGD) adolescents by a multidisciplinary team.

TGD adolescents have a gender identity that differs from the assigned gender at birth. Being TGD is an expected aspect of human development, and all gender identities are possible variations of a person's sexual identity as strongly emphasized by the World Health Organization and the American Psychiatric Association [1, 2].

Some TGD adolescents may have distress because of their gender incongruence, both psychological and physical [2]. Psychological distress seems to derive largely from living in contact with social prejudice and stigma of those who do not recognize the existence of gender variance as a normal expression of the wide spectrum, in which gender identities can develop [3]. Stigma is present also within healthcare as TGD people still face too many barriers in accessing care and have to confront with professionals who are not properly trained on gender care issues and therefore do not respond properly to TGD people needs [3]. Also, some evidence suggests that exposure to conversion therapy substantially increases the likelihood a transgender adolescent will attempt suicide and run away [4].

Physical intense distress may arise from puberty's physical changes that develop in an undesired/unwanted direction: For example, growth of facial and body hair, voice deepening and growth of genitalia, in those identified as male at birth, and breast development or onset of menses, in those identified as female at birth, can cause intense dysphoria in many TGD adolescents [2].

For both these reasons (minority stress and body related physical distress), TGD adolescents are a psychologically more vulnerable population with reported higher risk for anxiety and depression, self-harm, and suicidality [5]. Furthermore, psychological vulnerabilities and psychopathologies seem to have onset or worsen during puberty, a particularly challenging phase of life, where the distress of having to confront with unwanted (and out of control) bodily pubertal modifications plays an important role in psychological impairment.

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To reduce the abovementioned psychological and physical distress, in addition to buying time and creating rest to further explore one's gender affirming path, the use of GnRHa represents a valuable solution. Historically, the use of GnRHa in TGD adolescents was firstly introduced in the Netherlands in the late 1980 s by psychologist Peggy Cohen-Kettenis and endocrinologist Henriette Delemarre and is therefore also known as the "Dutch Protocol." In general, GnRHa medication is given as injections, either monthly or every three months. The goal of GnRHa administration in TGD adolescents is to reversibly suspend development of secondary sex characteristics that are not consistent with the adolescent's experienced gender. Their use within TGD adolescent care allows to extend the assessment phase in carefully selected TGD adolescents that satisfy specific clinical criteria. To this regard and according to international recommendations [5–7], it is important to underline that GnRHa are aimed at TGD adolescents (and never children) that have reached at least Tanner Stage 2 in light of the stability of gender identity starting from the pubertal age. Moreover, criteria for treatment require gender incongruence to be marked and sustained over time and the TGD adolescent to show emotional and cognitive maturity to provide informed consent for treatment. Furthermore, TGD adolescents must be informed about the potential loss of fertility and about the available options to preserve fertility [5, 8]. Suspending puberty could allow TGD adolescents to "buy time" and reflect in a more conscious way regarding gender identity and, more importantly, about further medical gender affirming steps with irreversible effects (gender affirming hormonal treatments or surgery). Moreover, the use of GnRHa is demonstrated to reduce the adolescents' distress for pubertal physical changes. Importantly, follow-up studies to date show that treatment with GnRHa can significantly reduce behavioral and emotional problems and suicidal ideation, as well as improve general psychological functioning in treated adolescents [9]. Some possible short-term physical symptoms, such as headaches, hot flashes, and fatigue, may be observed as a result of sex steroids withdrawal [10]. Regarding long-term effects, the main concerns may be related to the potential decrease in bone mineral density (BMD), interfering with the normal pubertal bone mass increment. The available literature [11, 12] demonstrates the BMD z-scores decreased during GnRHa treatment, but increased during gender-affirming hormone treatment, even though the catch up of bone mineral accrual may be incomplete. Lean body mass decreased during the first year of treatment in TGD youth, whereas fat tissue significantly increased. No sustained abnormalities of liver function or creatinine were encountered [13, 14]. Concerning cardiovascular issue, increase in blood pressure (BP), possibly due to estrogen depletion, was reported, but reversible upon cessation of triptorelin. Furthermore, BP levels did not meet criteria for hypertension, and the induction of puberty with gender-affirming testosterone treatment may restore pressure [15, 16]. Moreover, data about cardiovascular safety of gender affirming hormonal treatments suggest an increased risk of subclinical atherosclerosis in adults transgender AFAB but not in transgender AMAB, but additional studies are warranted [17, 18]. According to a recent multicenter study, there is no statistically significant difference in the odds of any cardiometabolic-related diagnosis in unadjusted or adjusted for GnRHa alone (without estradiol or testosterone) [19].

During this treatment, information on the gonadal axis suppression can be obtained through gonadotropin and sex steroids measurement, even if there is insufficient evidence for a specific monitoring scheme [6]. Thus, for all the above reasons, a close clinical, laboratory and instrumental (especially bone densitometry) monitoring of TGD adolescents during GnRHa treatment is highly recommended, following the Endocrine Society suggested clinical protocol [6].

At present, the use of GnRHa for TGD adolescents has been endorsed in the Standards of Care of the World Professional Association for Transgender Heath (WPATH) since their fifth edition in 1998 and by multiple medical societies, in particular by the Endocrine Society since 2009 [20, 21]. Currently, it is supported by international guidelines and recommendations that have been subscribed at a national level by several dedicated scientific societies, such as SIGIS, SIAMS, SIE, Italian Society of Pediatric Endocrinology and Diabetology (SIEDP) and Italian Observatory of Gender Identity (ONIG).

Despite this treatment option has currently become common practice in most gender identity clinics around the Western world, the use of GnRHa for TGD adolescents is still controversial and has not been endorsed worldwide [22]. In some cases, this treatment has been criticized as being experimental; however, possible negative consequences of not offering any medical option should also be considered. In this respect, the use of GnRHa was approved by the Italian Medicines Agency (AIFA), responsible for the regulatory activity of pharmaceuticals in Italy (determination No. 21,756/2019). Moreover, the use of GnRHa received a favorable opinion from the Italian National Committee of Bioethics (CNB) on July 13, 2018. We must stress-out that this medical intervention should be limited to those TGD adolescents that fulfill criteria for GnRHa and following a multidisciplinary and individualized evaluation performed by experienced gender teams as described in the determination by AIFA.

In conclusion, the use of GnRHa has so far proven to be a valuable medical option to be offered to TGD adolescents. At the same time, in view of the complex medical and

psychological intertwining of these interventions, their use within gender affirming paths needs to be supported on evidence based and clinical and scientific knowledge. Conversely, the dissemination of incorrect information, for example using an ideological and journalistic language (e.g., sex-changing treatments in young TGD people, acting against the law of nature), risks to damage the possibility of access gender affirming paths for young TGD people. This may have severe negative consequences on their psychological functioning and physical health both in the short and long terms. In fact, it has widely been described how accessing health care is associated with improvement of psychological functioning and decrease in suicidality in a vulnerable population. The task of professionals is, therefore, to spread a culture linked to transgender health issues based on scientific evidence and not on prejudice.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

eferences

1. World Health Organization (2019) International statistical classification of diseases and related health problems, 11th edn. https://icd.who.int/. Accessed 10 June 2023
2. American Psychiatric Association (2022) Diagnostic and statistical manual of mental disorders, 5th edn, text rev. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425787
3. Austin A, Craig SL, D'Souza S, McInroy LB (2022) Among transgender youth: elucidating the role of interpersonal risk factors. J Interpers Violence 37(5–6):NP2696–NP2718. https://doi.org/10.1177/08862605209155542
4. Campbell T, Rodgers YVM (2023) Conversion therapy, suicidality, and running away: an analysis of transgender youth in the US. J Health Econ 89:102750. https://doi.org/10.1016/j.jhealeco.2023.102750
5. Coleman E, Radix AE, Bouman WP et al (2022) Standards of care for the health of transgender and gender diverse people, version 8. Int J Transgend Health 23(Suppl 1):S1–S259. https://doi.org/10.1080/26895269.2022.2100644
6. Hembree WC, Cohen-Kettenis PT, Gooren L et al (2017) Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 102(11):3869–3903. https://doi.org/10.1210/jc.2017-01658
7. Fisher AD, Ristori J, Bandini E et al (2014) Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. J Endocrinol Invest 37(7):675–687. https://doi.org/10.1007/s40618-014-0077-6
8. Lee WG, Butler G, Carmichael P et al (2023) Urological and gynaecological considerations for the use of gonadotropin-releasing hormone analogues in transgender and nonbinary adolescents: a narrative review. Eur Urol Focus 9(1):35–41. https://doi.org/10.1016/j.euf.2022.11.002
9. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K (2022) Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care. JAMA Netw Open 5(2):e220978. https://doi.org/10.1001/jamanetworkopen.2022.0978
10. Carmichael P, Butler G, Masic U et al (2021) 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 16(2):e0243894. https://doi.org/10.1371/journal.pone.0243894
11. Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE (2020) Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones. J Clin Endocrinol Metab 105(12):e4252–e4263. https://doi.org/10.1210/clinem/dgaa604
12. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95:11–19. https://doi.org/10.1016/j.bone.2016.11.008
13. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE (2016) Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. J Sex Med 13(7):1125–1132. https://doi.org/10.1016/j.jsxm.2016.05.004
14. Klaver M, de Mutsert R, Wiepjes CM et al (2018) Early hormonal treatment affects body composition and body shape in young transgender adolescents. J Sex Med 15(2):251–260. https://doi.org/10.1016/j.jsxm.2017.12.009
15. Klink D, Bokenkamp A, Dekker C, Rotteveel J (2015) Arterial hypertension as a complication of triptorelin treatment in adolescents with gender dysphoria. Endocrinol Metab Int J 2(1):36–38. https://doi.org/10.15406/emij.2015.02.00008
16. Perl L, Segev-Becker A, Israeli G, Elkon-Tamir E, Oren A (2020) Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by testosterone treatment in transgender male adolescents: a pilot study. LGBT Health 7(6):340–344. https://doi.org/10.1089/lgbt.2020.0026
17. Moreira Allgayer RMC, Borba GDS, Moraes RS, Ramos RB, Spritzer PM (2023) The effect of gender-affirming hormone therapy on the risk of subclinical atherosclerosis in the transgender population: a systematic review. Endocr Pract 29(6):498–507. https://doi.org/10.1016/j.eprac.2022.12.017
18. Howerton I, Harris JK (2022) Transgender identity and cardiovascular disease. Transgend Health 7(5):407–415. https://doi.org/10.1089/trgh.2020.0188
19. Valentine A, Davis S, Furniss A et al (2022) Multicenter analysis of cardiometabolic-related diagnoses in transgender and gender-diverse youth: a PEDSnet study. J Clin Endocrinol Metab 107(10):e4004–e4014. https://doi.org/10.1210/clinem/dgac469
20. Levine SB, Brown GR, Coleman E et al (1998) The standards of care for gender identity disorders—Fifth edition. J Psychol Human Sex 11(2):1–34. https://doi.org/10.1300/J056v11n02_01
21. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA et al (2009) Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94(9):3132–3154. https://doi.org/10.1210/jc.2009-0345
22. de Vries ALC, Hannema SE (2023) Growing Evidence and remaining questions in adolescent transgender care. N Engl J Med 388(3):275–277. https://doi.org/10.1056/NEJMe2216191

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Original article

Association of Gender-Af rming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth

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A B S T R A C T

Purpose: There are no large-scale studies examining mental health among transgender and nonbinary youth who receive gender-af rming 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.

IMPLICATIONS AND CONTRIBUTION

Transgender and nonbinary youth have high risk of depression and suicide. Gender-af rming healthcare is associated with lower risk using adult samples. This large-scale study examines GAHT among transgender and nonbinary youth. Findings demonstrate that GAHT is signi cantly related to lower rates of depression and suicidality among transgender and nonbinary youth.

Transgender and nonbinary youth are at elevated risk for depression, thoughts of suicide, and attempted suicide compared to youth who are cisgender and heterosexual, as well as cisgender members of the lesbian, gay, bisexual, transgender, queer, and questioning (LGBTQ) community [1–3]. Mental health disparities among transgender and nonbinary youth stem from minority stress based on the harmful ways transgender and nonbinary youth are treated by others [4]. Feelings of gender dysphoria associated with incongruence between one s physical traits and gender identity are also associated with mental health challenges for transgender and nonbinary youth [5]. As such, both the treatment of gender dysphoria and the reduction of minority stress offer pathways toward reducing disparities in depression and suicidality found among transgender and nonbinary youth.

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The Minority Stress Model details how chronic stressful events such as gender identity–based stigma and rejection produce proximal processes such as internalized stigma and shame, which result in mental health challenges [6]. Although minority stress is associated with greater risk of anxiety, depression, and suicidality among transgender and nonbinary individuals [2,5], gender-af rming medical care has been associated with lower risk [7,8]. Gender-af rming medical care is one component of the larger process of gender af rmation, which may include social, legal, and medical changes. Social transition is the primary and most common component of gender af rmation for prepubertal youth and involves allowing them to present in the way that feels most authentic to them. Medical-af rming care can include treatments that postpone physical changes associated with puberty, as well as treatments that lead to changes that would af rm one s gender identity. Gonadotropin-releasing hormone analogs, commonly known as "puberty blockers," are used to delay the onset of puberty, while gender-af rming hormone therapy (GAHT) is used to promote gender-af rming physical changes. GAHT allows transgender and nonbinary youth to develop physical characteristics that align with their gender identity and is appropriate for those who have begun puberty or following the use of puberty blockers. Access to GAHT is especially important during adolescence because some effects of puberty are not easily reversed by GAHT in adulthood (e.g., testosterone s effects on voice) [9]. Qualitative data highlight ways transgender individuals have experienced distress due to the delay in GAHT, which results in them undergoing puberty associated with their sex assigned at birth [10,11]. Access to GAHT is an ongoing issue for transgender youth and their families, both due to a lack of competent providers in many communities and due to recent legislative efforts to criminalize medical providers and parents who provide GAHT to youth under the age of 18 [12,13]. Barriers to care are often greater for transgender and nonbinary youth of color who are unrepresented in gender specialty clinics and have more dif culties accessing gender-af rming care compared to White transgender and nonbinary youth [9].

A recent study based on the 2015 U.S. Transgender Survey found that transgender adults who received pubertal blockers as adolescents had signi cantly lower lifetime suicidal ideation compared to those who desired but did not receive it [8]. However, thus far, there are no large-scale studies comparing mental health and suicidality among transgender and nonbinary youth who wanted GAHT and received it to those who wanted it but did not receive it [14]. Three small clinical studies have examined GAHT in relation to mental health and suicidality among transgender and nonbinary youth. However, these clinical studies were not able to randomize youth to receive GAHT or include a control group. The rst study followed 47 transgender youth and found that mean levels of suicidality signi cantly decreased from 1.11 before starting GAHT to .27 when assessed approximately 1 year after beginning GAHT [7]. The second study of 128 transgender youth found small to moderate improvements in self-reported depressive symptoms (d .44) [15]. The third study examined 50 transgender youth at two 6-month intervals following the start of GAHT and found signi cant decreases in depression as measured by the Center for Epidemiologic Studies Depression Scale [16]. Each of these studies noted limitations related to not being able to control for the role of parental support, as each youth had at least one parent who supported their receipt of GAHT.

The present study draws from a large sample of transgender and nonbinary youth between the ages of 13–24 to examine the association between receipt of GAHT with self-reported depression, thoughts of suicide, and attempted suicide. Furthermore, because many current concerns around GAHT relate to their use in youth under the age of 18, these associations will also be examined separately for those under age 18.

Methods

Procedure

Data were from an online nonprobability sample collected between October and December 2020 of 34,759 youth aged 13–24 who resided in the U.S. and identi ed as LGBTQ. Youth were recruited via targeted ads on Facebook, Instagram, and Snapchat. Those who reported residing outside of the U.S., having an age below 13 or above 24, or being both heterosexual and cisgender were excluded from the sample. To approach a more representative sample, targeted recruitment was conducted to ensure adequate sample sizes with respect to geography and race/ethnicity. Quali ed respondents completed a secure online questionnaire that included a maximum of 142 questions. The survey employed two validity checks. The rst was an item that required youth to select a speci c response from the provided list. The second validity check screened for youth who responded inconsistently to the same item placed at two separate points in the survey. Each question related to mental health and suicidality was preceded by a message stating: "If at any time you need to talk to someone about your mental health or thoughts of suicide, please call The Trevor Project at 1-866-488-7386." Youth were able to select "decline to answer" for any questions in the survey that they did not want to answer. Respondents were eligible to be entered into a drawing for one of 100 gift cards worth 50 each by providing their email address after being routed to a separate survey. The research proposal was reviewed and approved by an independent Institutional Review Board, Solutions IRB. Youth participation was voluntary, and informed consent was obtained. We obtained a waiver of parental consent for youth aged 13–17 years as the research posed a minimal risk and could have presented potential harm for youth who were not out to their parents about their LGBTQ identity. No names or personal details were included to ensure con dentiality and privacy.

Measures

Gender-af rming hormone therapy use. Youth who indicated they were transgender or nonbinary were asked, "Are you currently taking gender-af rming hormones?" with response options that included, (1) "No, and I do not want to take them," (2) "No, but I would like to take them," and (3) "Yes." In logistic regression analyses, youth responses are coded as (0) "No, but I would like to take them" and (1) "Yes."

Depression. Current levels of depression were measured using the Patient Health Questionnaire-2 [17]. The Patient Health Questionnaire-2 was designed as a two-item screening tool for major depressive disorder in the past 2 weeks. Scores were dichotomized based on recommended guidelines for a total score of three or more being indicative of depression.

Suicidal thoughts and behaviors. Youth were rst presented with a question on whether they had seriously considered suicide in the past year. Those that answered, "yes" were subsequently asked how many times they had attempted suicide in the past year, with answers dichotomized into zero compared to one or more attempts. Both items are from the Centers for Disease Control and Prevention s Youth Risk Behavior Survey [18].

Demographic covariates. The following sociodemographic covariates were examined based on their potential relationships with suicidality and access to GAHT: age, socioeconomic status (just able to meet basic needs or less, more than able to meet basic needs), race (Alaska Native/American Indian, Asian/Paci c Islander, Black/African American, Latinx, multiracial, or White), and census region (Northeast, South, Midwest, West). Gender identity was measured using a two-stage question that rst asked, "What sex were youth assigned at birth, on your original birth certi cate," with response options of male or female. The second question asked, "Which of the following terms best describes your gender identity. We understand that there are many different ways youth identify, please pick the one that best describes you," with response options of boy/man, girl/woman, and nonbinary/genderfluid/gender nonconforming, as well as options to indicate the youth did not understand the question or were not sure of their gender identity. For those who indicated a known gender identity, the measures were combined to create categories of transgender girl/woman, transgender boy/man, and nonbinary. A single item was used to measure sexual orientation stating, "Which of these options best describes your sexual orientation. We understand that there are many different sexual identities please pick the one that best describes you," with response options of gay, lesbian, bisexual, pansexual, queer, questioning, or straight/heterosexual [19].

Additional covariates. Four additional covariates were included based on their potential relationships with both access to GAHT and risk of depression and suicidality among transgender and nonbinary youth. Parent support for a youth s gender identity was assessed by asking youth, "Do you have at least one parent who is supportive of your gender identity?" with answers of (1) "No," (2) "Yes," and (3) "I am not 'out about my gender to any of my parents." Youth s report of victimization based on their gender identity was assessed by asking, "Have you ever felt physically threatened or been physically abused because of your gender identity?" Response options were (0) "No" and (1) "Yes." Receipt of puberty blockers was assessed by an item placed immediately prior to the question on GAHT that asked, "Did you take medication designed to prevent or delay puberty (also known as puberty blockers)?" Response options were codes as (0) "No" and (1) "Yes." Exposure to gender identity conversion efforts (GICE) was assessed by asking, "Did you ever receive treatment from someone who tried to change your sexual orientation or gender identity (such as trying to make you straight or cisgender)?" Youth who did not undergo conversion efforts or who reported that they underwent conversion efforts related to only their sexual orientation were coded as (0) "No," while youth who reported undergoing GICE were coded as (1) "Yes."

Data analysis

SPSS version 28 was used in conducting all analyses [20]. Chi-squared tests of independence were used to examine the proportion of young people who used GAHT compared to those who wanted GAHT but did not receive it. A *t*-test was used to examine mean age differences. After adjustment for the aforementioned covariates, logistic regression was used to determine the odds of depression, past-year thoughts of suicide, and a past-year suicide attempt among those who received GAHT in comparison with those who wanted GAHT but did not receive it. To address the lack of research focused on gender-af rming medical care among transgender and nonbinary youth who are minors, analyses were also conducted separately among youth aged 13–17.

Participants

A total of 11,914 youth from unique IP address indicated that they were transgender or nonbinary. Our question on GAHT was placed toward the end of the survey, and as such 2,895 youth had missing data. Chi-squared tests of independence were used to compare the 9,019 youth who had GAHT data to the 2,895 who did not. There were no signi cant differences within sexual identity, socioeconomic status, census region, gender identity support from parents, gender identity-based victimization, or GICE. The proportion of transgender boys/men and nonbinary youth were comparable. There were slightly higher rates of transgender women in the sample with data on GAHT compared to those with missing data (8% vs. 6%, $^2(2)$ 13.21, p .001). The sample with data on GAHT had higher rates of multiracial youth (21% vs. 17%) and lower rates of White youth (55% vs. 60%) ($^2(5)$ 34.32, p .001). Age was examined using *t*-test analyses with the average age of the subset of youth with data on GAHT slightly greater (17.62) than those without it (17.30), $t(11{,}912$ 4.60), p .001.

Results

The majority of youth were nonbinary (63%), followed by transgender boy/man (29%) and transgender girl/woman (8%). The average age was 17.62 (standard deviation 3.21), and 27% reported that they were either just able to nancially meet basic needs or struggled to meet basic needs. Most youth resided in the South (36%), followed by West (27%), Midwest (22%), and Northeast (15%). Overall, 29% identi ed as bisexual, 26% as pansexual, 20% as gay or lesbian, 20% as queer, 4% as questioning, and 2% as heterosexual. The majority of the sample was non-Hispanic White (55%), followed by multiracial (21%), Latinx (12%), Asian/Paci c Islander (5%), Black (4%), and American Indian/Alaskan Native (2%).

Half of transgender and nonbinary respondents said they were not using GAHT but would like to receive it, 36% said they were not interested in receiving GAHT, and 14% said they were receiving GAHT. In bivariate analyses (Table 1), those who received GAHT were on average older, and a greater proportion reported that they struggled to meet basic needs or were just able to meet them, compared to those who wanted GAHT but did not receive it. Those who lived in the South were underrepresented among those who received GAHT when they desired it. Transgender girls/women and transgender boys/men were represented in greater proportions among those who received GAHT, while a greater proportion of those who were nonbinary reported wanting GAHT but not receiving it. White youth were the only race/ethnicity group that were represented in a greater proportion among those who received GAHT compared to those who wanted it but did not receive it. Transgender and nonbinary

Table
Sample characteristics of transgender and nonbinary youth aged 13–24 based on receipt of GAHT

	Received GAHT (n 1,216) Mean (SD) or % (n)	Wanted but did not receive GAHT (n 4,537) Mean (SD) or % (n)	
Age	19.95 (2.80)	16.91 (2.97)	$t(15,751)$ 33.26, p .001
Socioeconomic status			$^2(1)$ 17.11, p .001
More than meets basic needs	67.3 (794)	73.5 (2,947)	
Just meets basic needs or less	32.7 (385)	26.5 (1,063)	
Census region			$^2(3)$ 32.25, p .001
Northeast	17.2 (209)	14.0 (634)	
South	28.7 (349)	36.9 (1,676)	
Midwest	23.4 (285)	22.8 (1,035)	
West	30.7 (373)	26.3 (1,192)	
Gender identity			$^2(2)$ 374.88, p .001
Nonbinary	21.3 (259)	49.5 (2,245)	
Transgender boy/man	55.3 (673)	41.3 (1,874)	
Transgender girl/woman	23.4 (284)	9.2 (418)	
Sexual identity			$^2(5)$ 113.49, p .001
Gay/lesbian	25.6 (310)	17.9 (807)	
Heterosexual	4.5 (53)	1.8 (80)	
Bisexual	30.5 (369)	29.4 (1,325)	
Pansexual	16.4 (198)	27.8 (1,250)	
Queer	20.2 (244)	19.0 (845)	
Questioning	2.9 (35)	4.4 (196)	
Race/ethnicity			$^2(5)$ 63.34, p .001
American Indian/Alaskan Native	1.4 (16)	2.2 (98)	
Asian/Paci c Islander	3.1 (36)	4.6 (202)	
Black	1.7 (20)	3.4 (150)	
Latinx	8.8 (104)	12.4 (543)	
White	68.3 (805)	55.8 (2,441)	
Multiracial	16.7 (197)	21.5 (940)	

GAHT gender-af rming hormone therapy; SD standard deviation.

youth who identi ed as gay, lesbian, or heterosexual were represented in higher proportions among those who received GAHT compared to those who wanted it but did not receive it. Pansexual youth were underrepresented among those who wanted GAHT but did not receive it. Table 2 presents the characteristics of transgender and nonbinary youth among the

Table 2
Sample characteristics of transgender and nonbinary youth aged 13–17 based on receipt of GAHT

	Received GAHT (n 274) Mean (SD) or % (n)	Wanted but did not receive GAHT (n 2,961) Mean (SD) or % (n)	
Age	16.00 (1.03)	15.09 (1.36)	$t(13,233)$ 10.81, p .001
Socioeconomic status			$^2(1)$ 3.77, p .05
More than meets basic needs	86.3 (220)	81.3 (2,019)	
Just meets basic needs or less	13.7 (35)	18.7 (463)	
Census region			$^2(3)$ 14.50, p .01
Northeast	14.6 (40)	13.7 (405)	
South	26.3 (72)	37.4 (1,107)	
Midwest	24.8 (68)	22.0 (652)	
West	34.3 (94)	26.9 (797)	
Gender identity			$^2(2)$ 100.35, p .001
Nonbinary	15.3 (42)	46.7 (1,382)	
Transgender boy/man	74.8 (205)	46.5 (1,377)	
Transgender girl/woman	9.9 (27)	6.8 (202)	
Sexual identity			$^2(5)$ 52.85, p .001
Gay/lesbian	32.2 (88)	18.5 (544)	
Heterosexual	4.0 (11)	1.6 (46)	
Bisexual	33.0 (90)	31.3 (921)	
Pansexual	13.9 (38)	16.5 (486)	
Queer	13.6 (37)	27.0 (795)	
Questioning	3.3 (9)	5.0 (148)	
Race/ethnicity			$^2(5)$ 14.31, p .01
American Indian/Alaskan Native	1.9 (5)	2.5 (71)	
Asian/Paci c Islander	4.2 (11)	5.4 (152)	
Black	1.5 (4)	3.9 (111)	
Latinx	8.1 (21)	14.0 (396)	
White	58.8 (153)	50.2 (1,424)	
Multiracial	25.4 (66)	24.1 (683)	

GAHT-gender-af rming hormone therapy; SD standard deviation.

Table 3
Challenges among transgender and nonbinary youth aged 13–24 based on receipt of GAHT

	Received GAHT (n 1,216) % (n)	Wanted but did not receive GAHT (n 4,537) % (n)	
Gender support from parents			^{2}(2) 695.98, p .001
No	17.6 (210)	33.6 (1,451)	
Yes	79.8 (955)	38.2 (1,648)	
Not "out" to parents	2.6 (31)	28.2 (1,218)	
Gender identity-based victimization	61.9 (734)	49.2 (2,125)	^{2}(1) 59.56, p .001
Gender identity conversion efforts	14.7 (172)	13.9 (581)	^{2}(1) 0.42, p .52
History of puberty blocker use	11.0 (132)	1.0 (44)	^{2}(1) 315.80, p .001
Depression	60.8 (738)	75.0 (3,385)	^{2}(1) 95.38, p .001
Seriously considered suicide	43.9 (521)	57.1 (2,409)	^{2}(1) 65.89, p .001
Attempted suicide	14.6 (173)	23.2 (956)	^{2}(1) 40.24, p .001

GAHT gender-af rming hormone therapy.

subsample aged 13–17 based on whether they were able to obtain desired GAHT.

Those who had parental support for their gender identity comprised nearly 80% of youth who received GAHT. Among those who wanted GAHT but did not receive it, 38% had parental support (Table 3). Among those who received GAHT, 11% reported that they had ever used puberty blockers compared to only 1% of those who wanted GAHT but did not receive it. Less than 1% (.6%) of youth who reported not wanting GAHT had ever used puberty blockers. A higher percentage of youth who received GAHT experienced gender identity–based victimization compared to those who wanted GAHT but did not receive it. In bivariate analysis, a smaller percentage of transgender and nonbinary youth who received GAHT reported recent depression (61% vs. 75%), seriously considering suicide in the past year (44% vs. 57%) and attempting suicide in the past year (15% vs. 23%) compared to those who wanted GAHT but did not receive it. Similar patterns emerged among youth aged 13–17 compared to the full sample (Table 4); however, 94% of those 13–17 who received GAHT had parental support compared to 80% among the full sample. Additionally, a larger proportion of those aged 13–17 who received GAHT had used puberty blockers (24%) compared to the overall sample (11%).

In adjusted logistic regression models (Table 5), receipt of GAHT was associated with lower odds of recent depression (adjusted odds ratio [aOR] .73, p .001) and seriously considering suicide in the past year (aOR .74, p .001). The aOR for attempted suicide among the overall sample of transgender and nonbinary youth aged 13–24 did not reach statistical signi cance (aOR .84, p .16). Among those aged 13–17, receipt of GAHT was associated with nearly 40% lower odds of recent depression (aOR .61, p .01) and attempting suicide in the past year (aOR .62, p .05). For youth under age 18, the aOR for seriously considering suicide in the past year did not reach statistical signi cance (aOR .74, p .08).

Discussion

These ndings extend previous cross-sectional research conducted with transgender and nonbinary adults and provide support for a signi cant relationship between access to GAHT and lower depression and suicidality among transgender and nonbinary youth. Among the full sample and those under age 18, receipt of GAHT was associated with signi cantly lower odds of experiencing symptoms of depression in the previous 2 weeks. Although our study is not able to determine temporal patterns, it is unlikely that many transgender and nonbinary youth began GAHT subsequent to this 2-week time frame. The pattern of statistical signi cance for ndings related to past-year suicidality was less consistent, which may indicate challenges related to statistical power when examining fairly infrequent outcomes such as suicidal thoughts and behaviors, particularly among smaller subgroups of individuals [21]. However, overall, our results indicate signi cant relationships between receipt of GAHT and lower suicidality among transgender and nonbinary youth.

Bivariate ndings point to disparities in receipt of GAHT among subgroups of transgender and nonbinary youth. In particular, transgender and nonbinary youth living in the South had lower rates of accessing GAHT when they wanted it. This is also the region where the majority of bills to restrict access to gender-af rming care for transgender youth have been introduced subsequent to the collection of these data [22]. Overall youth who were able to

Table 4
Challenges among transgender and nonbinary youth aged 13–17 based on receipt of GAHT

	Received GAHT (n 274) % (n)	Wanted but did not receive GAHT (n 2,961) % (n)	
Gender support from parents			^{2}(2) 323.26, p .001
No	3.7 (10)	33.3 (933)	
Yes	93.7 (254)	37.2 (1,043)	
Not "out" to parents	2.6 (7)	29.5 (825)	
Gender identity-based victimization	57.5 (734)	48.6 (2,125)	^{2}(1) 7.66, p .01
Gender identity conversion efforts	13.1 (34)	13.6 (364)	^{2}(1) 0.05, p .82
History of puberty blocker use	24.4 (66)	1.3 (37)	^{2}(1) 422.86, p .001
Depression	60.9 (167)	77.9 (2,294)	^{2}(1) 39.83, p .001
Seriously considered suicide	51.1 (135)	61.6 (1,674)	^{2}(1) 10.97, p .001
Attempted suicide	16.0 (42)	27.7 (733)	^{2}(1) 16.67, p .001

GAHT gender-af rming hormone therapy.

Table 5
Multivariate adjusted logistic regression of gender-af rming hormone therapy on depression and suicidality among transgender and nonbinary youth

	Overall sample		Ages 13–17	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Depression	0.73 (0.61–0.88)	.001	0.61 (0.43–0.86)	.01
Seriously considered suicide	0.74 (0.62–0.88)	.001	0.74 (0.52–1.03)	.08
Attempted suicide	0.84 (0.66–1.07)	.16	0.62 (0.40–0.97)	.04

Adjusted for age, socioeconomic status, census region, gender identity, sexual orientation, race/ethnicity, parent support for gender identity, gender identity-based victimization, gender identity conversion efforts, and history of puberty blocker use.
aOR adjusted odds ratio; CI con dence interval.

access GAHT reported greater rates of nancial struggles; however, this was not true for the subsample aged 13–17. Our measure of socioeconomic status was based on household nances, which often look different for those 18 and older who may no longer be able to rely on their family s resources. As expected, youth over age 18 had higher rates of being able to access GAHT when they desired it. Among transgender and nonbinary youth, those who primarily reported a binary identity (i.e., transgender man or transgender woman) had higher rates of accessing GAHT compared to those who were nonbinary. Pansexual youth were also underrepresented among those who received GAHT; however, this relationship may also be related to nonbinary identities as pansexual was the most frequently reported sexual orientation among nonbinary youth. There were also disparities in access to GAHT across race/ethnicity. White youth represented 68% of those who received GAHT compared to 56% among those who wanted it but did not receive it, with LGBTQ youth of color reporting lower rates of obtaining GAHT. Furthermore, parental 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, including 94% of those aged 13–17. Together, these ndings indicate that youth receipt of gender-af rming care is based not only on their presenting concerns but also on their parent s level of support, geography, and their social identities, which relate to barriers to care among the broader population of youth as well [23–26]. To reduce disparities in youth access to GAHT there is a need to focus on increasing awareness and education around gender-af rming care for parents as well as among healthcare providers and others in positions to support youth health and well-being.

Some of the hesitance regarding gender-af rming care for transgender and nonbinary youth may be due to a misunderstanding of the causes of mental health challenges in transgender and nonbinary individuals, such as a failure to recognize ways incongruence between physical traits and one s gender identity can produce psychological distress marked by depression. High rates of depression, suicidal ideation, and suicide attempts among transgender youth are sometimes used by antitransgender politicians and activists to erroneously suggest that transgender identity is a mental health condition that can be treated through counseling and conversion efforts [27]. These individuals ignore the impacts of gender dysphoria and minority stress [28] and suggest that GAHT is not necessary if transgender youth can be counseled into accepting their sex assigned at birth. The ndings of this study demonstrate that GAHT could be a potential mechanism by which mental health and suicide disparities among transgender and nonbinary youth may begin to decrease. Furthermore, existing evidence suggests that regret is low for gender-af rming care interventions, with one study of 55 transgender adults who had received gender-af rming care as adolescents nding that not one experienced regret [29].

There remains a critical need for mental health outcomes data among transgender and nonbinary youth receiving GAHT, including through longitudinal studies. Large-scale longitudinal data collection will better elucidate the risks and bene ts of individual treatment options so that youth and their families can make evidence-informed decisions regarding care.

Limitations

This study boasts a large, diverse sample of transgender and nonbinary youth across the U.S.; however, some limitations should also be noted. First, causation cannot be inferred due to the study s cross-sectional design. It is possible that those who historically have higher rates of depression and suicidal thoughts and behaviors are also less able to seek or obtain GAHT. However, combined with repeated measures designs of other studies [7,15] it appears likely that receipt of GAHT may lead to reduced levels of depression and suicidality. Given existing research, it is unlikely that randomized controlled trials of GAHT for youth would be ethically appropriate. To better understand directionality, prospective longitudinal designs are needed. Additionally, our self-reported nonprobability sample may limit the generalizability of ndings and suggest the need for the inclusion of gender identity-speci c measures in larger probability samples. Finally, our study did not include variables to assess at what age youth began puberty blockers or GAHT or the duration for which they had been receiving them. Because younger transgender and nonbinary youth in our sample may have been eligible for either puberty blockers or GAHT, there may have been youth who were currently receiving the puberty blockers and not yet ready to start GAHT. However, this is a small part of our sample as only 20 youth aged 13–14 indicated that they had taken puberty blockers but had not accessed desired GAHT. Data on age and duration of access should be included in future studies to better understand the relationship between GAHT and mental health.

Unfortunately, efforts to legally restrict gender-af rming care for transgender and nonbinary youth may negatively impact mental health through two separate but linked pathways. The rst is by directly prohibiting medication that many of these youth rely on to reduce feelings of gender dysphoria. The second is by increasing minority stress through negative public attention and harmful rhetoric debating the rights of transgender and nonbinary youth to live their lives authentically. As such, efforts to address the mental health of transgender and nonbinary youth must also acknowledge and address the cumulative risk that antitransgender political statements and legislative efforts may have on their well-being.

As the evidence for gender-af rming care grows, medical and mental health organizations are increasingly expressing support for it. Many major medical and mental health organizations have guidelines for working with transgender individuals centered around respect for the patient and shared decision-making [30,31], with some organizations releasing statements explicitly opposing any efforts to prevent access to gender-af rming care [32,33]. Given the well-documented risks of negative mental health and suicide among transgender and nonbinary youth, it is necessary that those serving these youth provide care that is patient-centered, af rming, and evidence-based.

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References

[1] Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students 19 states and large urban school districts, 2017. MMWR Morb Mortal Wkly Rep 2019;68:67–71.
[2] Price-Feeney M, Green AE, Dorison S. Understanding the mental health of transgender and nonbinary youth. J Adolesc Health 2020;66:684–90.
[3] Toomey RB, Syvertsen AK, Shramko M. Transgender adolescent suicide behavior. Pediatrics 2018;142:e20174218.
[4] Meyer IH. Resilience in the study of minority stress and health of sexual and gender minorities. Psychol Sex Orientat Gend Divers 2015;2:209–13.
[5] Chodzen G, Hidalgo MA, Chen D, Garofalo R. Minority stress factors associated with depression and anxiety among transgender and gender-nonconforming youth. J Adolesc Health 2019;64:467–71.
[6] Hendricks M, Testa R. A conceptual framework for clinical work with transgender and gender nonconforming clients: An adaptation of the minority stress model. Prof Psychol Res Pract 2012;43:460–7.
[7] Allen L, Watson L, Egan A, Moser C. Well-being and suicidality among transgender youth after gender-af rming hormones. Clin Pract Pediatr Psychol 2019;7:302–11.
[8] Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics 2020;145: e20191725.
[9] Call DC, Challa M, Telingator CJ. Providing af rmative care to transgender and gender diverse youth: Disparities, interventions, and outcomes. Curr Psychiatry Rep 2021;23:1–10.
[10] Raj S. Alleviating anxiety and cultivating care: Young trans people in the family court of Australia. Aust Fem L J 2019;45:111–30.
[11] 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. Int J Transgend Health 2020;21: 3–15.
[12] Gridley SJ, Crouch JM, Evans Y, et al. Youth and caregiver perspectives on barriers to gender-af rming health care for transgender youth. J Adolesc Health 2016;59:254–61.
[13] Kremen J, Williams C, Barrera EP, et al. Addressing legislation that restricts access to care for transgender youth. Pediatrics 2021;147:e2021049940.
[14] Chew D, Anderson J, Williams K, et al. Hormonal treatment in young people with gender dysphoria: A systematic review. Pediatrics 2018;141: e20173742.
[15] Kuper LE, Stewart S, Preston S, et al. Body dissatisfaction and mental health outcomes of youth on gender-af rming hormone therapy. Pediatrics 2020; 145:e20193006.
[16] Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-af rming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. Int J Pediatr Endocrinol 2020; 2020:1–5.
[17] Richardson LP, Rockhill C, Russo JE, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. Pediatrics 2010; 125:e1097–103.
[18] Johns MM, Lowry RR, Haderxhanaj LT, et al. Trends in violence victimization and suicide risk by sexual identity among high school students youth risk behavior survey, United States, 2015–2019. MMWR Morb Mortal Wkly Rep 2020;79:19–27.
[19] DeChants J, Green AE, Price MN, Davis C. Measuring youth sexual orientation and gender identity. The Trevor Project. 2021. Available at: https://www.thetrevorproject.org/2021/07/28/measuring-youth-sexual-orientation-and-gender-identity/. Accessed August 20, 2021.
[20] IBM Corp. IBM SPSS Statistics for Macintosh, version 26.0. Armonk, NY: IBM Corp; 2019.
[21] O Connor RC, Portzky G. Looking to the future: A synthesis of new developments and challenges in suicide research and prevention. Front Psychol 2018;9:2139.
[22] Conron KJ, O Neill K, Vasquez LA. Prohibiting gender-af rming medical care for youth. The Williams Institute UCLA School of Law. 2021. Available at: https://williamsinstitute.law.ucla.edu/publications/bans-trans-youth-health-care/. Accessed August 20, 2021.
[23] Alegría M, Alvarez K, Ishikawa RZ, et al. Removing obstacles to eliminating racial and ethnic disparities in behavioral health care. Health Aff (Millwood) 2016;35:991–9.
[24] Clark BA, Marshall SK, Saewyc EM. Hormone therapy decision-making processes: Transgender youth and parents. J Adolesc 2020;79:136–47.
[25] Schnyder N, Lawrence D, Panczak R, et al. Perceived need and barriers to adolescent mental health care: Agreement between adolescents and their parents. Epidemiol Psychiatr Sci 2019;29:1–9.
[26] Hodgkinson S, Godoy L, Beers LS, Lewin A. Improving mental health access for low-income children and families in the primary care setting. Pediatrics 2017;139:e20151175.
[27] American Psychological Association. APA Resolution on gender identity change efforts. 2021. Available at: https://www.apa.org/about/policy/resolution-gender-identity-change-efforts.pdf. Accessed June 9 2021.
[28] Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental health of transgender children who are supported in their identities. Pediatrics 2016;137:e20153223.
[29] De Vries AL, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696–704.
[30] American Psychiatric Association. Position statement on access to care for transgender and gender diverse individuals. 2018. Available at: https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-2018-Discrimination-Against-Transgender-and-Gender-Diverse-Individuals.pdf. Accessed May 14, 2021.
[31] Rafferty J, Committee on Psychosocial Aspects of Child and Family Health. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. Pediatrics 2018;142:e20182162.
[32] Beers LS. American Academy of Pediatrics Speaks out against bills harming transgender youth. 2021. Available at: https://services.aap.org/en/news-room/news-releases/aap/2021/american-academy-of-pediatrics-speaks-out-against-bills-harming-transgender-youth/. Accessed May 14, 2021.
[33] American Academy of Child & Adolescent Psychiatry. Policy statement on conversion therapy. 2018. Available at: https://www.aacap.org/AACAP/Policy_Statements/2018/Conversion_Therapy.aspx. Accessed August 26, 2019.

Gender Identity 5 Years After Social Transition

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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; = 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.

Increasing numbers of children are socially transitioning to live in line with their gender identity, rather than the gender assumed by their sex at birth, a process that typically involves changing a child s pronouns, first name, hairstyle, and clothing. Some concerns about childhood social transitions have been raised,[1] including that these children may not continue to identify as transgender, rather they might "retransition" (also called a "detransition" or "desistence"), which some suggest could be distressing for youth.[1–3] Research has suggested that ages 10 to 13 years may be particularly key times for retransition and that identity may be more stable after this period for youth who show early gender nonconformity.[3]

Other clinicians argue that early social transitions can be beneficial for some gender-diverse youth.[4–6] Some clinicians and scholars who support early childhood social transitions encourage families to remain open to later retransitions,[7,8] which are seen by some as part of a youth s exploration of their gender.[9]

Unfortunately, very few data about retransitions exist in the scientific literature. We have been able to find limited data on the number of youth

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who socially transition in childhood and then go on to retransition afterward. One paper included 4 youth who socially transitioned; none of them had retransitioned 7 years later.[10] We know of 3 mentions of early-transitioning youth who retransition.[8,9] However, these papers include no mention of how many other youth the same clinical team saw who did not retransition, making it impossible to guess a retransition rate.

In the present paper, we aimed to compute an estimate of retransition among a cohort of more than 300 early-transitioning children. Here, we report the retransition rate an average of 5 years after initial (binary) social transition, as well as how many of these participants are living as binary transgender youth, nonbinary youth, and cisgender youth at the same timepoint.

METHODS

A total of 317 binary socially transitioned transgender children ($_{age}$ = 8.07; SD = 2.36; 208 initially transgender girls, 109 initially transgender boys; see Table 1 for additional demographics) joined this longitudinal study (The Trans Youth Project) between July 2013 and December 2017. For inclusion in The Trans Youth Project, children had to be between 3 and 12 years of age and had to have made a "complete" binary social transition,[10] including changing their pronouns to the binary gender pronouns that differed from those used at their births.

As part of the larger longitudinal study, parents and youth were regularly asked about whether they had begun using puberty blockers and/or gender-affirming hormones. At most visits, they were not asked about whether puberty had begun, though our available data suggests that because these youth had socially transitioned at such early ages, most participants were followed by an endocrinologist well before puberty began. The endocrinologists helped families identify the onset of Tanner 2 (the first stage of puberty) and prescribed puberty blockers within a few months of this time; therefore, the onset of puberty blockers is used as our proxy for the onset of puberty in youth who received blockers. Of the youth in this sample, 37 (11.7) had begun puberty blockers before beginning this study.

This study did not assess whether participants met criteria for the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, diagnosis of gender dysphoria in children. Many parents in this study did not believe that such diagnoses were either ethical or useful, even if they had been diagnosed, and some children did not experience the required distress criterion after transitioning. Based on data collected at their initial visit, these participants showed signs of gender identification and gender-typed preferences commonly associated with their gender, not their sex assigned at birth.[11] Further, parent report using the Gender Identity Questionnaire for Children[12] indicated that youth showed significant "cross-sex" identification and preferences (when scored based on sex at birth).[12]

Final identity classification for these analyses was based on our most recent interaction with the child and/or their parent before January 1, 2021. Because some families have not participated recently, we also separately report (Table 2) the results of the n = 291 youth with whom the research team had an interaction within the 2 years before that deadline. This additional analysis allows us to assess whether those who retransitioned were more likely to have missed their more recent appointments with our team. Importantly, only 1 of the 26 families with whom we did not meet in the past 2 years has formally dropped out of the study; the others often did not complete participation during these 2 years because of personal circumstances at the time we attempted re-recruitment. We anticipate that many in this group will participate again in the future.

TABLE Participant Demographics = 317)

Demographics	%
Race	
White, non-Hispanic	69
White, Hispanic	9
Black	2
Asian	3
Native American	1
Multiracial	17
Annual household income,	
25 000	3
25 001–50 000	10
50 001–75 000	21
75 001–125 000	31
>125 000	35
Location	
Northeast	15
Midwest/Upper Plains	21
Southeast	15
Mountain West	13
Paci c Northwest	20
Paci c South	16

Based on pronouns at follow-up, participants were classified as binary transgender (pronouns associated with the other binary assigned sex), nonbinary (they/them pronouns or, n = 3, a mix of they/them and binary pronouns), or cisgender (pronouns associated with their assigned sex). We confirmed this classification by reviewing other information available to the research team (eg, child s self-categorization in an interview or survey, e-mail communications with the parents). Only 1 classification was debatable; this participant was classified by pronouns (and in this paper) as nonbinary but could have been

TABLE 2 Participant Information and Current Identity at Last Visit Before January 1, 2021, Overall, for Those With Recent Visits Only, and by Initial Social Transition and Gender

	Total Sample	Recent Sample (With Visits in 2019 or 2020)	Sample Who Initially Socially Transitioned Before Age 6	Sample Who Initially Socially Transitioned at Age 6 or Later	Transgender Girls (At Recruitment)	Transgender Boys (At Recruitment)
Sample size	317	291	124	193	208	109
Assigned male at birth, %	65.6	65.3	73.4	60.6	100	0
Mean age at rst transition, y	6.5	6.4	4.3	7.9	6.2	7.1
Mean age at start of study, y	8.1	8.0	5.9	9.5	7.7	8.7
Average time since start of study, y	3.8	4.1	3.8	3.8	3.9	3.7
Average time since rst transition, y	5.4	5.7	5.4	5.4	5.5	5.3
Current identity, *n* (%)						
Binary transgender	298 (94.0)	276 (94.8)	112 (90.3)	186 (96.4)	194 (93.3)	104 (95.4)
Cisgender	8 (2.5)	6 (2.1)	7 (5.6)	1 (0.5)	7 (3.40)	1 (0.9)
Nonbinary	11 (3.5)	9 (3.1)	5 (4.0)	6 (3.1)	7 (3.40)	4 (3.7)

classified as binary transgender (and not retransitioned).

This study has been approved by the University of Washington and Princeton University institutional review boards.

RESULTS

The overall rate of retransition was 7.3 . An average of 5.37 years (SD = 1.74 years) after their initial binary social transition, most participants were living as binary transgender youth (94.0 ; Table 2). Included in this group were 4 individuals (1.3 of the total sample) who retransitioned twice (to nonbinary then back to binary transgender). Some youth (3.5) were currently living as nonbinary, including one who had retransitioned first to cisgender then to nonbinary. Finally, 2.5 were using pronouns associated with their sex at birth and could be categorized as cisgender at the time of data collection, including one who first retransitioned to live as nonbinary. Similar percentages were observed when examining the 291 youth who were in touch with the research team in the past 2 years (Table 2), when examining only those 280 youth who had not begun puberty blockers at the start of the study (Table 3), or if we examine only the 200 youth who had gone at least 5 years since their initial transition (Table 3).

We observed 1 potential (post hoc) age effect. Youth who initially socially transitioned before age 6 (n = 124), were more likely to be living as cisgender (n = 7; 5.6) than youth who transitioned at age 6 or later (n = 1 of 193; 0.5), Fisher exact test (comparing binary, cisgender, nonbinary; before vs. age 6 years or later), P = .02, although low rates of retransition were seen in both groups. In Table 2, we also report the results separately for children assigned male versus female at birth; this distinction was not significantly associated with later identity, P = .47, Fisher exact test. Finally, for exploratory purposes, in Table 3, we report outcomes separately for several subsets of our participants, including youth who had started puberty blockers, youth who had used puberty blockers and gender-affirming hormones, and youth who are at least 14 years old (the age at which past work[3] has suggested retransitions will be less likely).

DISCUSSION

Five years after an initial binary social transition, 7 of youth had retransitioned at least once. Most youth (94) were living as binary transgender youth at the time of data analysis, including 1.3 who retransitioned initially to cisgender or nonbinary and then retransitioned back to binary trans identities. A small number of youth were living as cisgender youth (2.5) or nonbinary youth (3.5). We observed comparable rates when examining all participants who began the study (n = 317), those who had been in touch with the research team in the last two years (n = 291), those who had gone at least 5 years since initial social transition (n = 200), and

TABLE 3 Participant Information and Current Identity at Last Visit Before January 1, 2021, as a Function of Stages of Medical Transition and/or Age

	Total Sample	Sample of Youth Who Had Not Begun Blockers at Start of the Study	Sample of Youth Who Have Begun Blockers (and Not Gender-Affirming Hormones) at the End of the Study	Sample of Youth Who Have Begun Gender-Affirming Hormones at the End of the study	Sample of Youth 5 y of Age Since Initial Binary Social Transition	Sample of Youth Who Are Currently 14 y of Age
Sample size	317	280	92	98	200	70
Assigned male at birth, %	65.6	69.6	57.6	58.2	69.0	52.9
Mean age at rst transition, y	6.5	6.1	6.6	8.4	6.2	8.9
Mean age at start of study, y	8.1	7.6	8.3	10.2	8.0	10.8
Average time since start of study, y	3.8	3.9	4	4.3	4.5	4.4
Average time since rst transition	5.4	5.5	5.8	6.1	6.4	6.3
Current identity						
Binary transgender	$n = 298$; 94.0%	$n = 263$; 93.9%	$n = 88$; 95.7%	$n = 97$; 99.0%	$n = 190$; 95.0%	$n = 69$; 98.6%
Cisgender	$n = 8$; 2.5%	$n = 8$; 2.9%	$n = 1$; 1.1%	$n = 0$	$n = 4$; 2.0%	$n = 1$; 1.4%
Nonbinary	$n = 11$; 3.5%	$n = 9$; 3.2%	$n = 3$; 3.3%	$n = 1$, 1.0%	$n = 6$; 3.0%	$n = 0$

those who started the study before beginning puberty blockers ($n = 280$). We found no differences as a function of participant sex at birth. We observed slightly higher rates of retransition, and particularly later cisgender identity, among youth who initially socially transitioned before age 6 years. However, even in these youth, retransition rates were very low.

Among those who had begun puberty blockers and/or gender-affirming hormones, only 1 had retransitioned to live as cisgender (and this youth had begun blockers, but not gender-affirming hormones). One likely reason so few retransitions to cisgender occurred among those accessing medical transition is that most retransitioning in this cohort happened at early ages. All but 1 of the 8 cisgender youth had retransitioned by age 9 years (the last retransition was at age 11 years). Some of these youth are still not eligible for blockers because they are still prepubertal; we anticipate that those who identify as cisgender are unlikely to seek blockers or hormones, but that the participants who have not begun puberty and who identify as binary transgender or nonbinary likely will.

Past work has suggested that the ages 10 to 13 years are an especially critical time for retransition.[3] In our sample, many of the youth who retransitioned did so before that time frame, particularly the cisgender youth. In the nonbinary group, however, 6 of 11 retransitioned between ages 10 and 13 years, with the remainder retransitioning before age 10. Importantly, our sample differed from the past work on which this age range was determined in several key ways, including that our participants socially transitioned at earlier ages (perhaps pushing retransitions earlier, too), had undergone complete social transitions including pronouns and names (not just hairstyle and clothing changes as in most cases in previous studies[3]), and are living at a different historic time in a different country. Any, or all, of these may turn out to be key differences related to age of retransition.

Our observed low retransition rate is consistent with a study in which 4 youth who had completely socially transitioned had not retransitioned 7 years later.[10] That finding is in the same ballpark as our study s estimate of 2.5 if we examine the percentage living as cisgender at the end of the study (ie, those "desisting" from gender-diverse outcomes). Together, these papers suggest this outcome is relatively rare in this group.

Our observation that few youth who have begun medical intervention have retransitioned to live as cisgender is consistent with findings in the literature. Several studies reporting on outcomes among transgender youth receiving blockers and gender-affirming hormones have reported relatively low rates of regret or stopping treatment,[13] which are potential indicators of retransition, though stopping treatment can occur for other reasons as well (eg, side

effects), as can regret (eg, experiences of transphobia).

Our key finding, that there was a relatively low rate of retransition about 5 years after initial social transition, may, on the surface, appear contradictory with past clinic-based research on what is sometimes called persistence and desistence[3] of childhood gender dysphoria. Several large studies attempted to recontact adolescents and adults who had previously been evaluated for gender dysphoria in childhood.[14–17] Many of those were formally diagnosed with what was, at the time, called gender identity disorder. Those studies reported that a minority of youth later identified in a way that might indicate a transgender identity by today s definition.

Interpretation of those results, and especially comparison with the present work, is difficult for several reasons. First, in past studies, when asked "are you a boy or a girl?" about 90 of the children supplied answers that aligned with their sex at birth,[18] leading some to question whether the majority of those children were the equivalent of transgender children today or not.[19–21] Second, participants in those studies were children between the 1960s and the 1990s, and many features of society have changed since then, including greater rates of acceptance and acknowledgment of transgender identities. Third, the parents of the youth in the current study support their children s identities, as indicated by their approval of their social transitions, whereas many of the parents of youth in past studies explicitly discouraged gender nonconformity or "cross-gender" identification.[15,22] In addition, it would have been exceedingly rare for youth in those studies to socially transition, especially completely.[1,10] Finally, there were substantial drop-out rates in all of the previous studies,[14,15,17] making the true estimates of persistence or desistence difficult to obtain.[19,21] Because there are so many possible contributors to differences in rates of persistence (in past work) and retransition in the current work, we urge caution about overinterpreting differences, or overconfidence about which contributing factors explain the differences.

There are also some reasons why we might have had such a low retransition rate. First, on average, participants had socially transitioned 1.6 years before joining our study. It is possible that some youth initially try socially transitioning and then change their minds quickly. Such youth would be unlikely to be enrolled in this study because their eligibility period would have been quite short and therefore the odds of finding the study and completing it would have been low. This means the children in our study may have been especially unlikely, compared with all children who transition, to retransition because they had already lived and presumably been fairly content with that initial transition for more than a year. Second, it is possible that families who failed to participate in the past 2 years of our study ($n = 26$) were disproportionately those whose children retransitioned and who were therefore hesitant to participate again. If true, their exclusion could have reduced our retransition rate. We are skeptical of this possibility for a few reasons. First, 4 of these participants did retransition and had told us about that outcome, so it does not appear that hesitancy in telling us was widespread in this group. Second, many of these families continue to be in touch with our research team and only missed participation because of ongoing personal issues (eg, COVID-19, emergency family circumstances). We anticipate that most of these families will be able to participate as we continue to follow these youth. Finally, from the beginning of the study, the research team has been clear in discussing with the families that we are open to any outcome in their youth.

As with past work, the present work has several key limitations. First, this is a volunteer community sample, meaning there could be biases in the kinds of families who sign up to participate. We know, for example, that unlike many samples of transgender youth, this sample of youth have normative levels of depression and only slight elevations in anxiety.[23] The parents of the participants in this study are disproportionately higher income and went to college at higher rates than the general population. We do not know whether these potential biases in the sample reflect biases in the cohort of children who socially transitioned in the mid-2010s in the United States and Canada. Therefore, whether the results generalize to youth without these characteristics is unknown.

Another potential limitation is that we used pronouns as the criterion for retransitions. Not everyone who, for example, uses they/them pronouns identifies as nonbinary and someone might identify as transgender even if they are currently using pronouns associated with their sex at birth. However, examination of other data provided by families suggests that our pronoun-based criteria were largely consistent with classification that would have arisen from other types of information provided to the research team (eg, labels used in an interview). Only 1 of the youth categorized as "retransitioned" might, by some other criteria, not meet that definition. However, because pronouns were the initial

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RESEARCH ARTICLE

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

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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

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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.

Introduction

Gender dysphoria (GD) describes the experience of incongruence between an individual's experienced gender and the sex they were assigned at birth. GD [1] in children and young people, also known as Gender Incongruence [2] and previously known as Gender Identity Disorder (GID), is associated with considerable distress or impairment in social, school or other important areas of functioning [3,4]. Interventions include psychosocial support, therapy and medical or surgical interventions to align the body with the identified gender [3,5]. Terminology in this field can be challenging [6]. Here we use birth-registered sex to refer to the sex assigned at birth by clinicians based upon external genitalia [6]. Gender identity refers to a young person's personal sense of their gender. We use the terms 'continuation' and 'discontinuation' to refer to GD across childhood and adolescence.

GD in adolescence is highly likely to continue into adult life where gender dysphoria persists after the onset of puberty [3]. Those with earlier onset or more intense GD and those in whom the development of secondary sexual characteristics in puberty is associated with increasing gender dysphoria or psychological distress are more likely to have persistent GD [3,7]. In adolescents with severe and persistent GD, international [8] and national [9–11] guidelines recommend the use of treatments to suppress the rise in sex hormones (oestradiol or testosterone) in young people during puberty. Gonadotropin releasing hormone analogues (GnRHa) are synthetic peptides that work by stimulating gonadotropin release in a tonic fashion which desensitises the gonadotropin receptors, resulting in reversible suppression of sex hormone production.

In GD, GnRHa can be used from the early/middle stages of puberty with the aim of delaying irreversible and unwanted pubertal body changes and giving young people the opportunity to explore their gender identity during a period when puberty is not advancing [3]. This period also allows clinicians more time to assess the stability of young people's gender identity [6]. Despite this treatment being given in mid-puberty it is also called early puberty suppression, where 'early' refers to earlier than the historic practice of suppression after completion of puberty.

Pubertal suppression is currently practised in the majority of international centres across Europe, the Americas and Australasia, as evidenced by a recently published survey of 25 international centres by the European Society of Paediatric Endocrinology (ESPE) [12]. Pubertal suppression with GnRHa as monotherapy is a time-limited strategy, due to the potential for side effects with long-term use. In the UK, for those commencing under age 15 years, use of GnRHa alone ceases after 16 years when young people face a decision to return to the sex hormones produced by their body or begin cross-sex hormones [5]. There are limited data on the outcomes of pubertal suppression in the treatment of young people with GD [3,13]. A recent

systematic review included data on the physical and mental health outcomes of pubertal suppression using GnRHa in over 500 young people [4]. Longer-term follow-up data on pubertal suppression in GD are limited to individuals from four cohorts [14–19].

In 2011 a study was begun to evaluate the proximal outcomes of mid-pubertal suppression using GnRHa in young people with persistent GD (see http://gids.nhs.uk/our-early-intervention-study). Use in the UK began after mid-pubertal suppression had been incorporated into international guidelines [20] and had become available in the USA [21,22], the Netherlands [15], Australia [23] and a number of European countries. The Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust, London, is a national service for children and young people with GD, drawing from England, Wales and Ireland. Mid-pubertal suppression was offered by the GIDS from 2011 initially only within an ethically approved uncontrolled observational research study with prospective data collection, where all participants received GnRHa. We anticipated that we would recruit 10–15 young people per year for 3 years and follow them up to the end of monotherapy with GnRHa. At the time, a randomised controlled study was not considered feasible due to very small numbers and inability to retain participants in the control arm, as the control treatment would have resulted in progression into near complete puberty and an increasing number of UK families were accessing mid-pubertal suppression internationally. Allocation blinding was also not considered feasible in young people using a product requiring monthly injections.

Here we describe the short-term outcomes of 44 young people with GD from this research cohort, recruited aged 12–15 years and followed to the end of GnRHa monotherapy after age 16 years. This paper describes their medical, psychological and social outcomes during the GnRHa treatment pathway up to the point of decisions about whether or not to undertake further physical treatment. The aims of the study as defined at inception in 2011 were:

1. To evaluate the benefits and risks for physical and mental health and wellbeing of mid-pubertal suppression in adolescents with GD
2. To add to the evidence base regarding the efficacy of GnRHa treatment for young people with GD
3. To evaluate continuation and discontinuation of GD and the continued wish for gender reassignment within this group.

Methods

We undertook an uncontrolled prospective observational study of GnRHa monotherapy in a highly selected group of young people with persistent and severe GD.

Participants

The cohort consisted of 44 sequentially eligible young people, aged 12 to 15 years, who were recruited between April 2011 and April 2014 and who commenced GnRHa treatment between June 2011 and April 2015. They were all recruited from patients referred to the GIDS.

Eligibility criteria were chosen to match those used for a Netherlands cohort [24], namely that the young person:

A. is aged 12–15 years

B. Psychological criteria

1. has been seen by the GIDS for at least 6 months and attended at least 4 interviews for assessment and therapeutic exploration of their gender identity development.

2. psychological stability sufficient to withstand the stresses of medical treatment for GID.
3. fulfils the following criteria relating to GID:
   a. Throughout childhood (defined as over 5 years) the adolescent has demonstrated an intense pattern of cross-gendered behaviours and cross-gender identity.
   b. The adolescent has gender dysphoria that is significantly increased with the onset of puberty. Following assessment the clinician(s) working with the young person deem that there is a high likelihood of the young person experiencing severe psychological distress consequent on experiencing full pubertal development before pubertal suppression is implemented.
4. The young person and their parents/guardians are actively requesting pubertal suppression.
5. is able to give informed consent.

C. Physical/medical criteria

1. is in established puberty:
   - For birth-registered males Tanner (genital and pubic hair (PH)) stage 3 and above.
   - For birth-registered females Tanner (breast and PH) stage 2 and above.
     The rationale for the sex difference was that the pubertal growth spurt which early intervention aims to avoid occurs typically two years earlier in females (Tanner stage 2–3) than in males (Tanner stage 3–4), thus earlier intervention is required in females.
2. has normal endocrine function and karyotype consistent with birth registered sex.

Note that the presence of mildly elevated androgens in birth registered females consistent with polycystic ovarian syndrome is not an exclusion criterion.

Exclusion criteria:

1. Inability to participate with full investigatory protocol e.g. needle phobia, failure to attend for tests and scans.
2. Body mass index (BMI) <2nd centile for age and birth-registered sex [20].
3. Serious psychiatric conditions (e.g. psychosis, bipolar condition, anorexia nervosa, severe body-dysmorphic disorder unrelated to GD).
4. Inability to give informed consent according to the Fraser/Gillick guidelines.
5. Low spine or hip bone mineral density (BMD) on DXA scan: more than 2 SD below expected BMD for age and birth-registered sex. In exceptional circumstances a low BMD was acceptable if:
   i. it was felt to be clinically appropriate by the treating clinicians, who felt that on the balance of risks, pubertal suppression was justified despite the later risk of osteoporosis
   ii. the young person and parents understood the risks of GnRHa treatment for bone density (i.e. potential risks of later osteoporosis)
   iii. The young person and parents consented to more frequent monitoring of BMD (repeat DXA scans 6 months after starting GnRHa and yearly thereafter while on GnRHa) despite the small DXA radiation dose

iv. The young person and parents consented to stopping treatment if raw BMD fell whilst on GnRHa.

The treatment

The treatment under study was suppression of puberty using the GnRHa *triptorelin* together with psychosocial support and therapy, from study entry until the end of the GnRHa monotherapy pathway at age 16 years or older. GnRHa monotherapy ceased when young people either started cross-sex hormones (and continued on GnRHa) or stopped GnRHa. Treatment duration was therefore from 1 to 4 or 5 years depending on age at study entry. Consenting young people were given triptorelin 3.75mg by intramuscular injection every 28 days during the treatment period. Two participants who found monthly injections difficult were moved to a ten-weekly preparation of 11.25mg of triptorelin. The aim of treatment was to suppress gonadotropins and sex hormones to near pre-pubertal levels [13]. Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. In addition local psychological services provided support for co-occuring difficulties for participants as required.

Procedures and pathway

All young people and families attending the GIDS during the study period were provided with an information leaflet about research underway within the unit. Those wishing to find out more about the study discussed it with their GIDS clinicians and those deemed likely to be eligible were given detailed written study information. Those wanting to participate were invited to a medical clinic at UCLH for an initial discussion. At the first medical clinic, young people and families were seen by a senior paediatric endocrinology clinician together with a senior GIDS clinician, who discussed with the family the then current state of knowledge and rationale for treatment, eligibility criteria and potential risks and benefits of participation. Risks included the anticipated side-effects of GnRHa treatment including symptoms resulting from the withdrawal of sex steroids (headaches, hot flushes), fatigue, loss of libido and low mood, the potential that treatment could influence the continuation of their GD and the potential for unknown risks. It was emphasised that young people needed to continue with both regular medical and psychosocial follow-up during the study and that treatment would cease if they did not comply with the treatment or monitoring requirements. A full medical history was elicited and the clinicians also reviewed a summary of the psychological history and assessment from the GIDS. In this visit information sheets were re-provided if families had lost them or forgotten details of the study. If young people and families remained interested in participation, medical investigations were organised and families were invited for a repeat discussion and a formal evaluation of eligibility at a second medical clinic visit approximately 3 months later. Families were asked to think about the issues raised in the meeting and to discuss with their GIDS clinicians if necessary, in order to discuss further at the second visit.

At the second medical clinic visit, the same clinicians repeated the discussion of risks and benefits and explored understanding with the young person and family. A chaperoned medical examination was undertaken including pubertal assessment and the results of medical investigations were reviewed. Endocrine and GIDS clinicians jointly reviewed eligibility and offered participation in the study to those deemed eligible.

The implications of treatment for fertility were discussed at the first and second medical visits and all young people were urged to consider storing gametes before starting GnRHa. Access to storage depended on regional availability within the NHS. Note that counselling on fertility

continued across the study, and clinicians periodically checked with young people who had decided against storage whether they wished to revisit their decision.

Informed consent was obtained in writing from both the young person and a parent or carer holding parental responsibility. The ability of the young person and parents to give informed consent was assessed jointly by the senior adolescent endocrine and GIDS clinicians, informed by written notes from the GIDS team. The consent forms were read with the young person and the parent by the clinicians to be sure they fully understood the information on the forms before signing.

48 young people and families attended the medical clinics for discussion of participation in the trial, of whom 44 wished to participate. Eight young people (7 birth assigned males) were not eligible for participation at the second medical visit as they were not yet sufficiently advanced in puberty. They were followed up every 3–6 months and entered the study subsequently when sufficiently advanced in puberty (median waiting time 7 months).

The date of signing the consent form was taken as the start of study treatment, although it frequently took one to three months for GnRHa treatment to start due to administrative requirements. Participants were followed up in the endocrine clinic, 3–6 monthly in the first 18 months and 12-monthly thereafter, till the end of the treatment pathway, defined as the date on or after the 16th birthday when a decision was made to either cease GnRHa or start cross-sex hormones. The final participant completed the pathway in February 2019.

Outcomes

The following data were collected:

A. Baseline explanatory variables

1. Sex and gender: Young people were classified by their sex assigned at birth (birth-registered sex) and self-identified gender.
2. Ethnicity: Ethnicity was obtained from clinic records. For analysis, ethnicity was grouped as white, South Asian, black or mixed.
3. Puberty: Pubertal status at baseline was classified using information on genital/breast and pubic hair Tanner stages as appropriate. This was summarized into a single pubertal stage, with the breast/genital stage taking precedence if there was discrepancy between breast/genital and public hair stage.
4. Clinical data: These consisted of a) identification of normal phenotype on physical examination for birth-registered sex; b) venepuncture assessment of endocrinology (gonadotropins, prolactin, oestrogen or testosterone, adrenal androgens, thyroid function; and a short synacthen test in birth-registered females only), karyotype, full blood count, renal and liver function, calcium and vitamin D; and c) imaging including wrist bone age and (in birth-registered females only) pelvic ultrasound scan. Medical assessment at baseline and follow-up was consistent with Endocrine Society guidelines [8,20].

B. Study outcomes

Study outcomes concerned domains including response to treatment, bone health, safety indicators and adverse events, psychological function; participant experience and satisfaction; and decisions regarding treatment following GnRHa. Outcome data were collected at routine clinic visits to GIDS or medical clinics at UCLH and timings therefore varied. For the purposes of these analyses, data for each participant were assigned to baseline (before treatment) and to the closest of the following outcome periods: 12, 24, 36 and 48 months on treatment. For safety and response to pubertal suppression outcomes, data were also examined at 6 months.

1. Response to pubertal suppression

Gonadotropins (LH, FSH), testosterone (in birth-registered males) and oestrogen (birth-registered females) were measured after venepuncture. Height, weight and blood pressure were recorded by trained clinic staff. BMI z-score for age and birth-registered sex was calculated [25]. Menarcheal status and presence/absence of menstrual periods was obtained by report from birth-registered females.

2. Bone health

Bone mineral content (BMC) and bone mineral density (BMD) in the lumbar (L1 to L4) spine and hip (total hip) were measured by dual energy X-ray absorptiometry (DEXA) scans using a Hologic Discovery QDR series model 010–1549 (Hologic Inc, Bedford, MA, USA). BMD z-scores for age and birth-registered sex appropriate to this machine were calculated [26]. BMD z-scores for spine and hip were further adjusted for height (height-adjusted z-scores) using published formulae [27].

3. Safety indicators and adverse events

Blood samples were collected by venepuncture for liver and renal function, full blood count, calcium and vitamin D, prolactin, adrenal androgens and thyroid function. Participants were routinely questioned about adverse events at medical clinic visits, including anticipated events such as headaches, hot flushes or fatigue plus any other unanticipated events.

4. Psychological function

Psychological outcomes included a clinical outcome routinely collected after GIDS appointments and a range of outcomes assessed using questionnaires. A standardised set of psychological questionnaires used in the GIDS clinic was completed at the time young people were deemed potentially eligible and referred to the medical clinic. Questionnaires were completed at home by the young person and parent between GIDS clinical meetings, and a research assistant followed up families to ensure their completion. Questionnaires were repeated approximately every 12 months on treatment.

i. General psychological functioning

The Child Behaviour Checklist (CBCL) (parent report) and Youth Self Report (YSR) (self-report) are general measures of psychological functioning and part of the Achenbach System of Empirically Based Assessment (ASEBA; www.aseba.org). The CBCL consists of 113 questions and is validated for children aged 6–18 years in international population samples [28]. The YSR consists of 112 questions and is validated in international populations of young people aged 11–18 years [29]. Questions in both are scored on a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often), with the time frame for item responses being the past six months. Scoring for both instruments provides a total problems score, an internalizing problems score (items which assess anxious/depressed, withdrawn-depressed, and somatic complaints) and an externalizing score (focusing on rule-breaking and aggressive behaviours). Each questionnaire was scored with Assessment Data Manager Software using ASEBA standard norms and t-scores were generated based on reference data for birth-registered sex and broad age-ranges (here 12–18 years). Higher scores indicate greater morbidity. To account for normative change within our age-range, we used international reference data [29] to transform YSR raw scores into z-scores for year of age. As reference data from the UK were not available, reference data from both Australia and the Netherlands were used.

ii. 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. We followed previous studies in calculating a self-harm index score to avoid multiple statistical comparisons across

correlated categorical-response variables. 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 behaviour.

iii. Health related quality of life (HRQoL)

This was assessed through separate young person and parent Kidscreen-52 questionnaires, each consisting of 52 items which assess HRQoL across ten dimensions: physical well-being; psychological well-being; moods and emotions; self-perception; autonomy; relations with parents and home life; social support and peers; school environment; social acceptance (bullying); and financial resources. All items use five-point Likert-style scales to assess either the frequency (never-seldom-sometimes-often-always) of certain behaviours/feelings or the intensity of an attitude (not at all–slightly-moderately-very-extremely). The measure was developed for young people aged 8–18 years, with the recall period of one week. The questionnaires provide scores in the form of continuous t-scores for the ten subscales derived from a multinational European sample [33]. Lower scores indicate lower HRQoL, i.e. greater morbidity.

iv. Body image

The Body Image Scale (BIS) is a self-report measure of 30 items used to assess body image satisfaction or dissatisfaction validated for age 12+. The instrument considers 30 body features which the respondent is asked to rate in terms of satisfaction on a five-point scale (1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied). The BIS provides a total score in the form of a continuous score for the total scale as well as for three subscales assessing primary sexual characteristics, secondary sexual characteristics and 'neutral' characteristics (i.e. non-sexual characteristics, e.g. nose) [34]. Higher scores represent higher degrees of body dissatisfaction.

v. Gender dysphoria

The Utrecht Gender Dysphoria Scale (UGDS) is a self-report measure used to assess the intensity of GD validated for age 12+. It comprises of 12 statements with agreement on a five-point scale (1 = agree completely, 2 = agree somewhat, 3 = neutral, 4 = disagree somewhat, and 5 = disagree completely). There are separate versions for birth-registered males and females. Items are summed to give a single total score, with higher scores indicating greater GD.

vi. Clinical outcomes

The Children's Global Assessment Scale (CGAS) is a rating of functioning in children and young people aged 6–17 years, extensively used as a routine clinical measure in child and adolescent mental health services in the UK. Treating clinicians assign young people a single score between 1 and 100, based on a clinician's assessment of a range of aspects related to a child's psychological and social functioning, with the time period being the previous month. Higher scores indicate better functioning, with categories ranging from 'extremely impaired' (1–10) to 'doing very well' (91–100) [35].

5. Participant experience and satisfaction with GnRHa

Young people were invited to participate in semi-structured qualitative interviews at 6–15 months and 15–24 months after starting GnRHa. Interviews were conducted in person or by telephone with a research assistant. If young people were unavailable, questions were posted to be completed and returned. The interview consisted of 12 questions related to changes young people had experienced in ten domains since starting on GnRHa: life overall, memory, focus, sense of direction, mood, energy levels, relationships with friends, relationships with family, gender role and sexuality. For each domain, young people were asked first about the general direction of change in that domain (whether changes were positive, neutral, negative or mixed positive and negative) and then asked for examples of changes experienced and why they assigned the chosen change rating. At the end of the interview two further questions were asked about change in any other experiences (i.e. allowing open ended responses) and whether

young people wished to continue on GnRHa treatment. Note there was no interview conducted before young people started GnRHa. Interviews were recorded in contemporaneous written notes by the researcher. The questionnaire is provided in the S1 Appendix.

6. Further treatment decisions

Decisions made at the end of the GnRHa pathway were recorded in terms of which if any further treatment for GD young people chose.

Note that other measures of gender dysphoria (Gender Identity Interview; Recalled Childhood Gender Identity Scale) were specified in our original protocol, however they were discontinued during the study as: a) they were historical instruments with poor construct validity and the binary references to male and female roles were challenging for some participants; and b) repeated questioning about gender dysphoria resulted in some distress to respondents. Our protocol had originally included the ASEBA Teacher Report Form (TRF), however we were unable to obtain data from teachers so this outcome was dropped. The Social Responsiveness Scale (SRS) was a baseline only assessment of autistic traits; these data will be analysed in the future.

Analysis plan

Analyses were conducted according to the Statistical Analysis and Dissemination Plan, lodged with the ethics committee that approved the study before the analysis started (see S2 Appendix: Statistical Analysis Plan). The analysis plan was designed to report data on all outcomes but to minimise the likelihood of chance findings due to the large number of outcomes and small sample size. Sample sizes necessarily varied across follow-up as young people were recruited at different ages (12–15 years) but left the study soon after their 16th birthday. All 44 participants had data at 12 months follow-up. As participants necessarily left the study soon after their 16th birthday, numbers reduced after 12 months follow-up as participants could no longer remain in the study. Note this does not represent drop-out. There were 24 left at 24 months, 14 at 36 months and 4 at 48 months. In view of this, outcome reporting was restricted to change from baseline to 12, 24 and 36 months. We made no attempt to account for missing data due to the small sample size and the likelihood of the data missing not at random.

We restricted analyses to primarily descriptive statistics, with formal statistical testing of change across the study restricted to six pre-specified outcomes, i.e.:

1. Overall psychological functioning
    a. parent report: CBCL total t-score
    b. young person self-report: YSR total t-score
2. Self-harm index
    a. parent report: CBCL self-harm index
    b. young person self-report: YSR self-harm index
3. Bone health
    a. BMD and BMC for lumbar spine
    b. BMD and BMC for hip

Assessment of change was through paired t-tests for normally distributed data and the Wilcoxon matched-pairs sign-rank test for non-normal data. The number of formal statistical tests conducted in the study was 16; with overall significance at $p = 0.05$ and a Bonferroni correction, the appropriate threshold for statistical significance is about $p = 0.003$.

In our results and conclusions we refer to change in outcomes only for those that were formally tested. Reporting for other continuous outcomes was restricted to mean and 95% confidence intervals (95%CI) or median and interquartile range (IQR). For categorical outcomes, simple proportions were reported. We reported laboratory tests as normal or abnormal based upon laboratory reference data for age, with the exception of gonadotropins. We did not report data where the sample size was less than 8.

Analysis of potential predictors of outcome was confined a priori to two factors, birth-registered sex and pubertal stage at baseline. Three pre-specified continuous outcomes were examined at 12 months, namely:

1. BMD for lumbar spine
2. YSR total t-score
3. CGAS score

Associations were examined using linear regression of follow-up score on baseline score, adding each baseline factor separately to the model and considering the interaction of predictor with baseline score. All analyses were conducted using Stata 16 (Statacorp, College Station TX).

Responses to the semi-structured interview questionnaires were analysed simply for thematic content in terms of the direction and amount of change that young people experienced in each domain. This involved coding responses about experiences since starting GnRHa into categories; i.e. either positive/improving, negative/deteriorating, both positive and negative, no change or not known. The question on change in sexuality was coded as yes change, no change or not known. Wishes to continue with GnRHa were coded as yes, no or don't know.

To compare our findings with the literature, we drew upon recent reviews [3,4,6,13] and updated a recent review [4] from 1 June 2017 to 31 December 2019 using the same search terms in Medline (see S1 Appendix).

Ethics

Ethical approval for the study was obtained from the National Research Ethics Service (NRES: reference 10/H0713/79) in February 2011. Study consent allowed the use of routinely collected clinical data (medical and psychological) as part of clinical treatment for the study. Study procedures including consent were reviewed by the UK Health Research Authority.

Data sharing. These are highly sensitive data from a small group of vulnerable young people treated in a single service and the risk of identification and disclosure is high. Research ethics permissions at the time the study was undertaken did not include permission to share data. After discussions with the Health Research Authority, UK, an anonymised dataset modified to remove sensitive data and minimise disclosure risk of personal information has been deposited with the UK Data Service.

Results

Participants received psychosocial assessment and support within the GIDS before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6). The median time between first medical assessment at UCLH and starting treatment was 3.9 months (IQR 3.0 to 8.4; range 1.6 to 25.7). Median time in the study was 31 months (IQR 20 to 42, range 12 to 59).

Baseline characteristics of the participants by birth-registered sex are shown in Table 1. Median age at consent was 13.6 years (IQR 12.8 to 14.6, range 12.0 to 15.3). A total of 25 (57%) were birth-registered as male and 19 (43%) as female. At study entry, birth-registered males

Table 1. Participant characteristics at baseline.

		Total sample	Birth-registered sex	
		n = 44	male	female
			n = 25	n = 19
Age at consent (years)	Median (IQR)	13.6 (12.8, 14.6)	13.4 (12.7, 14.1)	13.9 (13.5, 14.7)
Ethnic group n (%)	white	39 (89)	24 (96)	15 (79)
	South Asian	1 (2)	1 (4)	0
	black	2 (5)	0	2 (11)
	Mixed ethnicity	2 (5)	0	2 (11)
Pubertal status n (%)	Stage 2	0	0	0
	Stage 3	19 (43)	17 (68)	2 (10)
	Stage 4	16 (36)	5 (20)	11 (58)
	Stage 5	9 (21)	3 (12)	6 (32)
Menarcheal status n (%)	Premenarcheal	-	-	4 (21)
	Post-menarcheal	-	-	15 (79)
Time in study (months)	Median (IQR)	31 (20, 42)	37 (24, 43)	29 (17, 36)
Age at end of pathway (years)	Median (IQR)	16.1 (16.0, 16.4)	16.1 (16.0, 16.5)	16.1 (16.0, 16.3)

At baseline, 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. Eight participants (18%) had vitamin D insufficiency at baseline and were given vitamin D supplements.

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were predominantly in stage 3 puberty (68%) whilst birth-registered females were predominantly in stages 4 (58%) or 5 (32%) with 79% (15/19) post-menarcheal. 89% of participants were of white ethnicity. Birth-registered females were on average 6 months older than birth-registered males at study entry.

Response to treatment

All participants achieved adequate suppression of gonadotropins and sex hormones by 6 months (mean LH 0.5IU/L; mean FSH 1.4IU/L) and maintained it throughout the study (see Table 2). Liver function, basic haematology and biochemistry were normal in all participants at 3–6 months. All post-menarcheal birth-registered females reported amenorrhoea in the 3 months after starting GnRHa treatment and remained so throughout treatment. No participants reported progression in pubertal development. Height and weight were normal at baseline. Height growth continued through the study but more slowly than expected for age, thus

Table 2. Growth and gonadotropin levels at baseline, 12, 24 and 36 months.

Growth		Baseline		12 months		24 months		36 months	
		n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Height	z-score	44	0.4 (0.1, 0.7)	44	0.2 (-0.1, 0.4)	24	0.0 (-0.4, 0.4)	14	0.0 (-0.5, 0.5)
Weight	z-score	44	0.8 (0.4, 1.3)	44	0.8 (0.3, 1.3)	24	0.6 (-0.1 1.3)	14	1.0 (0.1, 1.9)
BMI	z-score	44	0.7 (0.2, 1.1)	44	0.7 (0.2, 1.2)	24	0.6 (-0.1, 1.3)	14	1.1 (0.3, 1.9)
Gonadotropins									
LH	IU/L	42*	4.2 (2.8, 5.6)	44	0.60 (0.42, 0.68)	17	0.40 (0.22, 0.60)	7	0.30 (0.14, 0.46)
FSH	IU/L	42*	3.9 (3.2, 4.5)	44	1.3 (1.0, 1.7)	17	1.0 (0.6, 1.5)	7	1.4 (0.7, 2.2)

*In two participants data recorded as normal at baseline were not available.

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height z-score fell over time (Table 2). Weight and BMI z-scores were stable from baseline to 24 months but increased at 36 months.

Three participants had brief periods off GnRHa prior to their 16th birthday. In one, treatment was withdrawn by clinicians due to non-attendance at clinics and restarted 4 months later. Another requested a period off GnRHa to think further about treatment in view of other things happening in their life; they restarted 4 months later. A third, birth-registered male, stopped GnRHa for 9 months to attempt to store sperm, contrary to their earlier decision not to, and restarted afterwards.

Median age at the end of the GnRHa pathway was 16.1 years (Table 1). A quarter of participants made their decision more than six months later, either because they wished to delay due to school exams or other events or because clinicians felt they were not yet ready to make the decision. One young person decided to stop GnRHa and not start cross-sex hormones, due to continued uncertainty and some concerns about side-effects of cross-sex hormones. The remaining 43 (98%) elected to start cross-sex hormones.

Bone mineral density. BMD was available on 44 participants at baseline, 43 at 12 months, 24 at 24 months and 12 at 36 months (Table 3). Numbers were lower for hip than for spine as some hip scans were not done for technical reasons. The table shows mean values at baseline and 12, 24 and 36 months, along with mean baseline values corresponding to the paired samples at each time point. There was no change from baseline in spine or hip at 12 months nor in hip at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline, as was lumbar BMC at 36 months. Lumbar and hip BMD age-adjusted z-scores were in the normal range at baseline but point-estimates fell at 12 and 24 months but not at 36 months. Point-estimates for height-adjusted z-scores for lumbar and hip BMD also fell at 12 and 24 months but not at 36 months.

Psychological outcomes. For the standardised questionnaires, baseline assessments were conducted at a median of 0.5 (IQR 0.4, 0.8) years before starting treatment, and were available for all 44 participants by self-report and 43 by parental report. Data on the CBCL, YSR, Kidscreen-52, BIS and CGAS were normally distributed whilst those for UGDS and the CBCL and YSR self-harm indices were skewed.

The first psychological follow-up was at a median of 13 (IQR 12, 14) months after start of treatment, with ASEBA data available for 41 participants (parent and self-report). ASEBA data at 24 months (median 25 (21, 28)) were available on 20 young people by parent report and 15 by self-report, and at 36 months (median 36 (29, 39)) on 11 by parent report and 6 by self-report.

Formal testing was undertaken only for key ASEBA outcomes (Table 4). For the CBCL total t-scores, there was no change from baseline to 12, 24 or 36 months. Similarly for the YSR total t-score, there was no change from baseline to 12 or 24 months; YSR data at 36 months (n = 6) were not analysed. There were no significant changes in parent-report CBCL self-harm index scores from baseline to 12, 24 or 36 months, nor for self-report YSR self-harm index scores.

Other psychological outcomes are described in Table 5. Point-estimates of scores on the Kidscreen-52, BIS, UGDS and CGAS showed little change over time."

The pre-specified outcomes of BMD at lumbar spine, YSR total t-score and CGAS score at 12 months, adjusted separately for birth-registered sex and baseline pubertal status, along with the baseline level of the outcome, are shown in Table 6. None of the outcomes were associated with birth-registered sex or pubertal status, and there were no important interactions.

Participant experience, satisfaction and side effects. 41 participants completed interviews at 6–15 months (median 9) and 29 at 15–24 months (median 21); 3 missed both. Fig 1 shows proportions with positive or negative changes for life overall, mood and friendships, with summary data for all questions shown in S1 Appendix (S1 and S2 Tables).

Table 3. Bone mineral density outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
		Baseline			Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Lumbar	BMC	44	39.5 (35.9, 43.1)	42	39.6 (35.8, 43.4)	41.2 (38.2, 44.2)	1.6 (0.2, 3.1)	0.03	24	34.1 (30.3, 37.9)	40.1 (36.7, 43.5)	6.0 (4.0, 7.9)	<0.0001
	BMD	44	0.76 (0.71, 0.80)	43	0.76 (0.71, 0.80)	0.77 (0.72, 0.81)	0.01 (-0.00, 0.03)	0.17	24	0.68 (0.63, 0.74)	0.73 (0.68, 0.78)	0.05 (0.03, 0.07)	0.0001
Hip	BMC	43	25.2 (23.2, 27.1)	39	25.5 (23.4, 27.6)	26.1 (24.4, 27.9)	0.7 (-0.2, 1.5)	0.13	22	23.9 (21.2, 26.6)	26.3 (24.1, 28.6)	2.4 (0.7, 4.1)	0.008
	BMD	43	0.80 (0.75, 0.86)	39	0.81 (0.75, 0.87)	0.82 (0.78, 0.86)	0.01 (-0.02, 0.05)	0.6	22	0.76 (0.68, 0.85)	0.79 (0.74, 0.84)	0.03 (-0.04, 0.10)	0.4
BMD z-scores	Spine	44	-0.3 (-0.7, 0.0)	43	-0.3 (-0.7, 0.1)	-1.0 (-1.3, -0.7)			24	-0.5 (-1.1, 0.0)	-1.5 (-2.1, -0.8)		
	HAZ spine	44	-0.5(-0.8, -0.1)	43	-0.4 (-0.8, -0.1)	-1.0 (-1.3, -0.6)			24	-0.7 (-1.2, -0.1)	-1.3 (-1.9, -0.7)		
	Hip	43	-0.5 (-0.9, -0.1)	39	-0.5 (-0.9, -0.1)	-1.0 (-1.3, -0.6)			21	-0.5 (-1.1, 0.1)	-1.4 (-2.0, -0.9)		
	HAZ hip	43	-0.7 (-1.0, -0.3)	39	-0.6 (-1.0, -0.2)	-0.9 (-1.3, -0.5)			21	-0.5 (-1.1, 0.1)	-1.2 (-1.7, -0.6)		
				36 months									
					Baseline for those followed up	Follow-up	Change	p					
				n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)						
Lumbar	BMC			12	37.05 (31.0, 43.1)	42.4 (37.4, 47.4)	5.3 (2.8, 7.8)	0.0007					
	BMD			12	0.72 (0.65, 0.80)	0.76 (0.70, 0.82)	0.03 (.00, 0.07)	0.05					
Hip	BMC			12	26.1 (22.1, 30.0)	26.8 (21.2, 32.3)	0.7 (-3.8, 5.2)	0.7					
	BMD			12	(0.82, 0.73, 0.91)	0.81 (0.74, 0.88)	-0.009 (-0.05, 0.03)	0.6					
BMD z-scores	Spine			12	-0.2 (-1.0, 0.6)	-1.5 (-2.2, -0.8)							
	HAZ spine			12	-0.4 (-1.2, 0.3)	-1.3 (-2.2, -0.5)							
	Hip			12	-0.3 (-1.3, 0.6)	-1.1 (-1.8, -0.5)							
	HAZ hip			12	-0.5 (-1.5, 0.5)	-1.0 (-1.8, -0.2)							

BMD: bone mineral density; BMC bone mineral content; HAZ height adjusted z-score.

BMD z-scores were not formally tested–see Methods.

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Most participants reported positive or a mix of positive-negative changes in their life at both time points. At 6–15 months 46% reported only positive changes, including feeling happier, relieved, less facial hair or stopping periods. A further 37% reported both positive and negative changes such as feeling happier but also experiencing hot flushes and headaches. In addition 12% reported overall negative changes namely hot flushes, tiredness, and feeling more emotional, while 5% reported no change. At 15–24 months, 55% reported solely positive changes such as feeling happier, no longer experiencing side effects and feeling more

Table 4. ASEBA outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
			Baseline		Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	mean (95% CI)	n	mean (95% CI)	mean (95% CI)	mean (95% CI)		n	mean (95% CI)	mean (95% CI)	mean (95% CI)	
Parent report CBCL	Total problems t-score	43	61.6(58.4, 64.7)	41	61.5(58.2, 64.7)	61.8(58.4, 65.1)	0.3(-2.0, 2.6)	0.8	20	61.2(56.5, 65.8)	60.2(54.6, 65.8)	-1.0(-4.0, 2.1)	0.5
	Externalising problems t-score	43	55.8(52.4, 59.3)	41	55.7(52.1, 59.3)	55.4(51.8, 59.0)			20	55.4(49.9, 60.9)	55.2(48.9, 61.5)		
	Internalising problems t-score	43	62.1(58.7, 65.5)	41	61.8(58.3, 65.3)	62.9(59.5, 66.3)			20	60.4(55.7, 65.1)	60.1(54.6, 65.6)		
Self-report YSR	Total problems t-score	44	57.9(55.0, 60.8)	41	57.6(54.5, 60.6)	58.4(54.6, 62.2)	0.8(-3.1, 4.8)	0.7	15	55.1(50.9, 59.2)	56.5(50.6, 62.5)	1.5(-3.4, 6.3)	0.5
	Total problems z-score (ref: Netherlands)	44	1.01(0.67, 1.36)	41	0.97(0.62, 1.33)	0.99(0.55, 1.42)			15	0.66(0.17,1.15)	0.65(-0.05, 1.36)		
	Total problems z-score (ref: Australia)	44	0.72(0.37, 1.06)	41	0.68(0.32, 1.03)	0.68(0.24, 1.12)			15	0.39(-0.11,0.89)	0.37(-0.32, 1.07)		
	Externalising problems t-score	44	52.3(49.2, 55.5)	41	52.3(49.2, 55.4)	52.5(48.7, 56.3)			15	53.1(48.5, 57.6)	52.3(45.3, 59.4)		
	Internalising problems t-score	44	58.0(54.9, 61.2)	41	57.7(54.3, 61.0)	60.1(55.9, 64.3)			15	53.9(49.9, 58.0)	55.9(50.8, 61.1)		
Self-harm scores													
Parent report CBCL	Median (IQR)	43	0(0, 1)	40	0(0, 1)	0(0, 1)		0.3	20	0(0, 1)	0(0, 1)		>0.9
Self-report YSR	Median (IQR)	43	0(0, 1)	39	0(0, 1)	0(0, 2)		0.4	15	0(0, 0)	0(0, 0)		0.3
				36 months									
					Baseline for those followed up	Follow-up	Change	**p**					
				n	mean (95% CI)	mean (95% CI)	mean (95% CI)						
Parent report CBCL	Total problems t-score			11	62.4(55.1, 69.6)	61.1(52.3, 69.9)	-1.3(-6.6, 4.0)	0.6					
	Externalising problems t-score			11	56.8(48.0, 65.6)	56.2(48.3, 64.1)							
	Internalising problems t-score			11	60.4(53.5, 67.2)	62.5(53.6, 71.5)							
Self-harm scores													
Parent report CBCL	Median (IQR)			11	0(0, 1)	0(0, 1)		0.8					

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comfortable with puberty suspended. A further 17% reported both positive and negative changes including less body hair but continued growth in height, or having clearer skin but also experiencing more hunger, weight gain and tiredness. 17% reported largely negative changes such as mood swings, tiredness and hot flushes whilst 10% reported no change.

Reports of change in mood were mixed. At 6–15 months, the majority reported mood to be improved (49%), mixed changes (such as both feeling happier but experiencing some mood swings; 15%) or no change (7%), however 24% reported negative changes in mood such as

Table 5. Other psychological outcomes at baseline, 12, 24 and 36 months.

		Baseline		12 months		24 months		36 months	
		n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)
Kidscreen-52 HRQOL									
Parent report CBCL t-scores	Physical wellbeing	42	44.9(41.4, 48.5)	36	40.4(37.5, 43.3)	14	40.5(36.8, 44.2)		
	Psychological Wellbeing	41	39.8(36.7, 42.8)	36	39.0(35.4, 42.6)	14	42.4(36.9, 48)		
	Moods and Emotions	41	40.6(37.6, 43.6)	36	41.2(37.3, 45.1)	14	42.5(36.3, 48.7)		
	Self-perception	42	34.6(32.6, 36.5)	36	34.8(32.0, 37.5)	14	34.8(31.3, 38.2)		
	Autonomy	42	46.2(43.2, 49.2)	36	48.2(45.0, 51.4)	14	46.7(41, 52.4)		
	Parent relations and home life	42	48.1(44.5, 51.6)	35	46.7(42.9, 50.5)	14	49.5(44.1, 54.9)		
	Social support and peers	39	48.0(44.7, 51.4)	36	51.9(48.4, 55.3)	13	51.4(45.6, 57.2)		
	School environment	42	38.2(35.0, 41.4)	35	39.4(35.3, 43.4)	13	43.7(36, 51.3)		
	Social acceptance	39	44.7(40.7, 48.7)	32	42.3(38.1, 46.4)	13	43.5(35.9, 51.2)		
	Financial resources	42	37.9(33.9, 41.9)	36	35.8(31.5, 40.2)	14	36.3(26.4, 46.3)		
Self-report t-scores	Physical wellbeing	42	45.1(41.8, 48.5)	36	41.5(38.0, 45.0)	13	43.9(38.9, 48.9)		
	Psychological Wellbeing	42	43.0(39.6, 46.4)	36	41.1(37.0, 45.2)	14	51(45.8, 56.2)		
	Moods and Emotions	42	46.3(42.7, 49.9)	36	43.9(40.4, 47.3)	14	50.1(45.5, 54.7)		
	Self-perception	42	38.8(36.7, 40.9)	36	37.9(35.1, 40.6)	14	43.1(39.9, 46.2)		
	Autonomy	42	46.6(43.6, 49.6)	36	46.7(42.9, 50.5)	13	51.9(47.4, 56.4)		
	Parent relations and home life	42	49.7(46.2, 53.2)	36	48.7(45.2, 52.3)	14	58.4(53.3, 63.5)		
	Social support and peers	37	45.6(42.5, 48.7)	35	48.1(44.6, 51.6)	14	49.7(44.3,55.1)		
	School environment	41	45.9(42.3, 49.4)	36	44.7(39.7, 49.7)	14	49(43.6, 54.3)		
	Social acceptance	41	47.4(43.5, 51.3)	33	45.5(40.9, 50.1)	13	53.6(46.3, 60.8)		
	Financial resources	42	42.2(38.1, 46.3)	34	43.2(38.2, 48.1)	14	46.3(39.1, 53.5)		
Body image scale	Overall score	42	3.1(2.8, 3.3)	40	3.2(3.0, 3.4)	16	3(2.7, 3.2)	8	3.1(2.4, 3.7)
	Primary characteristics score	42	4.5(4.2, 4.7)	39	4.3(4.2, 4.5)	16	4.5(4.3, 4.7)	8	4.2(3.9, 4.5)
	Secondary characteristics score	41	2.9(2.6, 3.1)	40	3(2.8, 3.3)	16	2.9(2.5, 3.2)	8	2.9(2, 3.8)
	Neutral characteristics score	42	2.5(2.203, 2.707)	40	2.7(2.5, 3.0)	-	-		
Utrecht Gender dysphoria score	Median (IQR)	41	4.8(4.6, 5.0)	40	4.7(4.6, 5.0)	18	4.7(4.3, 5.0)		
Clinical outcome									
CGAS global score	Mean (95% CI)	42	62.9(59.6, 66.2)	35	64.1(59.9, 68.3)	18	65.7(59.6, 71.8)	12	66.0(58.1, 73.9)

Note: Change in outcomes in this Table were not formally tested.

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Table 6. Associations between birth-registered sex and baseline pubertal status and outcomes at 12 months.

		Outcomes at 12 months adjusted for baseline								
		BMD at lumbar spine			YSR total t-score			GCAS score		
		n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p
Birth-registered sex										
Main effect (baseline value of outcome)		43	0.86 (0.75, 0.97)	<0.0001	41	0.43 (0.05, 0.82)	0.03	33	0.74 (0.42, 1.06)	<0.0001
Birth-registered sex	Male (ref)		0			0			0	
	Female		-0.02 (-0.05, 0.01)	0.2		2.1 (-5.2, 9.4)	0.6		-3.2 (-10.0, 3.5)	0.3
Pubertal status										
Main effect (baseline value of outcome)		43	0.85 (0.72, 0.97)	<0.0001	41	0.43 (0.01, 0.84)	0.04	33	0.69 (0.37, 1.00)	<0.0001
Pubertal stage at baseline	3		0.008 (-0.03, 0.04)	0.7		0.2 (-8.3, 8.7)	0.9		1.6 (-5.5, 8.8)	0.6
	4 (ref)		0			0			0	
	5		-0.009 (-0.05, 0.03)	0.7		0.4 (-9.9, 10.8)	0.9		-7.9 (-17.6, 1.8)	0.11

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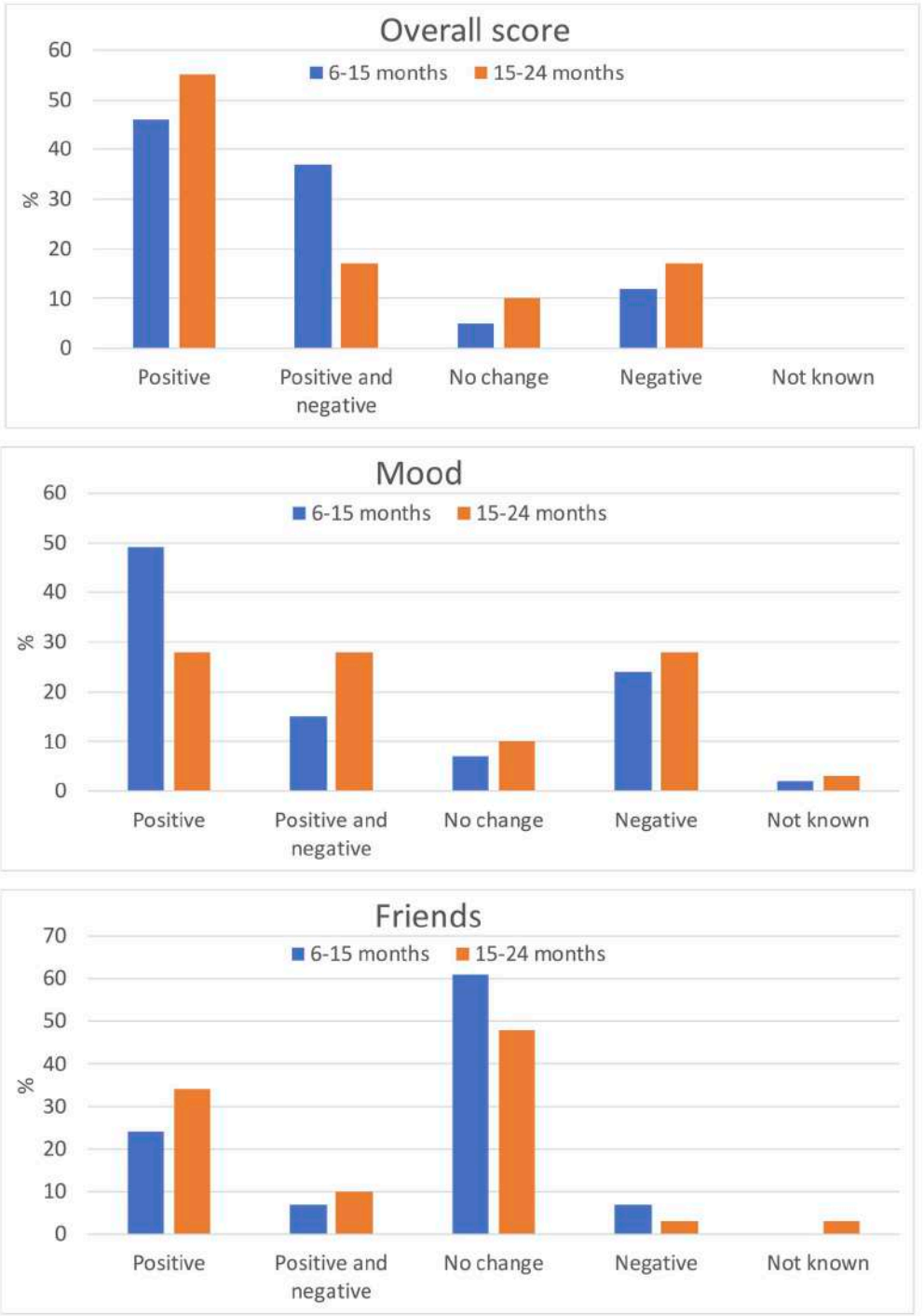

Fig 1. Ratings of change in life overall, mood and friendships at 6–15 months (n = 41) and 15–24 months (n = 29).

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experiencing more mood swings or feeling low. Findings at 15–24 months were similar. The most common negative change was reduced energy levels, reported by 29% at 6-15m and 38% at 15-24m.

Young people's reports of change in family and peer relationships were predominantly positive or neutral at both time points. Positive changes included feeling closer to the family,

Table 7. Adverse events reported across the study.

Participants	0-6m	7-12m	13-24m	25+m
	n = 44	n = 44	n = 36	n = 24
	n (%)	*n (%)*	*n (%)*	*n (%)*
Mild headaches or hot flushes	11 (25%)	10 (23%)	8 (22%)	4 (17%)
Moderate or severe headaches and hot flushes	2 (5%)	4 (9%)	1 (3%)	0
Fatigue—mild	2 (5%)	3 (7%)	3 (8%)	1 (4%)
Fatigue–moderate or severe	0	0	0	0
Mood swings	1 (2%)	0	0	0
Weight gain	1 (2%)	0	1 (3%)	0
Sleep problems	1 (2%)	0	1 (3%)	0
Other events	0	0	0	0
Total events recorded*	18	17	14	5

* individuals may have more than 1 event.

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feeling more accepted and having fewer arguments. Those reporting both positive and negative change reported feeling closer to some family members but not others. At 6–15 months, negative family changes were largely from family members not accepting their trans status or having more arguments. But by 15–24 months only one young person reported this. Improved relationships with peers related to feeling more sociable or confident and widening their circle of friends; negative changes related to bullying or disagreements at school. Again, at 15–24 months only one young person reported negative change, related to feelings of not trusting friends.

At 6–15 months, changes in gender role were reported by 66% as positive, including feeling more feminine/masculine, living in their preferred gender identity in more (or all) areas of life and feeling more secure in their gender identity, with no negative change reported. At 15–24 months, most reported no change although 41% reported positive changes including experimenting more with physical appearance and changing their details on legal documents.

All young people affirmed at each interview that they wished to continue with GnRHa treatment. Note that this was also the case when asked routinely at medical clinics (excepting those who briefly ceased GnRHa as noted above).

Adverse events. Adverse events are shown in Table 7. All adverse events were minor and anticipated, i.e. they were previously described in study participant information and/or noted in the triptorelin medication package inserts. Anticipated adverse events were common in the first two years, particularly mild headaches or hot flushes which were reported in 25% at 0-6m, 23% at 7-12m and 22% at 13-24m. Moderate or severe headaches and/or hot flushes were uncommon. Birth-registered females with distressing headaches or hot flushes were offered 'add-back' oestrogen therapy, and two accepted treatment briefly with very small doses of oestradiol, which was effective in reducing symptoms. Mild fatigue was reported by 5–8% over the first two years and no participants reported moderate or severe fatigue. Sleep problems, mood swings and weight gain were reported by very small numbers and in each case symptoms were mild. Adverse events were less common after 12 months of treatment.

Discussion

We report the short and medium-term outcomes of a prospective cohort of 44 young people with persistent and severe GD treated with GnRHa resulting in pubertal suppression from mid-puberty for 1–4 years. Young people were considered for recruitment after lengthy

assessment, spending an average of 2 years and up to 6 years within the GIDS psychological service before being referred to the endocrine clinic for assessment to enter the study. Medical assessment found no endocrine abnormalities at baseline. GnRHa treatment started in the majority of participants in later stages of puberty, with 57% in puberty stages 4 and 5 and 79% of birth-registered females being post-menarcheal. After starting GnRHa all quickly achieved and maintained suppression of pubertal hormones and none experienced pubertal progression. At the end of the study, 43 (98%) chose to start cross-sex hormones whilst one young person chose to stop GnRHa and continue with puberty consistent with their birth-registered sex.

As anticipated, pubertal suppression reduced growth that was dependent on puberty hormones, i.e. height and BMD. Height growth continued for those not yet at final height, but more slowly than for their peers so height z-score fell. Similarly for bone strength, BMD and BMC increased in the lumbar spine indicating greater bone strength, but more slowly than in peers so BMD z-score fell. These anticipated changes had been discussed with all participants before recruitment to the study. Young people experienced little change in mean weight or BMI z-score in the first two years. The rise in weight and BMI z-score at 36 months may represent a trend towards greater adiposity in those on GnRHa for a prolonged period, or reflect a higher baseline in this group.

Information on side-effects was available through routine reporting in medical clinics and in the participant experience interviews. Anticipated side effects of treatment were common, particularly mild symptoms directly related to suppression of sex hormones. Severe symptoms were uncommon. Fatigue or low energy was reported rarely in medical clinic assessments but frequently at interview (38% at 15-24m). The relationship of symptoms such as headaches, fatigue and sleep disturbance to GnRHa treatment is unclear as they are all very common in early adolescence [36,37], although a conservative perspective would regard them as side-effects of treatment.

Young people experienced little change in psychological functioning across the study. We found no differences between baseline and later outcomes for overall psychological distress as rated by parents and young people, nor for self-harm. Outcomes that were not formally tested also showed little change.

Participant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role. Smaller numbers reported having mixed positive and negative changes. A minority (12% at 6–15 months and 17% at 15–24 months) reported only negative changes, which were largely related to anticipated side effects. None wanted to stop treatment due to side effects or negative changes. We are not aware of comparative patient experience data from other cohorts.

The median age at consent in our study was very similar to that in the earliest published outcome study of mid-pubertal suppression using GnRHa treatment in Dutch young people (13.6 years) [24]. Similarly to this Dutch cohort, all but one of our participants elected to start cross-sex hormones after completing the GnRHa pathway. However they spent an average of 31 months on GnRHa compared with 23 months in the Dutch cohort [24]. In our study, the successful suppression of puberty and cessation of menses with GnRHa, the impact on height growth [4,16,38] and BMD [4,16] and the normality of liver and renal function through treatment were each consistent with previous reports [4,16].

Our findings that BMD increased over time in the lumbar spine but more slowly than in same age peers, resulting in a fall in z-score, are similar to others [4,14,39,40]. The fall in height-adjusted BMD z-score was consistent with but larger than the fall in height z-score. We found that birth-registered sex and pubertal status at baseline were not associated with later BMD. There is evidence that accretion of bone mass resumes and that BMD increases with the

start of cross-sex hormone therapy [4,14,39,41]. Future research needs to examine longer-term change in BMD in young people treated with mid-pubertal suppression.

We reported a range of adverse events previously described to be associated with pubertal suppression [42], with the exception of mild sleep disturbance although this is a known association with triptorelin use. As anticipated, the withdrawal of sex hormones produces symptoms such as headaches and lack of energy, although in the great majority (11 of 13 at 0–6 months; 10 of 14 at 7–12 months; 8 of 9 at 13–24 months) the symptoms were minor. Symptoms diminished over time as has previously been noted [4], and no young people chose to cease treatment due to the side-effects.

Our finding that 1 participant ceased pubertal suppression and did not commence cross-sex hormones is somewhat similar to the experience of one US cohort and a second Dutch cohort; Kuper et al. described that 2 of approximately 57 young people aged 10–15 years who commenced pubertal suppression treatment stopped this treatment without commencing cross-sex hormones [17]. Brik et al. reported that in a cohort of 137 young people who began GnRHa between 10 and 18 years and were followed until eligible to commence cross-sex hormones, 5 (3.6%) ceased treatment and did not later commence cross-sex hormones [19].

Three longitudinal studies from the Netherlands and the USA have examined psychological function over time in cohorts of young people treated with GnRHa and then cross-sex hormones [17,18,24], although the two US cohorts were of limited size. Our study adopted the same psychological outcome measures as the Dutch cohort, to facilitate comparison [24]. Mean baseline YSR scores in our cohort were similar to those previously reported in 141 young people aged 12–18 years from the London GIDS [43], and baseline CBCL and YSR scores were close to those at baseline from the original Dutch cohort [24]. A number of other studies have shown that young people with GD have higher scores on the CBCL or YSR than same-age population peers, and that they are similar to young people referred to clinical services for a range of mental health problems [44–46]. Population-based studies in America support higher baseline levels of mental health problems amongst young people with GD, with the prevalence of self-harm notably higher than for male or female peers [47,48]. Young people in our study had baseline YSR scores 0.7–1.0 SD higher than norms for age in comparable countries [29,46].

We found no evidence of change in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalising or externalising problems or self-harm. This is in contrast to the Dutch study which reported improved psychological function across total problems, externalising and internalising scores for both CBCL and YSR and small improvements in CGAS [24]. It also contrasts with a previous study from the UK GIDS of change in psychological function with GnRHa treatment in 101 older adolescents with GD (beginning $>$ 15.5 years) which reported moderate improvements in CGAS score over 12 months of GnRHa treatment [49]. CGAS scores in this previous study increased from 61 to 67 with GnRHa treatment, similar to those (63 at baseline, 66 at 24 months) in our study. Follow-up of the Kuper et al. cohort found non-significant changes in depression and anxiety scores in those (n = 25) who had only pubertal suppression treatment, although improvements were seen in the whole sample combining these with those receiving cross-sex hormones [17]. A second US cohort reported that in 23 young people who had received pubertal suppression (using GnRHa or anti-androgens in birth-registered males and either GnRHa or medroxyprogesterone in birth-registered females), there was a reduction in depression scores in birth-registered males but not females.

A recent large US survey found that those who received pubertal suppression in early or mid adolescence had lower odds of lifetime suicidal ideation when studied in adulthood compared with those who did not, regardless of whether they later received cross-sex hormones

and after adjustment for a range of confounding factors [50]. This implies an enduring benefit of pubertal suppression on psychological function, however the cross-sectional design and retrospective exposure classification means the findings require replication. Data are also available from other conditions in which GnRHa is used to suppress puberty during adolescence. A trial of GnRHa suppression of puberty during early adolescence in young people born small-for-gestational-age (SGA) who were also treated with human growth hormone (GH) reported that those treated with GnRHa had similar cognitive and psychological function in adult life to those treated only with GH [51].

The differences between our findings and the previous GIDS study re change in psychological function may relate simply to sample size. But why our findings differ from those of the Dutch study is unclear. They may relate to the timing of assessments; we assessed young people multiple times whereas in the Dutch study the second assessment was shortly before starting cross-sex hormone treatment. Alternatively, there may have been baseline differences in the two cohorts. Whilst some aspects of psychological function were similar, as noted above, the baseline CGAS scores were notably higher in the Dutch group (indicating better function). A previous international comparison study has found that young people aged 12–18 years with GD from the UK have higher scores indicating greater problems on the CBCL and YSR than those from the Netherlands, Belgium and Switzerland [52].

Psychological distress and self-harm are known to increase across early adolescence. Normative data show rising YSR total problems scores with age from age 11 to 16 years in non-clinical samples from a range of countries [29]. Self-harm rates in the general population in the UK and elsewhere increase markedly with age from early to mid-adolescence, being very low in 10 year olds and peaking around age 16–17 years [53–56]. Our finding that psychological function and self-harm did not change significantly during the study is consistent with two main alternative explanations. The first is that there was no change, and that GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people with GD. This is consonant with the action of GnRHa, which only stops further pubertal development and does not change the body to be more congruent with a young person's gender identity. The second possibility is that the lack of change in an outcome that normally worsens in early adolescence may reflect a beneficial change in trajectory for that outcome, i.e. that GnRHa treatment reduced this normative worsening of problems. In the absence of a control group, we cannot distinguish between these possibilities. We aimed to use normative reference data to examine this issue. However age- and gender-standardised t-scores for ASEBA and other outcomes cannot answer this question as they cover a very broad age range (e.g. 12–18 years). We had anticipated that z-scores on the YSR available by calendar year for two comparable countries (Netherlands; Australia) might be informative however confidence intervals were too wide to draw reliable inferences.

Gender dysphoria and body image changed little across the study. This is consistent with some previous reports [24] and was anticipated, given that GnRHa does not change the body in the desired direction, but only temporarily prevents further masculinization or feminization. Other studies suggest that changes in body image or satisfaction in GD are largely confined to gender affirming treatments such as cross-sex hormones or surgery [57]. We found that birth-registered sex and baseline pubertal status were not associated with later psychological functioning on GnRHa, consistent with previous reports [24,49].

These data correct reports from a recent letter by Biggs [58] which used preliminary data from our study which were uncleaned and incomplete data used for internal reporting. In addition there were many statistical comparisons which inflated the risk of type 1 error. Our statistical analysis plan restricted testing all outcomes for differences by sex due to the type 1

error risk. Contrary to Biggs's letter, we found no evidence of reductions over time in any psychological outcomes, and no material differences by sex.

Strengths and limitations

Our study provides comprehensive data on this cohort during follow-up, with an anonymised dataset containing standardised scores deposited to allow other researchers to replicate our findings where data-sharing allows. The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality. Further, many of the outcomes studied here, including psychological function, self-harm and BMD, undergo normative changes by age and developmental stage during puberty that could confound any observed effect of GnRHa treatment in an uncontrolled study. The analysis plan aimed to take these issues into account as far as possible, however this particularly limits the potential for the study to show benefits or harms from treatment. However, some conclusions can be drawn. It is unlikely that the reported adverse events such as headaches do not relate directly to GnRHa treatment. Equally, given that there were no changes in psychological function and differences in point estimates were minimal for nearly all outcomes, it is unlikely that the treatment resulted in psychological harm. Observational studies are important sources of data on harms of treatment [59–61].

Our data are subject to a number of other limitations. This was an unfunded study undertaken within a clinical service and we were dependent on the clinical service for data collection. There were varying sample sizes for differing tests as some participants did not attend certain investigations and some follow-up medical tests were processed locally to patients; these data are reported as normal or otherwise. Missing items on psychological questionnaires resulted in some unusable data. Some young people found repeated completion of questionnaires about gender issues intrusive and refused to complete them at later follow-ups, as has been reported in other studies [62]. This questionnaire fatigue also affected parent responses. Scoring of psychological questionnaire data was rechecked at the completion of the study however this was not possible in very small numbers of participants in whom only scale scores rather than individual item data were preserved during data migration in hospital clinical information systems. In sensitivity analyses, repeat analysis of ASEBA psychological outcomes restricted to those with rescored data showed highly similar findings to the full sample (see S3 Table in S1 Appendix).

A more detailed qualitative evaluation of participant experience was not possible due to lack of interviewer time, and reporting of interview data was restricted to perceptions of positive or negative change and the giving of examples.

Implications and conclusions

Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events. BMD increased with treatment in the lumbar spine and was stable at the hip, and BMD z-score fell consistent with delay of puberty. Overall participant experience of changes on GnRHa treatment was positive. We identified no changes in psychological function, quality of life or degree of gender dysphoria.

The great majority of this cohort went on to start cross-sex hormones, as was hypothesized given the severity and continuation of their GD. However one young person did not, providing some evidence that development of gender identity continues on GnRHa treatment and

confirming the importance of continuing supportive psychological therapy to allow further exploration of gender identity and a range of future pathways whilst on GnRHa.

This cohort will be followed up longer term to examine physical and mental health outcomes into early adulthood. However larger and longer-term prospective studies using a range of designs are needed to more fully quantify the harms and benefits of pubertal suppression in GD and better understand factors influencing outcomes [3]. These are beginning to be funded in a number of countries [63].(https://logicstudy.uk) Given that pubertal suppression may be both a treatment in its own right and also an intermediate step in a longer treatment pathway, it is essential for such studies to examine benefits and harms across the longer pathway including pubertal suppression and initiation of cross-sex hormones.

Supporting information

S1 Appendix.
(DOCX)

S2 Appendix. Statistical analysis plan.
(DOCX)

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References

1. Diagnostic and statistical manual of mental disorders (DSM-V). 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. International Statistical Classification of Diseases and Related Health Problems (ICD-11). Geneva: World Health Organisation, 2019.
3. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. Lancet Diabetes Endocrinol. 2017; 5(10):816–26. Epub 2017/05/27. https://doi.org/10.1016/S2213-8587(17)30099-2 PMID: 28546095.
4. 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). Epub 2018/03/09. https://doi.org/10.1542/peds.2017-3742 PMID: 29514975.

5. 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):631–6. Epub 2018/04/14. https://doi.org/10.1136/archdischild-2018-314992 PMID: 29650510.

6. Turban JL, Ehrensaft D. Research Review: Gender identity in youth: treatment paradigms and controversies. J Child Psychol Psychiatry. 2018; 59(12):1228–43. Epub 2017/10/27. https://doi.org/10.1111/jcpp.12833 PMID: 29071722.

7. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013; 52(6):582–90. Epub 2013/05/25. https://doi.org/10.1016/j.jaac.2013.03.016 PMID: 23702447.

8. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017; 102(11):3869–903. Epub 2017/09/26. https://doi.org/10.1210/jc.2017-01658 PMID: 28945902.

9. Oliphant J, Veale J, Macdonald J, Carroll R, Johnson R, Harte M, 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. Epub 2018/12/14. PMID: 30543615.

10. 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):132–6. Epub 2018/06/16. https://doi.org/10.5694/mja17.01044 PMID: 29902964.

11. Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics. 2018; 142(4). Epub 2018/09/19. https://doi.org/10.1542/peds.2018-2162 PMID: 30224363.

12. 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. Hormone research in paediatrics. 2018; 90(5):326–31. Epub 2019/01/30. https://doi.org/10.1159/000496115 PMID: 30695784.

13. Agana MG, Greydanus DE, Indyk JA, Calles JL Jr., Kushner J, Leibowitz S, et al. Caring for the transgender adolescent and young adult: Current concepts of an evolving process in the 21st century. Dis Mon. 2019; 65(9):303–56. Epub 2019/08/14. https://doi.org/10.1016/j.disamonth.2019.07.004 PMID: 31405516.

14. 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):E270–5. Epub 2014/11/27. https://doi.org/10.1210/jc.2014-2439 PMID: 25427144.

15. 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):843–7. Epub 2011/04/20. https://doi.org/10.1007/s10508-011-9758-9 PMID: 21503817.

16. 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):1125–32. Epub 2016/06/19. https://doi.org/10.1016/j.jsxm.2016.05.004 PMID: 27318023.

17. 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). Epub 2020/03/30. https://doi.org/10.1542/peds.2019-3006 PMID: 32220906.

18. Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. International Journal of Pediatric Endocrinology. 2020; 2020(1):8. https://doi.org/10.1186/s13633-020-00078-2 PMID: 32368216

19. 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):2611–8. Epub 2020/03/11. https://doi.org/10.1007/s10508-020-01660-8 PMID: 32152785.

20. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009; 94(9):3132–54. Epub 2009/06/11. https://doi.org/10.1210/jc.2009-0345 PMID: 19509099.

21. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012; 129(3):418–25. Epub 2012/02/22. https://doi.org/10.1542/peds.2011-0907 PMID: 22351896.

22. Meyer WJ 3rd. Gender identity disorder: an emerging problem for pediatricians. Pediatrics. 2012; 129 (3):571–3. Epub 2012/02/22. https://doi.org/10.1542/peds.2011-3696 PMID: 22351880.

23. 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):578–81. Epub 2012/05/25. https://doi.org/10.5694/mja12.10222 PMID: 22621149.

24. 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):2276–83. Epub 2010/07/22. https://doi.org/10.1111/j.1743-6109.2010.01943.x PMID: 20646177.

25. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child. 1995; 73(1):25–9. https://doi.org/10.1136/adc.73.1.25 PMID: 7639544

26. Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. J Clin Endocrinol Metab. 2007; 92(6):2087–99. Epub 2007/02/22. https://doi.org/10.1210/jc.2006-2553 PMID: 17311856.

27. Zemel BS, Leonard MB, Kelly A, Lappe JM, Gilsanz V, Oberfield S, et al. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab. 2010; 95(3):1265–73. Epub 2010/01/28. https://doi.org/10.1210/jc.2009-2057 PMID: 20103654.

28. 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):1269–77. Epub 1997/09/18. https://doi.org/10.1097/00004583-199709000-00020 PMID: 9291729.

29. Verhulst FC, Achenbach TM, van der Ende J, Erol N, Lambert MC, Leung PW, et al. Comparisons of problems reported by youths from seven countries. Am J Psychiatry. 2003; 160(8):1479–85. Epub 2003/08/06. https://doi.org/10.1176/appi.ajp.160.8.1479 PMID: 12900311.

30. 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):513–20. Epub 2016/05/31. https://doi.org/10.1016/j.jaac.2016.04.001 PMID: 27238070.

31. Van Meter AR, Algorta GP, Youngstrom EA, Lechtman Y, Youngstrom JK, Feeny NC, et al. Assessing for suicidal behavior in youth using the Achenbach System of Empirically Based Assessment. Eur Child Adolesc Psychiatry. 2018; 27(2):159–69. Epub 2017/07/28. https://doi.org/10.1007/s00787-017-1030-y PMID: 28748484.

32. 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):431–42. Epub 2015/08/01. https://doi.org/10.1007/s00787-015-0745-x PMID: 26226917.

33. Ravens-Sieberer U, Gosch A, Rajmil L, Erhart M, Bruil J, Power M, et al. The KIDSCREEN-52 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Value Health. 2008; 11(4):645–58. Epub 2008/01/09. https://doi.org/10.1111/j.1524-4733.2007.00291.x PMID: 18179669.

34. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. Arch Sex Behav. 1975; 4 (6):639–56. Epub 1975/11/01. https://doi.org/10.1007/BF01544272 PMID: 1212093.

35. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983; 40(11):1228–31. Epub 1983/11/01. https://doi.org/10.1001/archpsyc.1983.01790100074010 PMID: 6639293.

36. Viner RM, Clark C, Taylor S, Bhui K, Klineberg E, Head J, et al. Risk factors for persistent fatigue in adolescents: A population-based study. Journal of Adolescent Health. 2006; 38(2):113–4. https://doi.org/10.1016/j.jadohealth.2005.11.080

37. Krogh AB, Larsson B, Linde M. Prevalence and disability of headache among Norwegian adolescents: A cross-sectional school-based study. Cephalalgia. 2015; 35(13):1181–91. Epub 2015/02/28. https://doi.org/10.1177/0333102415573512 PMID: 25720767.

38. 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. 2019. Epub 2019/12/14. https://doi.org/10.1515/jpem-2019-0045 PMID: 31834861.

39. 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; 95:11–9. Epub 2016/11/16. https://doi.org/10.1016/j.bone.2016.11.008 PMID: 27845262.

40. 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):1077–81. Epub 2019/09/01. https://doi.org/10.1515/jpem-2019-0046 PMID: 31472062.

41. Rothman MS, Iwamoto SJ. Bone Health in the Transgender Population. Clin Rev Bone Miner Metab. 2019; 17(2):77–85. Epub 2019/08/28. https://doi.org/10.1007/s12018-019-09261-3 PMID: 31452648.

42. Panagiotakopoulos L. Transgender medicine—puberty suppression. Rev Endocr Metab Disord. 2018; 19(3):221–5. Epub 2018/08/17. https://doi.org/10.1007/s11154-018-9457-0 PMID: 30112593.

43. Skagerberg E, Davidson S, Carmichael P. Internalizing and Externalizing Behaviors in a Group of Young People with Gender Dysphoria. Int J Transgenderism. 2013; 13(3):105–12. https://doi.org/10.1080/15532739.2013.822340

44. Zucker KJ. Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues. Arch Sex Behav. 2019; 48(7):1983–92. Epub 2019/07/20. https://doi.org/10.1007/s10508-019-01518-8 PMID: 31321594.

45. Zucker KJ, Bradley SJ, Owen-Anderson A, Kibblewhite SJ, Wood H, Singh D, et al. Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. J Sex Marital Ther. 2012; 38(2):151–89. Epub 2012/03/07. https://doi.org/10.1080/0092623X.2011.611219 PMID: 22390530.

46. Levitan N, Barkmann C, Richter-Appelt H, Schulte-Markwort M, Becker-Hebly I. Risk factors for psychological functioning in German adolescents with gender dysphoria: poor peer relations and general family functioning. Eur Child Adolesc Psychiatry. 2019; 28(11):1487–98. Epub 2019/03/17. https://doi.org/10.1007/s00787-019-01308-6 PMID: 30877477.

47. Becerra-Culqui TA, Liu Y, Nash R, Cromwell L, Flanders WD, Getahun D, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. Pediatrics. 2018; 141(5). Epub 2018/04/18. https://doi.org/10.1542/peds.2017-3845 PMID: 29661941.

48. Taliaferro LA, McMorris BJ, Rider GN, Eisenberg ME. Risk and Protective Factors for Self-Harm in a Population-Based Sample of Transgender Youth. Arch Suicide Res. 2019; 23(2):203–21. Epub 2018/02/21. https://doi.org/10.1080/13811118.2018.1430639 PMID: 29461934.

49. 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):2206–14. Epub 2015/11/12. https://doi.org/10.1111/jsm.13034 PMID: 26556015.

50. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics. 2020. Epub 2020/01/25. https://doi.org/10.1542/peds.2019-1725 PMID: 31974216.

51. Goedegebuure WJ, van der Steen M, de With JL, Hokken-Koelega A. Cognition, Health-Related Quality of Life, and Psychosocial Functioning After GH/GnRHa Treatment in Young Adults Born SGA. J Clin Endocrinol Metab. 2018; 103(11):3931–8. Epub 2018/08/24. https://doi.org/10.1210/jc.2018-01463 PMID: 30137415.

52. de Graaf NM, Cohen-Kettenis PT, Carmichael P, de Vries ALC, Dhondt K, Laridaen J, et al. Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: a clinical comparison study between four clinics. Eur Child Adolesc Psychiatry. 2018; 27(7):909–19. Epub 2017/12/20. https://doi.org/10.1007/s00787-017-1098-4 PMID: 29256158.

53. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatry. 2013; 70(3):300–10. Epub 2013/01/11. https://doi.org/10.1001/2013.jamapsychiatry.55 PMID: 23303463.

54. Jung KY, Kim T, Hwang SY, Lee TR, Yoon H, Shin TG, et al. Deliberate Self-harm among Young People Begins to Increase at the Very Early Age: a Nationwide Study. Journal of Korean medical science. 2018; 33(30):e191. Epub 2018/07/24. https://doi.org/10.3346/jkms.2018.33.e191 PMID: 30034304.

55. Morey Y, Mellon D, Dailami N, Verne J, Tapp A. Adolescent self-harm in the community: an update on prevalence using a self-report survey of adolescents aged 13–18 in England. J Public Health (Oxf). 2017; 39(1):58–64. Epub 2016/02/20. https://doi.org/10.1093/pubmed/fdw010 PMID: 26892623.

56. Stallard P, Spears M, Montgomery AA, Phillips R, Sayal K. Self-harm in young adolescents (12–16 years): onset and short-term continuation in a community sample. BMC psychiatry. 2013; 13:328. Epub 2013/12/04. https://doi.org/10.1186/1471-244X-13-328 PMID: 24294921.

57. Becker I, Auer M, Barkmann C, Fuss J, Moller B, Nieder TO, 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):2335–47. Epub 2018/08/09. https://doi.org/10.1007/s10508-018-1278-4 PMID: 30088234.

58. Biggs M. Gender Dysphoria and Psychological Functioning in Adolescents Treated with GnRHa: Comparing Dutch and English Prospective Studies. Arch Sex Behav. 2020; 49(7):2231–6. Epub 2020/07/01. https://doi.org/10.1007/s10508-020-01764-1 PMID: 32594279.

59. Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006; 174 (5):645–6. Epub 2006/03/01. https://doi.org/10.1503/cmaj.051484 PMID: 16505461.

60. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane database of systematic reviews. 2014;(4):MR000034. Epub 2014/05/02. https://doi.org/10.1002/14651858.MR000034.pub2 PMID: 24782322.

61. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med. 2011; 8(5): e1001026. Epub 2011/05/12. https://doi.org/10.1371/journal.pmed.1001026 PMID: 21559325.

62. Olson-Kennedy J, Chan YM, Rosenthal S, Hidalgo MA, Chen D, Clark L, et al. Creating the Trans Youth Research Network: A Collaborative Research Endeavor. Transgend Health. 2019; 4(1):304–12. Epub 2019/11/09. https://doi.org/10.1089/trgh.2019.0024 PMID: 31701011.

63. Olson J, Chan Y-M, Garofalo R, Spack NP, Chen D, Clark L, 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. https://doi.org/10.2196/14434 PMID: 31290407

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Invited Commentary | Pediatrics

Pubertal Blockade and Subsequent Gender-Affirming Therapy

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For youth who identify as transgender or are unsure and wish to explore possibilities before the development of permanent secondary sex characteristics, use of a gonadotropin-releasing hormone analogue (GnRHa) is a key medical option. Sometimes colloquially called "puberty blockers," they have been used safely for decades in children with precocious puberty[1] and endometriosis,[2] among other medical indications. Multiple professional societies now endorse pubertal blockade for youth with gender dysphoria.[3,4] Recently, the use of GnRHa has received attention because of legislated concerns regarding the medical and surgical treatment of transgender youth, including criminalizing the provision of this care in some states.[5] Without evidence, the assumption has been made that GnRHa treatment leads to increased ultimate use of gender-affirming therapy (GAT) in transgender youth and that prescription of a GnRHa inappropriately advances the decision to start GAT. The article by Nos et al[6] provides data to the contrary—that this therapy can be offered both for mental health and cosmetic benefits without the concern of increasing the subsequent use of GAT.

An understanding of the medical management of a transgender child or adolescent is needed to appreciate the issues at hand.[3,4,7] A GnRHa is more potent than native GnRH and produces initial stimulation of pituitary gonadotrophs, with increased secretion of follicle-stimulating hormone, luteinizing hormone, and gonadal hormones, followed by downregulation of the pituitary-gonadal axis. As sex steroid secretion is inhibited, the development of pubertal changes ceases. Pubertal blockade with a GnRHa buys time for a child or adolescent, pausing puberty and allowing for the exploration of gender identity. Initiated early in puberty, the GnRHa delays the development of irreversible pubertal changes and, in some cases, eliminates the need for subsequent surgery. GnRHa therapy is reversable; discontinuation leads to prompt resumption of the pituitary-gonadal axis. Although pubertal blockade and GAT are often prescribed as complementary approaches, they are separate phases in transgender treatment.[3]

Through a retrospective cohort study of billing and pharmacy records, Nos and colleagues[6] explored the timely question of whether GnRHa use was associated with subsequent use of GAT among transgender and gender-diverse adolescents. They reviewed data between 2009 and 2018 from the US Military Healthcare System. Participants had at least 2 transgender-related encounters, with the first occurring between ages 10 and 17 years, and at least 1 encounter after the participant's 14th birthday (the earliest a clinician would start GAT according to current guidelines).[3,4,7] The sample included 434 adolescents, with 71.9% assigned female at birth and 69.1% having an enlisted insurance sponsor. Younger patients (aged 10-13 years) were more likely to start GnRHa therapy than older (aged 14-17 years) patients: 57.1% vs 10.1%. Patients who were assigned male at birth were more likely to receive GnRHa than those assigned female but were not more likely to be prescribed gender-affirming hormones. In fact, patients who were prescribed GnRHa were less likely to start GAT within 6 years of the first encounter than those who were not (hazard ratio, 0.52; 95% CI, 0.37-0.71). For clinicians, the salient point is that the prescription of a GnRHa did not imply the ensured subsequent use of GAT. The findings suggest that clinicians can offer GnRHa therapy without the concern of influencing the future use of GAT. The decision to initiate GnRHa therapy represents an independent therapeutic decision for a clinician, ideally working in concert with a multidisciplinary team of both medical and mental health clinicians.[5]

Limitations of the study of Nos and colleagues[6] merit discussion. They included younger children compared with earlier studies, which is a strength of the study, but as younger age was associated with higher GnRHa discontinuation rates, this could explain the finding. However, overall,

few patients discontinued treatment. Data were also extracted from an administrative database that did not afford information on the reasons why a clinician initiated therapy or not, and why patients chose to continue or discontinue the treatment. Patients could have obtained prescriptions outside of the Military Healthcare System that were not captured. However, the high costs out of pocket or through private insurance make this possibility unlikely. Lack of official approval for GAT coverage before 2016 may have influenced the decisions of patients or clinicians. Finally, there may be inherent biases among military medical personnel regarding gender identity and potential reluctance to provide treatment. The reasons could be personal ones or related to a lack of expertise. Replication of these results in a different study setting will be important to expand the generalizability of the current findings.

A question that arises in the course of transgender care is whether GnRHa therapy has long-term adverse medical consequences, including effects on bone health. More than one-half of an individual's bone density is acquired during adolescence, and transgender youth assigned male at birth are known to be at higher risk for low bone density even before GnRHa therapy.[7] Understanding whether GnRHa use is associated with fracture risk will be the critical long-term question that must be answered in future studies. In pediatrics, we are often left needing to weigh risks vs benefits, with limited available evidence, and needing to prescribe medications off-label. For the adolescent who goes on to receive GAT, theoretically and anecdotally, reintroduction of sex steroids appears to mediate skeletal gains, especially for transgender male individuals. In considering bone health and other health outcomes, optimizing bone density must be balanced with the known benefits of GnRHa for gender dysphoria, including decreased suicidal ideation.[6] Concerns about skeletal losses become less significant in an adolescent with active suicidal ideations. Although the significance of the risks may be unclear, there is strong evidence regarding the benefits of GnRHa in transgender youth: it can be a life-changing and lifesaving treatment for a vulnerable population who is at high risk for anxiety, depression, and suicide.[4,5,7]

The treatment decisions for transgender youth can be complex, with many factors that need to be considered. The novel findings provided by the study of Nos and colleagues[6] add to the growing body of work demonstrating that GnRHa therapy is a safe and necessary component of transgender care, especially for children or adolescents with gender dysphoria. Their results emphasize that use of GnRHa and subsequent GAT are different phases of treatment, and their use should be guided by independent decisions that a clinician makes separately. From a cosmetic standpoint, it is much easier to treat a patient if pubertal changes have only just begun to develop, and gender dysphoria subsides as the worry of continued development of secondary sex characteristics comes to a halt. We hope that an enhanced understanding of transgender medical management, including the separate phases of therapy, and how a GnRHa works therapeutically, will help to dispel myths. The study by Nos and colleagues[6] is hopefully one step forward in that direction. One phase of transgender treatment does not and should not dictate the next phase, thereby enabling clinicians to individualize care. Perhaps, even moving away from the term "puberty blocker" and instead describing mechanistically and clinically how these agents work will help return the focus of gender care to what matters most: the health and wellness of the child or adolescent.

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REFERENCES

1. Magiakou MA, Manousaki D, Papadaki M, et al. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab*. 2010;95(1):109-117. doi:10.1210/jc.2009-0793

2. Gallagher JS, Missmer SA, Hornstein MD, Laufer MR, Gordon CM, DiVasta AD. Long-term effects of gonadotropin-releasing hormone agonists and add-back in adolescent endometriosis. *J Pediatr Adolesc Gynecol*. 2018;31(4):376-381. doi:10.1016/j.jpag.2018.03.004

3. 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

4. Rafferty J; Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*. 2018;142(4):e20182162. doi:10.1542/peds.2018-2162

5. Kremen J, Williams C, Barrera EP, et al; Gender Multispecialty Service (GeMS) Team. Addressing legislation that restricts access to care for transgender youth. *Pediatrics*. 2021;147(5):e2021049940. doi:10.1542/peds.2021-049940

6. 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

7. Bachrach LK, Gordon CM. Bone health among transgender youth: what is a clinician to do? *Pediatrics*. 2021;148(4):e2021051137. doi:10.1542/peds.2021-051137

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Physiologic and metabolic characteristics of a cohort of transgender and gender-diverse youth in the United States

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Abstract

Purpose: The purpose of this study is to describe baseline physical and laboratory characteristics of participants in the largest prospective study of transgender and gender-diverse (TGD) youth in the United States.

Methods: Participants were recruited from four clinics which specialize in the care of TGD youth prior to starting either GnRH analogs for pubertal suppression or gender-affirming hormone treatment. Anthropometric and laboratory measurements were abstracted from the medical chart. Baseline characteristics including height, weight, BMI, blood pressure, and laboratory measurements were compared to age-matched National Health and Nutritional Examination Survey (NHANES) comparison group.

Results: Seventy-eight TGD youth with an median age of 11 years (range 8–14 years) were recruited prior to pubertal suppression, of whom 41 (53%) were designated male at birth, and 296 participants with an median age of 16 years (range 12–20 years) were recruited prior to beginning gender-affirming hormones, of whom 99 (33%) were designated male at birth. The mean HDL-C was lower in study participants when compared to NHANES participants (50.6 ± 12.3 mg/dL vs. 53.3 ± 13.3 mg/dL, p = 0.001). Otherwise, the study cohorts were similar in terms of BMI, proportion of overweight and obesity, blood pressure, and baseline laboratory variables.

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Conclusions: Prior to starting gender-affirming treatment, TGD youth are physiologically similar to the general population of children and adolescents in the United States, with the exception of slightly lower HDL-C. Evaluation of this cohort over time will define the physiological effects of pubertal blockade and gender-affirming hormone treatment.

Implications and Contributions: This study describes the baseline metabolic and physiologic characteristics of a large multi-site cohort of transgender and gender-diverse (TGD) youth in the United States. TGD youth had lower HDL-C than the general United States population but were otherwise similar in terms of their anthropometric, metabolic, and physiologic parameters.

Keywords

Transgender; gender-diverse; adolescent; transgender health; gender-affirming hormones

INTRODUCTION

Increasing numbers of transgender/gender-diverse (TGD) youth, individuals whose gender identity does not align with their sex designated at birth, are seeking medical care in the United States.[1] Despite these increasing numbers, there is a paucity of data detailing the risks and benefits of gender-affirming medical treatments, and current guidelines are based primarily on expert opinion.[2,3] Gender-affirming medical care for transgender youth includes gonadotropin-releasing hormone analog (GnRHa) treatment for those in early puberty to halt the further development of secondary sex characteristics discordant with the youth's identified gender, as well as initiation of gender-affirming hormone (GAH) treatment (i.e., estrogen in transfeminine individuals and testosterone in transmasculine individuals) to induce secondary sex characteristics consistent with the youth's affirmed gender.

Sex steroids are believed to have a significant effect on cardiovascular health, and cardiovascular disease (CVD) is more common in cisgender men than cisgender women.[4] There is greater cardiovascular morbidity among transgender adults, with an increased risk of myocardial infarction in both transgender women and transgender men compared to cisgender women.[5,6] However, it is unclear if TGD youth carry increased risk for CVD at baseline, or if cardiovascular morbidity can be attributed to GAH treatment.

Anthropometric and metabolic features are potentially modifiable risk factors for CVD, and changes in these factors have been described in adults treated with GAH. Individuals treated with testosterone have metabolic changes associated with an increased risk of CVD including increased hemoglobin levels, systolic blood pressure and low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C). Individuals treated with combined estrogen and antiandrogens have decreased hemoglobin levels, which are also associated with an increased risk of CVD. Both transwomen and transmen on GAH treatment have higher triglyceride levels, which are associated with an increased risk of CVD. [7,8]

While anthropometric and metabolic changes have been described with GAH treatment in adults, it is unclear if TGD youth have metabolic risk factors at baseline prior to initiating

GnRHa or GAH treatment. For example, transgender men have been reported to have an increased prevalence of polycystic ovary syndrome (PCOS), a condition associated with risk factors such as obesity and dyslipidemia.[9–11] Available studies describing the characteristics of transgender youth in the United States have been small, have focused on older adolescents, and have primarily examined self-reported physical and mental health.[12–14] The few studies exploring metabolic characteristics of adolescent gender-affirming care were conducted in European centers that rarely initiate GAH treatment prior to age 16 years and treat a population that is neither ethnically nor racially representative of the United States.[15–17] There are currently no large published studies describing the anthropometric and metabolic characteristics of this population in the US.

The Trans-Youth Care (TYC) Study is an observational multi-site study among four academic medical centers with multidisciplinary clinics dedicated to serving TGD youth: Children's Hospital Los Angeles/University of Southern California, Boston Children's Hospital/Harvard Medical School, the Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University, and the Benioff Children's Hospital/University of California San Francisco.[18]

Here we present the baseline anthropometric and metabolic characteristics of participants in the Trans-Youth Care Study, the largest study of transgender and gender diverse youth in the United States.

METHODS

The TYC Study is a multi-site, longitudinal, observational study of gender-affirming medical care of TGD children and adolescents in the United States. The research protocol was approved by the Institutional Review Boards at all study sites. A full description of the study protocol is published for reference.[18] Briefly, TGD youth seeking treatment for gender dysphoria between July 2016 and September 2018 were recruited into one of two cohorts based on their intent to initiate GnRHa or GAH treatment. Participants were excluded if they could not read or understand English, had serious psychiatric symptoms, or were otherwise unable to provide informed consent or complete the study activities. Participants in the GnRHa and GAH cohorts completed questionnaires evaluating their mental health, psychosocial functioning, and gender identity. Ferriman-Gallwey scores were collected via participant self-report. Anthropometric, physiologic, and laboratory data were collected as part of the routine medical care of the participant and abstracted from the medical record. For the analyses in this report, data from the GnRHa cohort were restricted to participants who were in early puberty (Tanner Stages II and III), and data from the GAH cohort were restricted to those were in mid- to late puberty (Tanner Stages III, IV, V) unless they had prior GnRHa exposure.

Z-scores and percentiles were determined based on the Centers for Disease Control (CDC) growth data for the participants sex designated at birth.[19] Using United States census data, participants' ZIP codes were matched to average median household median incomes.[20] To provide a comparison group, 2015–2016 data from the National Health and Nutrition

Examination Survey (NHANES) were used to create cohorts of participants in the same age range as the study cohorts.[21]

Mean and standard deviation were used to summarize normally distributed variables, median and range were used to summarize non-normally distributed variables, and comparisons were made via Student's t-test and the Mann-Whitney test, respectively. Race, sex designated at birth, and estimated household income as derived by ZIP code (see above) were used as covariates. Pearson's r was used to assess linear correlations, and regression was utilized to adjust for covariates. Proportions were compared using Fisher's exact test. A p value of < 0.05 was considered significant, with no adjustment for multiple testing for this descriptive analysis. Stata Statistical Software: Release 16 (College Station, TX) was used for calculations.

RESULTS

GnRHa Cohort

Demographics—Seventy-eight TGD participants who were Tanner Stage II or III, of whom 41 (53%) were designated male at birth and 37 (47%) were designated female at birth, were included in the analysis (Table 1). Fourteen participants who were recruited prior to starting GnRH analogs for pubertal suppression were in late puberty or post-puberty (i.e., Tanner Stage IV or V) and were excluded from this analysis (Figure 1). The median age was 10 years (range 8–13 years) for participants designated female at birth and 11 years (range 9–14 years) for participants designated male at birth.

Of the participants who were designated male at birth, 18 (43%) identified as female, 20 (49%) identified as transgender female, two (5%) identified as gender fluid, and one (2%) identified as non-binary. Of the participants who were designated female at birth, 20 participants (54%) identified as male, 15 (41%) as transgender male, and 2 (5%) as non-binary. There was no difference in racial/ethnic makeup between birth-designated male and birth-designated female participants. There were a greater proportion of TYC participants who were white compared to the NHANES comparison group (57% vs. 34% , $p < 0.0001$), and there were a smaller proportion of participants with estimated household income < $55,000 (17% vs. 56%, $p < 0.0001$); there was no difference between those designated male and female at birth.

Anthropometric Measurements—There was no difference in mean height, weight, or BMI Z-scores (calculated for birth-designated sex), for blood pressure, or for the prevalence of obesity between participants designated female and male at birth (Table 2). For birth-designated males, there was a significant decrease in height Z-score with increasing participant age (Supplemental Figure 1). Otherwise there was no correlation between participant age and height, weight, or BMI Z-score.

When compared to the NHANES comparison group there was no difference in mean height, height Z-score, weight, or weight Z-score. The participants in the GnRHa cohort did have slightly lower mean BMI Z-scores (0.36 ± 1.06 vs. 0.64 ± 1.11) and a smaller proportion of participants who were classified as obese than the NHANES comparison group (6% vs.

17%), but these differences were not significant once controlled for race and estimated household income (p = 0.5 and 0.2, respectively) (Supplemental Figure 3).

The GnRHa participants had higher systolic and diastolic blood pressure measurements than the NHANES age-matched controls (111 ± 11 mmHg vs. 104 ± 9 mmHg, p < 0.001; 63 ± 8 mmHg vs. 54 ± 9 mmHg, p < 0.001 when controlled for sex designated as birth, race, and estimated household income), and there were a greater proportion who would be classified as hypertensive based on systolic blood pressure measurement (12% vs. 3%, p = 0.002).

Gender-Affirming Hormone Cohort

Demographics—One participant recruited prior to starting GAH was in early puberty (Tanner II) and was excluded, leaving two hundred and ninety-six participants for analysis in this cohort(Figure 1); 99 (33%) were designated male at birth, and 197 (67%) were designated female at birth (Table 1). Of these, thirteen (4%) designated male participants and seven (2%) designated female participants had previously used a GnRHa for pubertal blockade. The median age of participants was 16 years (range 12–20 years) and similar to those designated male and female at birth. Of the participants who were designated male at birth, 44 (44%) identified as female, 50 (50%) identified as transgender female, 1 (1%) identified as gender queer, and 3 (3%) identified as non-binary. Of the participants who were designated female at birth, 82 participants (42%) identified as male, 103 (53%) as transgender male, 2 (1%) identified as gender fluid, 1 (0.5%) as gender queer, and 9 (5%) as non-binary. The racial and ethnic distribution was similar between both designated-sex groups.

Similar to the GnRHa cohort, the GAH cohort had a greater proportion of participants who were white when compared to NHANES (63% vs. 36%, p < 0.0001) and a smaller proportion of participants with estimated household income < $55,000 (21% vs. 58%, p < 0.001). The rate of current tobacco use (defined as daily, weekly, or monthly use in the past three months) was 9% in the GAH cohort, similar to the published rate for 8^{th}, 10^{th}, and 12^{th} grade students (5.4%, p = 0.4).[22]

Anthropometric Measurements—For the analysis of anthropometric measurements, GAH cohort participants who had previously used GnRHa were excluded. With these participants excluded, there was no difference in height Z-score between those designated male and those designated female at birth (Table 2); however when compared to the NHANES age-matched comparison group TGD participants who were designated female at birth were taller (height Z-score 0.15 ± 1.03 vs. −0.17 ± 1.08, p = 0.006 when controlled for race and estimated household income).

There was a difference in weight and BMI Z-scores between designated sex groups, with those designated female at birth having significantly higher weight Z-score and BMI Z-score than those designated male at birth (0.78 ± 1.05 vs 0.42 ± 1.25, p = 0.013; 0.74 ± 1.07 vs. 0.34 ± 1.26, p = 0.02, respectively). The majority of participants had BMIs in the normal weight category (56%); 24% were overweight and 18% were obese. This distribution was not different between participants designated female and male at birth (p = 0.5).

Participants who were designated male at birth had higher BMI Z-scores (0.34 ± 1.26 vs. −0.23 ± 0.44) than the NHANES comparison group ($p < 0.001$ controlled for race and estimated household income). Those designated female at birth had weight and BMI Z-scores comparable to those of the NHANES comparison group ($p = 0.6$ and $p = 0.7$ respectively). Despite the difference in BMI Z-scores in those designated male at birth, the distribution of obesity categories of the TGD participants was similar to those in the NHANES cohort, with the majority classified as normal weight (62%), 25% overweight, and 12% obese ($p = 0.4$) (Supplemental Figure 3).

As was seen in the GnRHa cohort, the mean systolic and diastolic blood pressures were higher in the TGD participants than in the NHANES group, (116 ± 11 mmHg vs. 111 ± 10 mmHg, $p < 0.001$; 65 ± 9 mmHg vs. 61 ± 11 mmHg, $p < 0.001$) when controlled for sex designated at birth, race, and estimated household income. Likewise, there was a greater proportion of TGD participants with systolic (9% vs. 3%, $p < 0.001$) and diastolic (3% vs. 0.5%, $p = 0.001$) blood pressure in the hypertensive range. There was no difference in the proportion of participants with blood pressure in the hypertensive range between designated males and designated females.

Laboratory Measurements—Participants with prior GnRHa exposure and one participant with a known diagnosis of type 1 diabetes mellitus were excluded from analysis of laboratory values. There have been reports of increased prevalence of hyperandrogenemia and polycystic ovarian syndrome (PCOS) in TGD youth designated female at birth. [9–11] For that reason we examined baseline levels of free testosterone as well as hirsutism as assessed by Ferriman-Gallwey scores in transmasculine youth. Although the majority of the participants designated female at birth had free testosterone levels in the normal range, there were seven participants (4%) who had free testosterone levels higher than the upper limit of normal for an adult female. There were six (4%) participants who had Ferriman-Gallwey scores indicating moderate to severe hirsutism (> 15) (Supplemental Figure 2). There was no significant relationship between free testosterone level and Ferriman-Gallwey score ($p = 0.4$). Testosterone, estradiol, and prolactin measurements were in the normal range for sex designated at birth and Tanner Stage.

Given reports of poor cardiovascular outcomes in transgender adults, we examined baseline markers of cardiovascular risk such as lipid measurements. TGD participants had levels of total and LDL-C that were similar to NHANES values (Figure 2). The proportion of participants with total cholesterol or LDL-C in the ‘poor’ range (> 200 mg/dL or >130 mg/dL, respectively) were similar across birth sex and when compared to the NHANES cohort.

In contrast, TGD participants did have significantly lower HDL-C compared to NHANES participants when controlled for BMI, race, sex designated at birth, and estimated household income (50.6 ± 12.3 mg/dL vs. 53.3 ± 13.3 mg/dL, $p = 0.001$) (Table 3 and Figure 2). Similarly, there was a significantly higher proportion of participants with HDL cholesterol less than 40 mg/dL (19%), a level deemed ‘poor’ by the National Heart, Lung, and Blood Institute[23], as compared to age matched NHANES participants (13%, $p = 0.03$). However, when comparing subgroups based on sex designated at birth, only those designated female at

birth had a higher a proportion of low HDL-C than their NHANES counterparts (designated male 28% vs. 19%, p = 0.1; designated female 15% vs. 7%, p = 0.005). There was no significant difference between the lipid measurements of participants who indicated that they currently used tobacco products and those who did not indicate current tobacco use.

The majority of participants had hemoglobin A1c (HgbA1c) in the normal range, although there were 8 participants (6%) with HgbA1c in the pre-diabetes range (5.7–6.4%) and two participants (1%) with HgbA1c in the diabetic range (> 6.4%); this was not statistically different than the NHANES comparison group (p = 0.05)

DISCUSSION

The TYC study is the largest prospective study of gender-affirming medical treatments in the United States. Here we present a baseline description of laboratory and physiologic findings for two cohorts of transgender youth recruited for this longitudinal observational study; one prior to initiating GnRHa for pubertal blockade and a second prior to initiating gender-affirming sex-steroid treatment.

There have been several recent reports of increased cardiovascular risk in transgender adults and negative changes in LDL-C and HDL-C with testosterone therapy in transgender adults.[8,24–26] We found that, even prior to starting hormonal treatments, HDL-C was lower in our cohort of TGD participants compared to NHANES comparison group; this difference was not attributable to differences in BMI, race, or socioeconomic status as estimated by household income by ZIP code. HDL-C is an important marker of cardiovascular risk, and increasing HDL-C is considered an important step in reducing the risk of poor metabolic and cardiovascular outcomes later in life.[28,29] In a meta-analysis of studies of adult cisgender individuals, a 1 mg/dL increase in HDL-C was associated with a 2–3% decreased in cardiovascular risk.[30] Thus, the difference between TGD and NHANES individuals of 2.7 mg/dL represents a 5–8% increase in cardiovascular risk in the TGD population. Low HDL-C levels are associated with tobacco use, obesity, and low rates of exercise.[27] The rate of tobacco use in our cohort was similar to rates in U.S. adolescents and there was no difference in lipid measurements between those who indicated they had used tobacco and those who did not.

Increasing physical activity has been shown to improve HDL-C [31], and transgender adolescents have lower self-reported physical activity as compared to their cis-gender peers, likely secondary to a more negative perception of their body and lack of supportive environments and opportunities (i.e., gyms, teams, etc.).[32,33] Further research is required to investigate if lower levels of physical activity lead to lower HDL-C in this group; however, those adolescents presenting for gender affirming care with unfavorable HDL-C at baseline should be counseled to increase physical activity in an effort to mitigate the risk presented by low HDL-C.

There have been anecdotal reports of increased BMI amongst transmasculine individuals in an effort to conceal female-associated fat distribution.[34] However, our data suggest that this is not a widespread phenomenon, as we found no difference in BMI Z-score or the

proportion of overweight and obese individuals for transmasculine TYC participants when compared to the NHANES comparison group for either the GnRHa or GAH cohort. Likewise, there have been concerns that transfeminine individuals may strive for a lower BMI in pursuit of a more stereotypically feminine physique.[34–36] However, we did not find any difference between BMI Z-score or percentage of transfeminine participants classified as underweight in the blocker cohort compared to the NHANES controls, and in fact, the transfeminine participants in the GAH cohort had slightly higher, not lower, BMI Z-scores than the NHANES controls.

The negative correlation observed between height Z-score and age for birth-designated male participants in the GnRHa cohort is an expected consequence of recruiting individuals by pubertal stage. Participants who remain in early puberty (Tanner II or III) at older ages will be relatively shorter than their peers who have already experienced a pubertal growth spurt.

Both systolic and diastolic blood pressure measurements were higher than NHANES measurements in both cohorts and both sex designated at birth groups. We suspect that this systematic difference may not represent a true difference between TGD youth and the general population, but rather is secondary to different methodologies and environments between clinic measurements captured by the TYC study and those utilized by the NHANES study.[37] For example, the typical “white-coat hypertension” of a clinic visit may be further enhanced by the stress of anticipating a sensitive discussion of gender identity.

There has been suggestion of a link between masculine gender identity and exposure to androgens, supported by reports of an increased prevalence of PCOS and elevated androgen levels amongst transgender men.[9–11] A more recent report using contemporary criteria for PCOS did not find an increased prevalence of PCOS in transgender men, but there was an increased incidence of biochemical hyperandrogenism.[38] In our cohort of transmasculine participants studied prior to GAH, 4% had an elevated free testosterone level greater than the upper limit of normal for a female. Although not sufficient for a diagnosis of PCOS, this result is similar to prevalence data for PCOS amongst women of reproductive age in the United States in general.[38] Thus, our data do not suggest an increased prevalence of PCOS in transmasculine youth.

The data here represent a baseline description of a diverse sample of TGD youth recruited from four geographically diverse sites in the United States. The sites are all large, urban, university-based referral centers, and thus our study fails to capture TGD individuals who access medical care at rural or community sites or those who are unable to access gender-affirming care. The bias introduced by recruitment from urban centers and by participation in a research study in general resulted in a higher average socioeconomic status and greater predominance of white participants than the general US population. Although this was controlled for in the analysis presented here, it may affect the generalizability of results.

CONCLUSION

TGD children and adolescents recruited for the TYC study had lower HDL-C than the general United States population but otherwise are similar in terms of their anthropometric,

metabolic, and physiologic parameters. More research is needed to identify additional factors that may explain lower HDL-C in TGD youth. Counseling regarding optimizing modifiable risk factors to improve cardiovascular outcomes such as smoking cessation and improvement in physical activity levels should be offered to youth who enter medical gender transition with an unfavorable HDL-C. Forthcoming data on this cohort as they embark on gender-affirming treatment will be valuable in guiding practitioners caring for this population with much-needed information on the outcome of currently used medical treatments on anthropometric measurements and metabolic outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

TGD	Transgender/gender-diverse
GnRHa	Gonadotropin-releasing hormone analog
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
GAH	Gender-affirming hormones
NHANES	National Health and Nutritional Examination Survey
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol

REFERENCES

[1]. Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and Adolescents With Gender Identity Disorder Referred to a Pediatric Medical Center. Pediatrics 2012;129:418–25. [PubMed: 22351896]

[2]. Hembree WC, Cohen-Kettenis PT, Gooren LJ, et al. Endocrine Treatment of Gendersphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102:3869–903. [PubMed: 28945902]

[3]. Reisner SL, Deutsch MB, Bhasin S, et al. Advancing Methods for U.S. Transgender Health Research. Curr Opin Endocrinol Diabetes Obes 2016;23:198–207. [PubMed: 26845331]

[4]. Wada H, Miyauchi K, Daida H. Gender differences in the clinical features and outcomes of patients with coronary artery disease. Expert Rev Cardiovasc Ther 2019;17:127–33. [PubMed: 30569774]

[5]. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: A case-control study. Eur J Endocrinol 2013;169:471–8. [PubMed: 23904280]

[6]. Nota NM, Wiepjes CM, de Blok CJM, et al. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation 2019;139:1461–2. [PubMed: 30776252]

[7]. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2017;102:3914–23. [PubMed: 28945852]

[8]. Irwig MS. Cardiovascular health in transgender people. Rev Endocr Metab Disord 2018;19:1–9. [PubMed: 30101364]

[9]. Balen AH, Schachter ME, Montgomery D, et al. Polycystic ovaries are a common finding in untreated female to male transsexuals. Clin Endocrinol (Oxf) 1993;38:325–9. [PubMed: 8458105]

[10]. Futterweit W, Weiss RA, Fagerstrom RM. Endocrine evaluation of forty female-to-male transsexuals: Increased frequency of polycystic ovarian disease in female transsexualism. Arch Sex Behav 1986;15:69–78. [PubMed: 3964071]

[11]. Bosinski HAG, Peter M, Bonatz G, et al. A higher rate of hyperandrogenic disorders in female-to-male transsexuals. Psychoneuroendocrinology 1997;22:361–80. [PubMed: 9279941]

[12]. Rider GN, McMorris BJ, Gower AL, et al. Health and Care Utilization of Transgender and Gender Nonconforming Youth: A Population-Based Study. Pediatrics 2018;141:e20171683. [PubMed: 29437861]

[13]. Olson J, Schrager SM, Belzer M, et al. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. J Adolesc Heal 2015;57:374–80.

[14]. Jarin J, Pine-Twaddell E, Trotman G, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 2017;139:e20163173. [PubMed: 28557738]

[15]. 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;15:251–60. [PubMed: 29425666]

[16]. Tack LJW, Heyse R, Craen M, et al. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. J Sex Med 2017;14:747–57. [PubMed: 28499525]

[17]. Tack LJW, Craen M, Lapauw B, et al. Pro- and Anti-androgenic Progestins in Transgender Youth: Differential Effects on Body Composition and Bone Metabolism. J Clin Endocrinol Metab 2018;103:2147–56. [PubMed: 29672753]

[18]. Olson-Kennedy J, Chan Y-M, Garofalo R, et al. The Impact of Early Medical Treatment in Transgender Youth: The Trans Youth Care Study (Preprint). JMIR Res Protoc 2019.

[19]. CDC Growth Charts. United States. 2000.

[20]. Household Income in the Past 12 Months 2017.

[21]. National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2015.

[22]. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future: National survey results on drug use 1975–2018. 2018 Overview: Key findings on adolescent drug use. Natl Inst Drug Abus Natl Institutes Heal 2019:1–104.

[23]. Daniels SR, Benuck I, Christakis D, et al. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. vol. NIH Public. 2012.

[24]. Elamin MB, Garcia MZ, Murad MH, et al. Effect of sex steroid use on cardiovascular risk in transsexual individuals: A systematic review and meta-analyses. Clin Endocrinol (Oxf) 2010;72:1–10. [PubMed: 19473174]

[25]. Chew D, Anderson J, Williams K, et al. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 2018;141:e20173742. [PubMed: 29514975]

[26]. Getahun D, Nash R, Flanders WD, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: A cohort study. Ann Intern Med 2018;169:205–13. [PubMed: 29987313]

[27]. Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: A consensus statement from the National Lipid Association. J Clin Lipidol 2013;7:484–525. [PubMed: 24079290]

[28]. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122:198–208. [PubMed: 18596007]

[29]. Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet 2014;384:618–25. [PubMed: 25131981]

[30]. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8–15. [PubMed: 2642759]

[31]. Strong WB, Malina RM, Blimkie CJR, et al. Evidence based physical activity for school-age youth. J Pediatr 2005;146:732–7. [PubMed: 15973308]

[32]. Muchicko MM, Lepp A, Barkley JE. Peer victimization, social support and leisure-time physical activity in transgender and cisgender individuals. Leis Loisir 2014;38:295–308.

[33]. Jones BA, Arcelus J, Bouman WP, et al. Sport and Transgender People: A Systematic Review of the Literature Relating to Sport Participation and Competitive Sport Policies. Sport Med 2017;47:701–16.

[34]. Ålgars M, Alanko K, Santtila P, et al. Disordered eating and gender identity disorder: A qualitative study. Eat Disord 2012;20:300–11. [PubMed: 22703571]

[35]. Jones BA, Haycraft E, Murjan S, et al. Body dissatisfaction and disordered eating in trans people: A systematic review of the literature. Int Rev Psychiatry 2016;28:81–94. [PubMed: 26618239]

[36]. McClain Z, Peebles R. Body Image and Eating Disorders Among Lesbian, Gay, Bisexual, and Transgender Youth. Pediatr Clin North Am 2016;63:1079–90. [PubMed: 27865334]

[37]. Center for Disease Control & Prevention. NHANES 2015–2016 Anthropometry Procedures Manual. 2016.

[38]. Mueller A, Gooren LJ, Naton-Schötz S, et al. Prevalence of polycystic ovary syndrome and hyperandrogenemia in female-to-male transsexuals. J Clin Endocrinol Metab 2008;93:1408–11. [PubMed: 18211977]

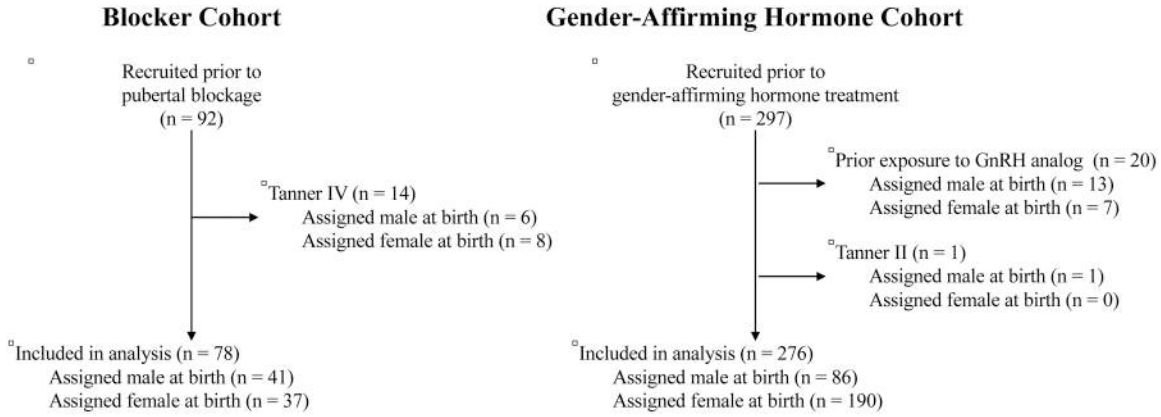

Figure 1.
Flowsheet of subject selection.

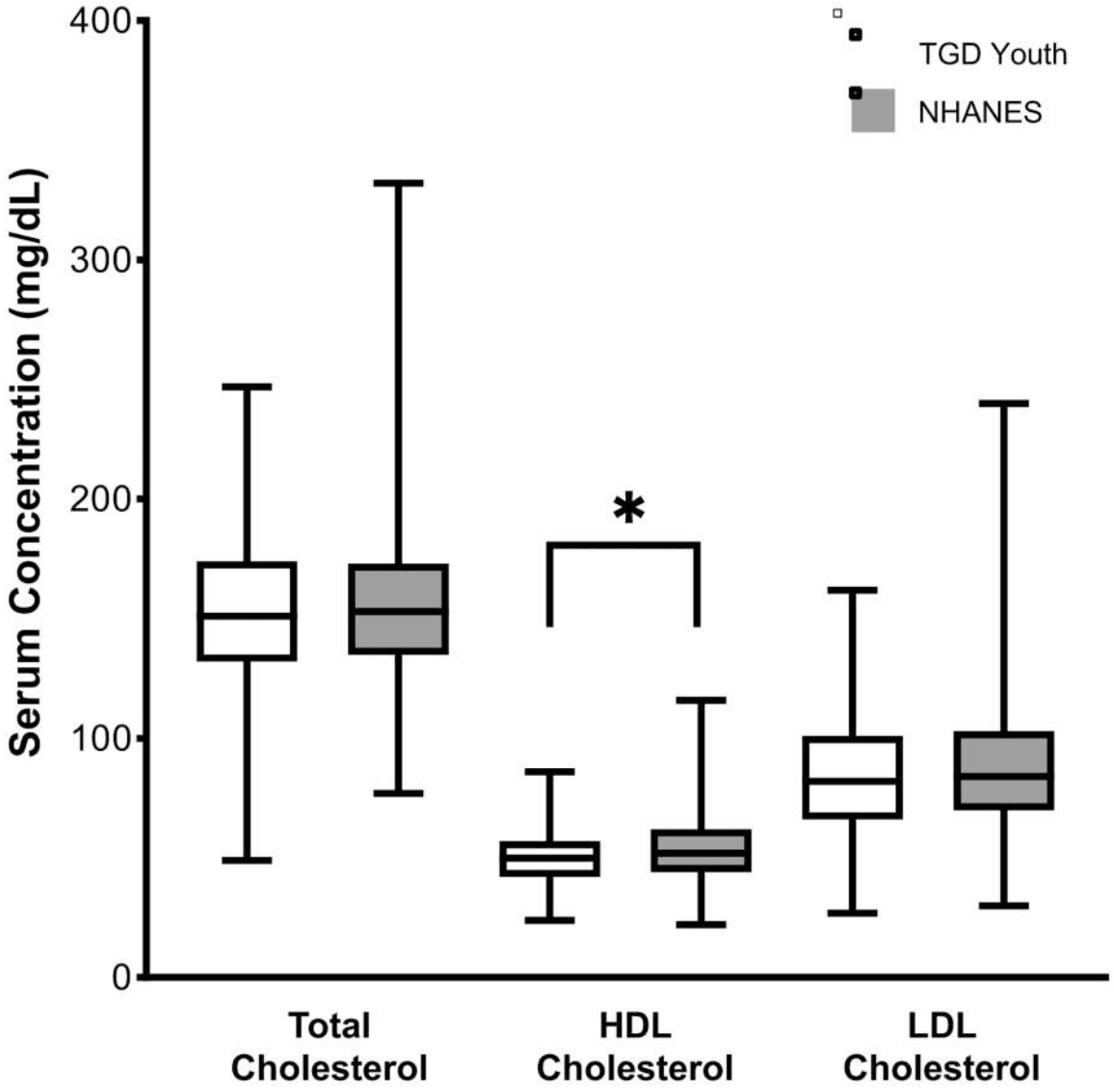

Figure 2. Cholesterol measurements of participants in the gender-affirming hormone cohort.
Box represents interquartile range. Central line is the median of the sample. Minimum and maximum values are represented by the black lines. The asterisk indicates a significant difference (p = 0.001) in HDL cholesterol between study participants and NHANES participants.

Table 1.

Baseline characteristics of participants

	Puberty Blocker Cohort			Gender-Affirming Hormone Cohort		
	Total (n = 78)	**Assigned male at birth (n = 41)**	**Assigned female at birth (n = 37)**	**Total (n = 296)**	**Assigned male at birth (n = 99)**	**Assigned female at birth (n = 197)**
Age, median (range), y	11 (8 – 14)	11 (9 – 14)	10 (8 – 13)	16 (12 – 20)	16 (12 – 20)	16 (12 – 20)
Affirmed Gender, n (%)						
Female	17 (22%)	18 (43%)	0 (0)	44 (15%)	44 (44%)	0 (0)
Male	21 (27%)	0 (0)	20 (54%)	82 (28%)	0 (0)	82 (42%)
Transgender Female (male-to-female)	20 (26%)	20 (49%)	0 (0)	50 (17%)	50 (50%)	0 (0)
Transgender Male (female-to-male)	15 (19%)	0 (0)	15 (41%)	103 (35%)	0 (0)	103 (53%)
Gender Fluid	2 (3%)	2 (5%)	0 (0)	2 (1%)	0 (0)	2 (1%)
Gender Queer	0 (0)	0 (0)	0 (0)	2 (1%)	1 (1%)	1 (0.5%)
Non-binary	3 (4%)	1 (2%)	2 (5%)	12 (4%)	3 (3%)	9 (5%)
Other	0 (0)	0 (0)	0 (0)	1 (0.3%)	1 (1%)	0 (0)
Race/Ethnicity, n (%)						
White	44 (57%)	17 (43%)	27 (73%)	187 (63%)	64 (65%)	123 (63%)
Black or African-American	3 (4%)	2 (5%)	1 (3%)	13 (4%)	4 (4%)	9 (5%)
Asian	1 (1%)	1 (3%)	0 (0)	13 (4%)	4 (5%)	9 (5%)
American Indian/Alaska Native	1 (1%)	1 (3%)	1 (3%)	3 (1%)	0 (0)	3 (1.5%)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	1 (0.3%)	0 (0)	1 (0.5%)
Multi-Race	9 (12%)	5 (13%)	4 (11%)	9 (3%)	5 (5%)	4 (2%)
Other	1 (1%)	1 (3%)	0 (0)	3 (1%)	2 (2%)	1 (0.5%)
Hispanic or Latino	14 (18%)	10 (25%)	4 (11%)	63 (21%)	16 (16%)	47 (24%)
Unknown	5 (6%)	4 (10%)	1 (3%)	4 (1%)	4 (4%)	0 (0)
Tanner Stage, n (%)						
II	50 (64%)	32 (78%)	18 (49%)	9 (3%)	9 (10%)	0 (0)
III	28 (36%)	9 (22%)	19 (51%)	9 (3%)	6 (7%)	3 (2%)
IV	-	-	-	27 (9%)	9 (10%)	18 (10%)
V	-	-	-	228 (84%)	66 (73%)	162 (89%)
Unknown	0 (0)	0 (0)	0 (0)	23 (8%)	9 (9%)	14 (7%)
Current tobacco use, n (%) *	-	-	-	26 (9%)	12 (14%)	14 (7%)

	Puberty Blocker Cohort			Gender-Affirming Hormone Cohort		
	Total (n = 78)	**Assigned male at birth (n = 41)**	**Assigned female at birth (n = 37)**	**Total (n = 296)**	**Assigned male at birth (n = 99)**	**Assigned female at birth (n = 197)**
Median Household Income of reported ZIP Code, n (%)						
< $54,999	13 (17%)	10 (24%)	3 (8%)	59 (21%)	24 (26%)	35 (19%)
$55,000 – $74,999	19 (25%)	7 (17%)	12 (33%)	65 (24%)	21 (23%)	44 (24%)
$75,000 – $99,999	19 (25%)	12 (29%)	7 (19%)	86 (31%)	25 (27%)	61 (33%)
>$100,000	26 (34%)	12 (29%)	14 (39%)	68 (24%)	23 (25%)	45 (24%)
Unknown	1 (1%)	0 (0)	1 (3%)	18 (6%)	6 (6%)	12 (6%)
Caregiver employment status, n (%) **						
Unemployed	-	-	-	11 (4%)	8 (8%)	3 (2%)
Employed part time	-	-	-	10 (3%)	2 (2%)	8 (4%)
Employed full time	-	-	-	265 (90%)	88 (89%)	177 (90%)
Retired	-	-	-	5 (2%)	0 (0)	5 (3%)
Unknown				5 (2%)	1 (1%)	4 (2%)
Caregiver education status, n (%) **						
Less than high school	-	-	-	10 (3%)	5 (5%)	5 (3%)
High school graduate	-	-	-	98 (33%)	31 (31%)	67(34%)
Bachelor’s degree	-	-	-	63 (21%)	23 (23%)	40 (20%)
Master’s degree	-	-	-	58 (20%)	15 (15%)	43 (22%)
Professional or doctorate degree	-	-	-	28 (9%)	11 (11%)	17 (9%)
Unknown				39 (13%)	11 (11%)	25 (13%)

* Current use was defined as daily, weekly, or monthly use in the past three months.

** Caregiver employment and education status were not collected for participants in the puberty blocker cohort.

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Table 2

Anthropometric measurements of participants compared to matched NHANES comparison group

	Puberty Blocker Cohort						Gender-Affirming Hormone Cohort *					
	TGD Youth			Matched NHANES Comparison Group			TGD Youth			Matched NHANES Comparison Group		
	Total (n = 78)	Assigned male at birth (n = 41)	Assigned female at birth (n = 37)	Total (n = 1125)	Assigned male at birth (n = 578)	Assigned female at birth (n = 547)	Total (n = 276)	Assigned male at birth (n = 86)	Assigned female at birth (n = 190)	Total (n = 1095)	Assigned male at birth (n = 547)	Assigned female at birth (n = 548)
Height, mean (SD), cm		151.5 (8.1)	145.4 (9.7)	-	147.5 (15.1)	144.8 (12.8)	-	173.6 (7.6)‡	163.3 (6.6)≠	-	169.6 (10.4)	159.5 (8.1)
Height Z-score, mean (SD)	0.29 (1.10)	0.37 (1.06)	0.19 (1.15)	0.17 (1.03)	0.25 (1.02)	0.1 (1.03)	0.09 (1.00)†	−0.25 (0.93)	0.15 (1.03)≠	−0.12 (1.06)	−0.08 (1.03)	−0.17 (1.08)
Weight, mean (SD), kg	43.3 (11.6)	45.5 (11.5)	40.8 (11.3)	45.4 (17.8)	46.1 (19)	44.6 (18.4)	68.8 (18.7)	72.3 (19.0)	67.3 (18.4)≠	67.6 (21.2)	71.4 (22.6)	63.9 (18.9)
Weight Z-score, mean (SD)	0.36 (1.10)	0.44 (1.08)	0.27 (1.12)	0.61 (1.18)	0.66 (1.21)	0.55 (1.15)	0.67 (1.12)†	0.42 (1.25)	0.78 (1.05)	0.59 (1.23)	0.58 (1.27)	0.6 (1.19)
BMI, mean (SD), kg/m^2	19.4 (3.7)	19.6 (3.5)	19.1 (3.9)	20.5 (5.1)	20.5 (5.2)	20.6 (5.0)	24.8 (6.3)	23.7 (5.7)	25.2 (6.5)	24.7 (6.6)	24.6 (6.7)	24.9 (6.5)
BMI Z-score, mean (SD)	0.36 (1.06)	0.39 (1.10)	0.32 (1.02)	0.64 (1.11)	0.66 (1.15)	0.63 (1.08)	0.62 (1.15)	0.34 (1.26)‡	0.74 (1.07)	0.30 (0.98)	−0.23 (0.44)	0.71 (1.08)
BMI categories, n (%)												
Underweight	1 (1%)	1 (2%)	0 (0)	7 (0.6%)	4 (0.7%)	3 (0.6%)	4 (2%)	1 (1%)	3 (2%)	16 (2%)	7 (1%)	9 (2%)
Normal weight	53 (68%)	28 (68%)	25 (68%)	650 (58%)	342 (59%)	308 (56%)	152 (56%)	51 (62%)	101 (53%)	557 (53%)	294 (55%)	263 (50%)
Overweight	19 (24%)	10 (24%)	9 (24%)	277 (25%)	132 (23%)	145 (26%)	66 (24%)	21 (25%)	45 (24%)	250 (24%)	113 (21%)	137 (26%)
Obese	5 (6%)	2 (5%)	3 (8%)	191 (17%)	100 (17%)	91 (16%)	50 (18%)	10 (12%)	40 (21%)	238 (22%)	120 (23%)	118 (22%)
Systolic blood pressure, mean (SD), mmHg	111 (11)†	112 (11)≠	110 (11)≠	104 (9)	105 (10)	103 (9)	116 (11)†	120 (12)≠	114 (10)≠	111 (10)	114 (10)	108 (9)
Diastolic blood pressure, mean (SD), mmHg	63 (8)†	63 (9)≠	62 (8)≠	54 (9)	53 (13)	54 (13)	65 (9)†	67 (10)≠	64 (9)≠	61 (11)	60 (12)	61 (10)
Systolic blood pressure > 95th percentile, n (%)	9 (12%)†	5 (12%)≠	4 (11%)	36 (3%)	17 (3%)	19 (4%)	24 (9%)†	9 (11%)≠	15 (8%)≠	28 (3%)	16 (3%)	12 (2%)

	Puberty Blocker Cohort						Gender-Affirming Hormone Cohort *					
	TGD Youth			Matched NHANES Comparison Group			TGD Youth			Matched NHANES Comparison Group		
	Total (n = 78)	Assigned male at birth (n = 41)	Assigned female at birth (n = 37)	Total (n = 1125)	Assigned male at birth (n = 578)	Assigned female at birth (n = 547)	Total (n = 276)	Assigned male at birth (n = 86)	Assigned female at birth (n = 190)	Total (n = 1095)	Assigned male at birth (n = 547)	Assigned female at birth (n = 548)
Diastolic blood pressure > 95th percentile, n (%)	4 (5%)†	2 (5%)‡	2 (5%)‡	4 (0.4%)	1 (0.2%)	3 (0.6%)	9 (3%)†	5 (6%)‡	4 (2%)‡	5 (0.5%)	3 (0.6%)	2 (0.4%)

* Participants with prior GnRH analog use and known diagnosis of type 1 diabetes mellitus were excluded from the analysis.

† $p < 0.05$ when compared to NHANES comparison group matched by age and sex assigned at birth and adjusted for race and estimated household income.

‡ $p < 0.05$ when compared to NHANES age-matched comparison group by sex assigned at birth.

Table 3

Laboratory measurements of participants in the gender-affirming hormone cohort compared to age-matched comparison group from NHANES

	Gender-Affirming Hormone Cohort*			Matched NHANES Comparison Group		
	Total (n = 276)	**Assigned male at birth (n = 86)**	**Assigned female at birth (n = 190)**	**Total (n = 1095)**	**Assigned male at birth (n = 547)**	**Assigned female at birth (n = 548)**
Estradiol, median (interquartile range), pg/mL						
Tanner IV	-	20 (13 – 21)	53 (24 – 139)	-	-	-
Tanner V	-	22 (17 – 25)	44 (21 – 90)	-	-	-
Total Testosterone, median (interquartile range), ng/dL						
Tanner IV	-	277 (144 – 424)	25 (16 – 30)	-	-	-
Tanner V	-	426 (295 – 573)	26 (18 – 36)	-	-	-
Free Testosterone, median (interquartile range), pg/mL						
Tanner IV	-	4 (3 – 52)	2.5 (1.5 – 3.0)	-	-	-
Tanner V	-	71 (14 – 91)	2.4 (1.3 – 3.5)	-	-	-
Prolactin, mean (SD), ng/mL	-	8.8 (4.1)	-	-	-	-
Total Cholesterol, mean (SD) mg/dL	155 (33)	149 (34)	157 (32)	157 (30)	154 (30)	159 (30)
Total Cholesterol > 200 mg/dL, n (%)	19 (8%)	7 (7%)	14(8%)	73 (8%)	34 (7%)	39 (9%)
HDL Cholesterol, mean (SD) mg/dL	50.6 (12.3) †	45.6 (10.7) ‡	52.6 (12.4) ‡	53.3 (13.3)	51.1 (12.8)	55.6 (13.4)
HDL Cholesterol < 40 mg/dL, n (%)	45 (19%) †	19 (28%)	26 (15%) ‡	125 (13%)	91 (19%)	34 (7%)
LDL Cholesterol, mean (SD) mg/dL	84.8 (26.2)	81.5 (29.8)	86.2 (24.4)	88.7 (26.7)	88.6 (27.7)	88.8 (25.7)
LDL Cholesterol > 130 mg/dL, n (%)	12 (6%)	5 (8%)	7 (5%)	24 (6%)	14 (7%)	10 (5%)
HgbA1c, mean (SD), %	5.2 (0.5)	5.3 (0.3)	5.2 (0.5)	5.3 (0.4)	5.2 (0.3)	5.2 (0.4)
HgbA1c 5.7% – 6.4%, n (%)	8 (6%)	2 (6%)	6 (6%)	35 (4%)	15 (3%)	20 (5%)
HgbA1c > 6.4%, n (%)	2 (1%)	0 (0)	2 (2%)	2 (0.2%)	0 (0)	2 (0.5%)

*Participants with prior GnRH analog use were excluded

†p < 0.05 when compared to NHANES age-matched comparison group.

‡p < 0.05 when compared to NHANES age-matched comparison group by sex assigned at birth

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Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body image dissatisfaction

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ABSTRACT

Objective: Transgender/non-binary (TNB) youth are at increased risk for anxiety, depression, and suicidality compared to cisgender youth. Gender affirming hormone therapy (GAHT, i.e., testosterone or estrogen) is a standard of care option for TNB youth, and we have recently shown that GAHT (testosterone) in transgender youth assigned a female sex at birth is associated with reductions in internalizing symptomatology. The current analysis explores: 1) whether these benefits are observed in *both* TNB youth assigned female at birth (TNB_{AFAB}) and TNB youth assigned male at birth (TNB_{AMAB}) and 2) the extent to which body image dissatisfaction and alteration in neural circuitry relate to internalizing symptoms.

Method: The current study is an expansion of a previous publication from our lab that explored the association between gender-affirming testosterone and internalizing symptomatology. While participants in our previous study consisted of 42 TNB_{AFAB} youth, participants in the current study included adolescent TNB_{AFAB} receiving GAHT (n = 21; GAHT+) and not receiving GAHT (n = 29; GAHT-) as well as adolescent GAHT+ TNB_{AMAB} (n = 15) and GAHT- TNB_{AMAB} (n = 17). Participants reported symptoms of trait and social anxiety, depression, suicidality in the past year, and body image dissatisfaction. Brain activation was measured during a face processing task designed to elicit amygdala activation during functional MRI.

Results: GAHT+ TNB_{AFAB} had significantly lower rates of social anxiety, depression, and suicidality compared to GAHT- TNB_{AFAB}. While there were no significant relationships between estrogen and depression and anxiety symptoms, longer duration of estrogen was related to less suicidality. Both testosterone and estrogen administration were related to significantly lower rates of body image dissatisfaction compared to GAHT- youth. No significant differences emerged for BOLD response in the left or right amygdala during the face processing task, however, there was a significant main effect of GAHT on functional connectivity between the right amygdala and the ventromedial prefrontal cortex, such that GAHT+ youth had stronger co-activation between the two regions during the task. Body image dissatisfaction, greater functional connectivity, their interaction effect, and age predicted depression symptomatology and body image dissatisfaction additionally predicted suicidality in the past year.

Conclusion: The current study suggests that GAHT is associated with fewer short-term internalizing symptoms in TNB_{AFAB} than in TNB_{AMAB}, although internalizing symptoms among TNB_{AMAB} may diminish with longer durations of estrogen treatment. Controlling for age and sex assigned at birth, our findings indicate that less body image dissatisfaction and greater functional connectivity between the amygdala and ventromedial prefrontal cortex were both predictors of fewer levels of internalizing symptoms following GAHT.

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1. Introduction

Increases in internalizing disorders (anxiety and depression) during adolescence have been attributed to both neurobiological and social changes that occur during this period of development (Andrews et al., 2021). For example, social networks and social functioning become increasingly important to one's mental wellbeing (Verboom et al., 2014), and surges of gonadal hormones (i.e., testosterone and estrogen) are believed to affect the structural and functional development of the brain during puberty (Andrews et al., 2021). In presumed cisgender samples, the increase in internalizing symptoms is more pronounced in females than males and has been at least partially attributed to gonadal hormones, particularly estrogen (Kessler, 2003). For transgender adolescents, a sizeable literature identifies that minority stress contributes to mental health disparities (Valentine and Shipherd, 2018). Understanding the potential direct physiological effects of gonadal hormones on emotional functioning, in addition to the indirect mechanisms that hormones have on others' perception of gender, is also important.

In addition to the social and biological factors impacting cisgender youth, transgender adolescents also experience dysphoria related to gender-incongruent body maturation, heightened levels of social rejection, diminished social support (Valentine and Shipherd, 2018), and rates of anxiety, depression, and suicidality that are severalfold higher than in cisgender teens (Becerra-Culqui et al., 2018). While internalized transphobia, compounded minority stress, and frequent discrimination exacerbate internalizing symptoms (Valentine and Shipherd, 2018), hormonal therapies are standard therapeutic options to alleviate these symptom burdens. Recent studies have indicated that gender affirming hormone therapy (GAHT; testosterone and estrogen) and support from family and friends are associated with reduced internalizing symptoms and improved quality of life (Chen et al., 2023; Kuper et al., 2020; Olsavsky et al., 2023), however, little is known regarding the impact of GAHT on neural circuitry related to emotion regulation. Therefore, the current investigation aims to expand understanding of the role that GAHT has on internalizing symptoms by examining both psychological and linked neural mechanisms of hormone treatment.

We recently reported significantly lower levels of anxiety, depression, and suicidality in a group of transgender youth assigned female at birth (AFAB) receiving testosterone treatment relative to transgender youth AFAB not receiving testosterone (Grannis et al., 2021). GAHT was associated with less body image dissatisfaction and greater neural co-activation of the amygdala (involved in processing emotional content) and the ventromedial prefrontal cortex (vmPFC; involved in the cognitive control of emotion processing). This connectivity pathway has been shown to be disrupted in multiple psychiatric disorders, including anxiety and depression (Jalbrzikowski et al., 2017). In samples of post-pubertal presumed cisgender individuals, the amygdala-vmPFC pathway has been shown to be differentially associated with internalizing symptoms depending on sex (Burghy et al., 2012). However, it is still uncertain whether gonadal hormones or social factors are primarily responsible for developing this differential neural connectivity pathway.

The current analyses expand upon our previous findings. We hypothesize that GAHT is associated with fewer internalizing symptoms in both transgender/non-binary (TNB) youth assigned female at birth (TNB_{AFAB}) and TNB youth assigned male at birth (TNB_{AMAB}). Further, we examine the associations between internalizing symptoms, body image dissatisfaction, and amygdala-vmPFC connectivity. In exploratory analyses we investigate how duration of GAHT is associated with internalizing symptoms. To achieve this, 8 TNB_{AFAB} participants have been added to our previous sample in addition to a sample of TNB_{AMAB} youth.

2. Materials and methods

2.1. Participants and demographics

TNB adolescents between the ages of 9–21 were recruited from a gender development clinic at a large children's hospital between 2018 and 2022. Participants were eligible if they met diagnostic classification of gender dysphoria based on comprehensive mental health evaluation by a provider specializing in gender development and had no MRI contraindicators (e.g., braces, metal implants, etc.). Of the 101 eligible participants approached, 83 agreed to participate, and 82 youth enrolled. Demographic information is reported in Table 1 and additional information regarding gender identity is reported in Supplemental Materials S1. All study procedures were approved by the local institutional review board, none of which subjected participants to dysphoria-inducing stimuli. Prior to participation, consent/assent was obtained from all participants.

2.2. GAHT status

Electronic medical records were reviewed to determine if participants were receiving GAHT (GAHT+) or not (GAHT-). Of the 82 enrolled youth, 50 were TNB_{AFAB} and 32 were TNB_{AMAB}. Twenty-one of the 50 TNB_{AFAB} received injections of testosterone and 15 of the 32 TNB_{AMAB} received estrogen via transdermal patch or oral tablets. Thirteen participants (TNB_{AFAB}=3, TNB_{AMAB}=10) received puberty blockers or Spironolactone as monotherapy at the time of data collection and were included in the GAHT- group. GAHT duration is reported in Table 1A and additional information regarding recruitment and GAHT status is included in Supplemental Materials S2.

2.3. Self-report measures and MRI data collection

To assess differences in internalizing symptomatology, trait anxiety (Birmaher et al., 1999), social anxiety (Liebowitz, 1987), depression (Kovacs, 1985), and frequency of past year suicidal ideation (Osman and Bagge, 2001) were measured. Body image dissatisfaction (Lindgren and Pauly, 1975) was measured to assess dysphoria related to various aspects of one's body. All measures were self-reported by participants. Nine participants did not complete the MRI; however, their data were retained in analyses that did not include MRI data to maximize sample size and reduce potential bias.

Amygdala response and amygdala-vmPFC co-activation was assessed while viewing emotional facial stimuli inside the scanner (Hariri et al., 2000). Task design and acquisition parameters are described in (Grannis et al., 2021). Briefly, the task involved participants viewing unknown faces that were making either "angry" or "fearful" facial expressions. BOLD response was combined across these two expressions and was compared to when participants viewed either circles or ovals as a baseline contrast.

2.4. Statistical analysis

2.4.1. Demographic analyses

Group differences on all demographic measures were assessed using ANOVAs. Significant age differences were found between GAHT+ and GAHT- participants within both TNB_{AFAB}, $t(48) = 4.38$, $p < 0.001$, and TNB_{AMAB}, $t(26) = 3.24$, $p < 0.01$. Therefore, age was included as a covariate in all models.

2.4.2. Neuroimaging analyses

To build on previous findings (Grannis et al., 2021), group differences in BOLD response were tested within each amygdala and a generalized psychophysiological interaction (gPPI) analysis was computed to examine the functional co-activation between the right amygdala and vmPFC ($k = 138$, $x = 3$, $y = -59$, $z = -2$) during the face

versus shapes contrast. Additional information regarding this analysis is presented in Supplemental Materials S3.

2.4.3. Mental health and body image dissatisfaction analyses

Group differences in self-reported measures of internalizing symptoms and body image dissatisfaction were examined with multiple ANCOVAs, which included sex assigned at birth (SAAB), GAHT status, and their interaction as effects of interest, and age as a covariate. Post-hoc analyses were performed to interpret the interaction effects and exploratory analyses were performed on GAHT duration. To assess the relationship between SAAB, body image dissatisfaction, neural connectivity, and internalizing symptoms, multiple ANCOVA models were created with the inclusion of body image dissatisfaction, amygdala-vmPFC connectivity, their interaction term, and age as regressors.

3. Results

3.1. Internalizing disorders

No main effects of GAHT across SAAB were found for internalizing symptoms. However, significant interactions between SAAB and GAHT were present for social anxiety, $F(1, 72) = 5.14$, $p = 0.03$, $\eta^2 = 0.07$, depression, $F(1, 77) = 5.36$, $p = 0.02$, $\eta^2 = 0.07$, and suicidality in the past year, $F(1,77) = 5.06$, $p = 0.03$, $\eta^2 = 0.06$. Post-hoc *t*-tests revealed that GAHT+ TNB_{AFAB} reported fewer symptoms relative to GAHT- TNB_{AFAB} (see Table 1D); no GAHT effect was found for TNB_{AMAB}. No interaction was observed for trait anxiety, $F(1,75) = 2.00$, $p = 0.16$, $\eta^2 = 0.03$, although, 82.5% of participants reported anxiety symptoms above the clinical cutoff score of 25 (M=43.56, SD=16.88).

Table 1
displays differences in (A) demographic, (B) gender identity, and (C) racial and ethnic information, as well as differences in (D) mental health and body image dissatisfaction, accounting for age as a covariate. Significance was tested within sex assigned at birth comparing the GAHT+ youth to the GAHT- youth, as well as across all four groups. Multiple responses were enabled for race and ethnicity. In section A, GAHT duration is presented in months. A full break-down of gender identities is presented in Supplemental Materials (S1).

(A) Demographic information							
	AFAB			AMAB		Omnibus	
	GAHT+ *M*(SD)	GAHT- *M*(SD)	*t*(df)	GAHT+ *M*(SD)	GAHT- *M*(SD)	*t*(df)	*F* (df1,df2)
Age (years)	17.04 (1.18)	15.24 (1.72)	4.38 (47.92)* **	17.64 (0.86)	16.27 (1.49)	3.24 (26.11)* *	0.44 (1,78)
GAHT duration	12.87 (9.94)	–	–	13.53 (8.69)	–	–	–
(B) Gender identities							
	AFAB			AMAB			Omnibus
	GAHT+ n(%)	GAHT- n(%)	χ^2 (df)	GAHT+ n(%)	GAHT- n(%)	χ^2 (df)	χ^2 (df)
Binary	20 (95.24)	25 (86.21)	–	11 (73.33)	12 (70.59)	–	–
Non-Binary	0 (0.00)	1 (3.45)	–	2 (13.33)	3 (17.65)	–	–
Binary and Non-Binary	1 (4.76)	3 (10.34)	–	2 (13.33)	2 (11.76)	–	–
(C) Racial and ethnic information							
	AFAB			AMAB		Omnibus	
	GAHT+ n(%)	GAHT- n(%)	χ^2 (df)	GAHT+ n(%)	GAHT- n(%)	χ^2 (df)	χ^2 (df)
Race							
Asian	0 (0.00)	0 (0.00)	–	1 (6.67)	0 (0.00)	1.17 (1)	4.52 (3)
Black or African American	3 (14.29)	1 (3.45)	1.94 (1)	0 (0.00)	1 (5.88)	0.91 (1)	3.79 (3)
Multiracial	3 (14.29)	3 (10.34)	0.18 (1)	1 (6.67)	1 (5.88)	0.01 (1)	0.95 (3)
Native American or American Indian	1 (4.76)	1 (3.45)	0.05 (1)	0 (0.00)	1 (5.88)	0.91 (1)	0.88 (3)
Other	0 (0.00)	0 (0.00)	–	0 (0.00)	0 (0.00)	–	–
White	14 (66.67)	22 (75.86)	0.51 (1)	13 (86.67)	12 (70.59)	2.71 (1)	3.70 (3)
Prefer not to answer	0 (0.00)	2 (6.90)	1.51 (1)	0 (0.00)	2 (11.76)	1.88 (1)	3.84 (3)
Ethnicity							
Hispanic/Latinx	4 (19.05)	1 (3.44)	3.29 (1)	0 (0.00)	1 (5.88)	0.91 (1)	6.14 (3)
Non-Hispanic/Latinx	17 (80.95)	28 (96.56)	3.29 (1)	15 (100.00)	16 (94.12)	0.91 (1)	6.14 (3)
(D) Mental health and body image dissatisfaction							
	AFAB			AMAB		Omnibus	
	GAHT+ *M*(SD)	GAHT- *M*(SD)	*F* (df1,df2)	GAHT+ *M*(SD)	GAHT- *M*(SD)	*F* (df1,df2)	*F* (df1,df2)
SCARED	38.75 (17.41)	50.25 (14.12)	7.76 (1,45)* *	40.07 (20.17)	41.29 (15.19)	0.08 (1,29)	2.00 (1,75)
CDI	13.38 (7.81)	18.34 (7.02)	5.62 (1,47)*	18.13 (8.13)	15.47 (7.14)	0.03 (1,29)	5.36 (1,77) *
LSAS	50.21 (22.34)	78.62 (31.41)	14.80 (1,42)* **	64.07 (38.62)	59.53 (32.94)	0.20 (1,29)	5.14 (1,72) *
Suicidality	1.95 (0.92)	2.86 (1.46)	3.05 (1,47)	2.73 (1.83)	2.18 (1.38)	0.38 (1,29)	5.06 (1,77) *
BID	92.29 (19.74)	103.14 (18.99)	7.46 (1,47)* *	85.33 (16.21)	88.53 (29.01)	4.88 (1,29)*	1.24 (1,77)

GAHT=Gender Affirming Hormone Therapy, specifically testosterone and estrogen. SCARED=Screen for Child Anxiety Related Emotional Disorders; higher values indicate greater generalized anxiety symptoms. CDI=Children's Depression Inventory; higher values indicate greater depression symptoms. LSAS=Leibowitz Social Anxiety Scale; higher values indicate greater social anxiety. Suicidality refers to the frequency of suicidal ideation and/or attempts in the past year. BID=Body Image Dissatisfaction; higher values indicate greater dissatisfaction with one's body image. Gender identities categorized as binary included: male, female, female-to-male (FTM), male-to-female (MTF), trans-male/trans-man, and trans-female/trans-woman. Gender identities categorized as non-binary included: genderqueer, gender non-conforming, gender-variant, gender fluid, gender expansive, intersex, androgynous, nonbinary, two spirited, third gender, and agender. Gender identities that were not able to be collapsed into this binary categorization included: transgender, trans*r/trans asterisk, transsexual, cross dresser, not sure, and other.
* $p < 0.05$
* * $p < 0.01$
* ** $p < 0.001$

3.2. Body image

We found main effects for both SAAB, $F(1,77) = 10.81$, $p < 0.01$, $\eta^2 = 0.12$, and GAHT treatment, $F(1,77) = 9.61$, $p < 0.01$, $\eta^2 = 0.11$, on body image dissatisfaction. In contrast with internalizing symptoms, we did not find an interaction effect for SAAB by GAHT on this measure, $F(1,77) = 1.24$, $p = 0.27$, $\eta^2 = 0.02$.

Post-hoc tests revealed that the SAAB effect was driven by TNB_{AMAB} reporting less body image dissatisfaction (M=87.03, SD=23.57) than TNB_{AFAB} (M=98.58, SD=19.86), across GAHT groups. The GAHT effect was driven by GAHT+ youth reporting less body image dissatisfaction (M=89.39, SD=14.44) than GAHT- youth (M=97.74, SD=23.97; see Table 1D).

3.3. GAHT duration

We assessed the relationship between GAHT duration on internalizing symptoms and body image dissatisfaction among the GAHT+ group. In multiple ANCOVAs, significant main effects of duration emerged for depression, $F(1,31) = 5.45$, $p < 0.05$, $\eta^2 = 0.15$, suicidality in the past year, $F(1,31) = 16.69$, $p < 0.001$, $\eta^2 = 0.35$, and body image dissatisfaction, $F(1,31) = 7.04$, $p < 0.05$, $\eta^2 = 0.19$, such that longer duration of GAHT was associated with less body image dissatisfaction and fewer depression and suicidality symptoms across SAAB.

A main effect of SAAB was found for suicidality in the past year, $F(1,31) = 11.14$, $p < 0.01$, $\eta^2 = 0.26$, reflecting higher levels of suicidality in the GAHT+ TNB_{AMAB} subgroup than the GAHT+ TNB_{AFAB} subgroup. An interaction between SAAB and GAHT duration was also found for suicidality in the past year, $F(1,31) = 6.60$, $p < 0.05$, $\eta^2 = 0.18$. Although TNB_{AMAB} had, on average, more symptoms of suicidality than TNB_{AFAB}, longer duration of estrogen had a stronger association with fewer symptoms of suicidality than corresponding durations of testosterone.

3.4. Neuroimaging analysis

Analysis of amygdala-vmPFC coupling revealed a main effect of GAHT, $F(1,66) = 7.78$, $p < 0.01$, $\eta^2 = 0.11$, reflecting greater coupling in GAHT+ than GAHT- groups. No effects were found for SAAB, $F(1,64) = 0.04$, $p = 0.85$, $\eta^2 < 0.001$, or the interaction of SAAB and GAHT, $F(1,66) = 0.10$, $p = 0.75$, $\eta^2 < 0.01$, (Fig. 1).

3.5. Relationship between internalizing disorders, body image dissatisfaction, and neural circuitry

Multiple exploratory ANCOVAs were computed to assess whether group effects on internalizing symptoms were driven more by body image dissatisfaction or functional connectivity between the amygdala and vmPFC, controlling for age. Models were run separately for depression, past year suicidality, trait anxiety, and social anxiety. In the depression model, there were independent contributions of body image dissatisfaction, $F(1,61) = 18.02$, $p < 0.001$, $\eta^2 = 0.23$, and amygdala-vmPFC connectivity, $F(1,61) = 6.27$, $p < 0.05$, $\eta^2 = 0.09$, such that more body image dissatisfaction was associated with more depressive symptoms and less amygdala-vmPFC connectivity was associated with more depressive symptoms. There was a significant interaction of body image dissatisfaction and functional connectivity, $F(1,61) = 6.61$, $p < 0.05$, $\eta^2 = 0.10$, such that the shared variance of more body image dissatisfaction and less functional connectivity was associated with more depressive symptoms. Furthermore, body image dissatisfaction predicted suicidality in the past year, $F(1,61) = 18.01$, $p < 0.001$, $\eta^2 = 0.23$, but neither amygdala-vmPFC connectivity nor the interaction between body image dissatisfaction and functional connectivity reached significance. Neither body image dissatisfaction nor amygdala-vmPFC connectivity reached significance for trait or social anxiety.

3.6. Additional exploratory analyses

With great caution required for interpretation due to very small

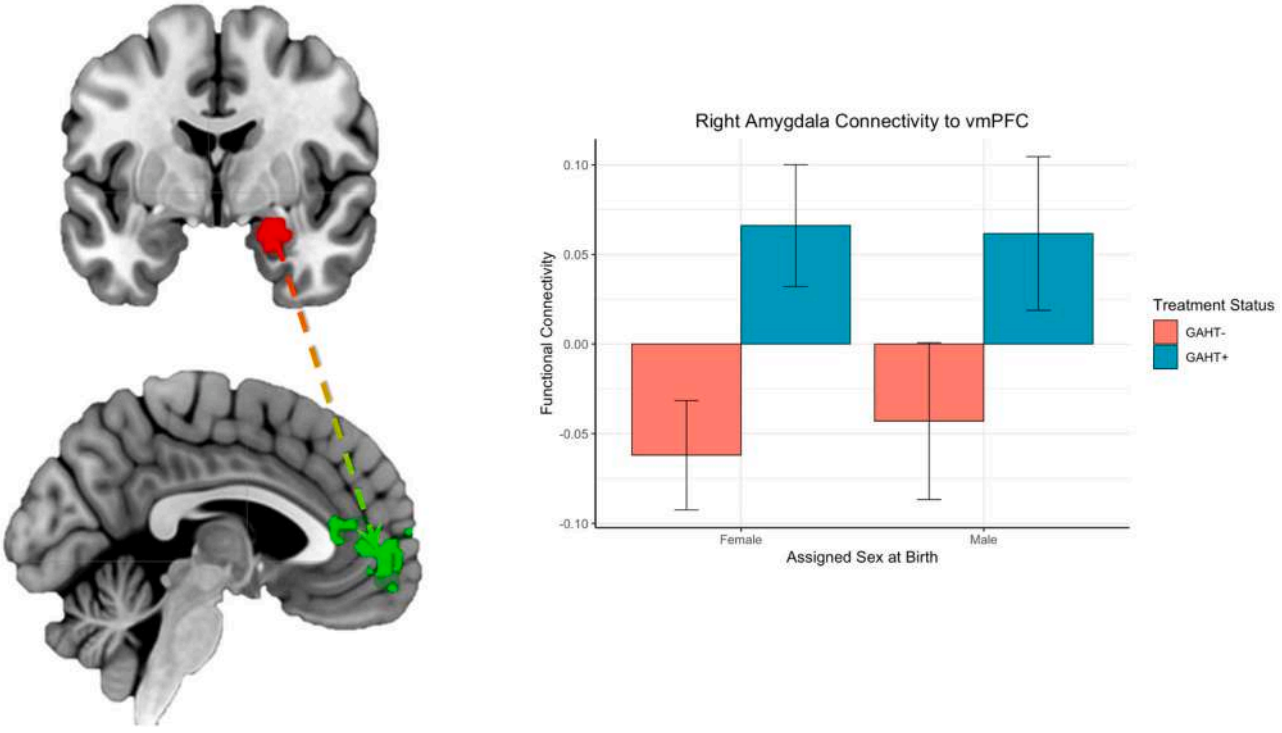

Fig. 1. Functional connectivity between the right amygdala and the vmPFC during a face presentation task is greater in GAHT+ transgender youth than in GAHT- youth.

sample size, analyses were recomputed within the TNB_{AMAB} cohort to describe the differences between youth receiving estrogen, youth receiving other gender-affirming medication (e.g., Lupron, Histrelin, Spironolactone), and youth not receiving any gender-affirming medication. A detailed report is presented in Supplemental Materials (S4), showing that there were no group differences in internalizing symptoms, consistent with prior literature (De Vries et al., 2011), or amygdala-vmPFC connectivity. There was, however, a significant difference between youth receiving other gender-affirming medication and youth not receiving any gender-affirming medication in body-image dissatisfaction, such that youth receiving medication had less body image dissatisfaction, consistent with previous literature (Kuper et al., 2020).

4. Discussion

The current study expands on our previous report examining the effects of GAHT on internalizing symptoms, body image dissatisfaction, and neural circuitry in TNB_{AFAB} by including GAHT+ and GAHT- TNB_{AMAB}, as well as 8 additional TNB_{AFAB} participants. In contrast to our previous findings – in which testosterone treatment in TNB_{AFAB} was associated with less anxiety, depression, and suicidality – we did not find similar differences in the group of TNB_{AMAB}. Despite the lack of significant main effects, however, we found that prolonged administration of estrogen was associated with *fewer* symptoms of suicidality. Mirroring reports among presumed cisgender adolescents (Kessler, 2003), it is noteworthy that GAHT- TNB_{AFAB} reported more internalizing symptoms and higher body image dissatisfaction than GAHT+ and GAHT- TNB_{AMAB} (Table 1D). While exogenous estrogen effects on internalizing symptoms seem to take longer than testosterone effects, it is important to note that GAHT+ TNB_{AMAB} had relatively fewer symptoms than GAHT- TNB_{AFAB}, suggesting that other factors, such as SAAB and the accompanying gender norms and expectations, may be important when considering the relationship between GAHT and internalizing symptoms. These findings should be interpreted cautiously due to the small sample size; however, we note recent studies reporting more internalizing symptoms in TNB_{AFAB} than TNB_{AMAB} (Chen et al., 2023; Kuper et al., 2020).

Exploratory analyses revealed that GAHT duration was associated with internalizing symptoms, such that longer duration of GAHT was negatively associated with body image dissatisfaction and symptoms of depression and suicidality. While previous studies have demonstrated an association between better mental health and testosterone administration (Baker et al., 2021; Grannis et al., 2021; Nguyen et al., 2018), the current study adds to the sparse literature around mental health and exogenous GAHT, and particularly estrogen, in adolescents and suggests the effect may continue to improve over time.

A secondary goal of our study was to further probe the roles that GAHT might play in alleviating internalizing symptoms by reducing body image dissatisfaction and/or by directly moderating neural circuitry involved in emotion regulation. In this study, we found that GAHT was associated with significantly lower body image dissatisfaction and greater functional connectivity between the amygdala and vmPFC in a task designed to engage the amygdala. In our model in which both body image dissatisfaction and functional connectivity were used as predictors of internalizing symptoms, we found evidence that both factors and their interaction were predictors of depression, while only body image dissatisfaction was a predictor of suicidality in the past year. While these findings indicate multiple mechanisms of internalizing symptom reduction; future studies should further explore how this knowledge can influence clinical management of internalizing symptoms. For example, an important aspect missing from this study is appearance congruence (i.e., the degree to which one's physical appearance aligns with their gender identity), which GAHT has been shown to improve (Chen et al., 2023). Improvements in appearance congruence, due to GAHT, likely impact youths' mental health by changing the likelihood of experiencing gender minority stress.

The current study adds to the nascent literature surrounding adolescent gender-affirming estrogen administration on brain function and mental health and begins to elucidate the relationship between GAHT and mental health. Despite these important contributions, the study is limited by its cross-sectional design, small sample size, and omission of mental health related considerations, such as length of mental health interventions and information regarding psychiatric co-occurrences (e.g., autism). Additionally, serum levels were not collected and GAHT dosages and administration routes were retrieved from the medical charts and too heterogenous to effectively model in analyses with our sample sizes. Future studies should consider these aspects in the study design phase to appropriately account for them during analyses. As this was a study designed to investigate testosterone and estrogen, a further limitation is the decision to include youth receiving puberty blockers or Spironolactone as monotherapy in the GAHT- group. While this subgroup of participants presumably feels better due to the avoidance of further development of undesired secondary sex characteristics (Kuper et al., 2020), we are under-powered to explore this relationship. While Supplemental Materials (S4) details our approach to addressing this limitation, future studies should make a concerted effort to achieve consistency in their GAHT- reference groups to bolster confidence that differences are in fact due to hormone administration.

As most of our participants went on to receive GAHT after study completion (see S2), future studies should employ targeted recruitment approaches to adequately capture and model the broad factors impacting transgender youth development and wellbeing, particularly for youth not able to access GAHT. Further, future studies should focus on other critically important psychological aspects of gender, such as societal norms and expectations, and social relationships with family and peers in understanding the mental health challenges of transgender adolescents. We believe the current findings provide important preliminary information on some of the complex aspects of gender care that can help guide youth and their families on their decision to undergo GAHT.

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Declaration of Competing Interest

none.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106319.

References

Andrews, J.L., Ahmed, S.P., Blakemore, S.J., 2021. Navigating the social environment in adolescence: the role of social brain development. Biol. Psychiatry 89 (2), 109–118. https://doi.org/10.1016/j.biopsych.2020.09.012.

Baker, K.E., Wilson, L.M., Sharma, R., Dukhanin, V., McArthur, K., Robinson, K.A., 2021. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. J. Endocr. Soc. 5 (4), 1–16. https://doi.org/10.1210/jendso/bvab011.

Becerra-Culqui, T.A., Liu, Y., Nash, R., Cromwell, L., Flanders, D., Getahun, D.G.S.V., Hunkeler, E.M., Lash, T.L., Millman, A., Quinn, V., Robinson, B., Roblin, D., Sandberg, D.E., Siverberg, M.J., Tangpricha, V., Goodman, M., 2018. Mental health of transgender and gender nonconforming youth compared with their peers. Pediatrics 141 (5).

Birmaher, B., Brent, D., Chiappetta, L., Bridge, J., Monga, S., Baugher, M., 1999. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): A replication study. J. Am. Acad. Child Adolesc. Psychiatry 38 (10), 1230–1236. https://doi.org/10.1097/00004583-199910000-00011.

Burghy, C.A., Stodola, D.E., Ruttle, P.L., Molloy, E.K., Armstrong, J.M., Oler, J.A., Fox, M.E., Hayes, A.S., Kalin, N.H., Essex, M.J., Davidson, R.J., Birn, R.M., 2012. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat. Neurosci. 15 (12), 1736–1741. https://doi.org/10.1038/nn.3257.

Chen, D., Berona, J., Chan, Y.-M., Ehrensaft, D., Garofalo, R., Hidalgo, M.A., Rosenthal, S.M., Tishelman, A.C., Olson-Kennedy, J., 2023. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N. Engl. J. Med. 388 (3), 240–250.

De Vries, A.L., Steensma, T.D., Doreleijers, T.A., Cohen-Kettenis, P.T., 2011. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. J. Sex. Med. 8 (8), 2276–2283.

Grannis, C., Leibowitz, S.F., Gahn, S., Nahata, L., Morningstar, M., Mattson, W.I., Chen, D., Strang, J.F., Nelson, E.E., 2021. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys, 105358-105358 Psychoneuroendocrinology 132 (July). https://doi.org/10.1016/j.psyneuen.2021.105358.

Hariri, A.R., Bookheimer, S.Y., Mazziotta, J.C., 2000. Modulating emotional responses: Effects of a neocortical network on the limbic system. NeuroReport 11 (1), 43–48. https://doi.org/10.1097/00001756-200001170-00009.

Jalbrzikowski, M., Larsen, B., Hallquist, M.N., Foran, W., Calabro, F., Luna, B., 2017. Development of white matter microstructure and intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex: Associations with anxiety and depression. Biol. Psychiatry 82 (7), 511–521.

Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74 (1), 5–13. https://doi.org/10.1016/S0165-0327(02)00426-3.

Kovacs, M., 1985. The children's depression inventory (CDI). Psychopharmacol. Bull. 21 (4), 995-995.

Kuper, L.E., Stewart, S., Preston, S., Lau, M., Lopez, X., 2020. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 145 (4). https://doi.org/10.1542/PEDS.2019-3006.

Liebowitz, M., 1987. Social phobia. Mod. Probl. Pharm. 22, 141–173.

Lindgren, T.W., Pauly, I.B., 1975. A body image scale for evaluating transsexuals. Arch. Sex. Behav. 4 (6), 639–656. https://doi.org/10.1007/BF01544272.

Nguyen, H.B., Chavez, A.M., Lipner, E., Hantsoo, L., Kornfield, S.L., Davies, R.D., Epperson, C.N., 2018. Gender-Affirming Hormone Use in Transgender Individuals: Impact on Behavioral Health and Cognition. Curr. Psychiatry Rep. 20 (12) https://doi.org/10.1007/s11920-018-0973-0.

Olsavsky, A.L., Grannis, C., Bricker, J., Chelvakumar, G., Indyk, J.A., Leibowitz, S.F., Mattson, W.I., Nelson, E.E., Stanek, C.J., Nahata, L., 2023. Associations between gender-affirming hormonal interventions & social support with transgender adolescents' mental health. J. Adolesc. Health.

Osman, A., Bagge, C., 2001. The suicidal behaviors questionnaire-revised (SBQ-R): Validation with clinical and nonclinical samples. Psychol. Assess. 8 (4), 443–454.

Valentine, S.E., Shipherd, J.C., 2018. A systematic review of social stress and mental health among transgender and gender non-conforming people in the United States. Clin. Psychol. Rev. 66 (617), 24–38. https://doi.org/10.1016/j.cpr.2018.03.003.

Verboom, C.E., Sijtsema, J.J., Verhulst, F.C., Penninx, B.W., Ormel, J., 2014. Longitudinal associations between depressive problems, academic performance, and social functioning in adolescent boys and girls. Dev. Psychol. 50 (1), 247.

Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands

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Summary

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.

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Introduction

Transgender people diagnosed with gender dysphoria experience distress due to gender incongruence—ie, a discrepancy between their gender identity and sex assigned at birth. Many transgender people desire to align their physique to match their gender identity. Consequently, the development of secondary sex characteristics during puberty can aggravate distress for transgender adolescents.

Around 1998, a revolutionary treatment protocol to suppress pubertal development was introduced in the Netherlands for transgender adolescents.[1,2] Following a thorough diagnostic evaluation, suppression of pubertal development is usually achieved with use of a gonadotropin-releasing hormone agonist (GnRHa). Such suppression of puberty can avert stressful changes in physical characteristics while providing time for a young person's exploration of their gender identity, and bridging the time until a person becomes eligible for gender-affirming hormones. The effects of GnRHa on the gonadal axis are fully reversible.[3]

This protocol became known as the Dutch Protocol and has become part of routine care for adolescents diagnosed with gender dysphoria in many gender identity clinics internationally. However, puberty suppression for individuals under 18 years has recently become a subject of public debate and legal measures have even been taken to ban its use.[4,5] Although short-term studies have shown beneficial effects of puberty

Research in context

Evidence before this study

Medical treatment consisting of puberty suppression and gender-affirming hormones for people younger than 18 years diagnosed with gender dysphoria has been surrounded by controversy since it was introduced around 20 years ago. Although there has been a steep increase in people requesting this treatment, concerns exist regarding possible regret and discontinuation of gender-affirming hormones in adulthood. To collect evidence on this topic, we searched PubMed with "gender dysphoria", "puberty suppression", and related terms, for literature published between database inception and Aug 31, 2022. A previous study found that 74·4% of individuals who had started gender-affirming hormones before age 18 years were still on gender-affirming hormone treatment 4 years after starting medical treatment. However, it remains unclear what proportion of people who started medical treatment for gender dysphoria specifically with puberty suppression before age 18 years, and who then received gender-affirming hormones, continue gender-affirming hormone treatment into adulthood.

Added value of this study

We found that most (98%) individuals diagnosed with gender dysphoria who started medical treatment with puberty suppression when younger than 18 years and went on to receive gender-affirming hormones were still receiving gender-affirming hormones at follow-up. Studies on continuation rates of medical treatment in this particular population were absent. Our findings could help guide the public and legal debate regarding initiation of medical treatment for gender dysphoria in young people.

Implications of all the available evidence

Discontinuation of medical treatment for gender dysphoria in adulthood, among those who start treatment before age 18 years appears to be uncommon in the Netherlands.

suppression for mental and physical outcomes,[6] the treatment is regarded by some people as experimental because long-term follow-up is lacking.

As increasing numbers of adolescents are referred to gender identity clinics around the globe, it is important to answer outstanding questions, such as whether the desire for gender-affirming treatment in adolescence lasts throughout adult life.[7–9] Steensma and colleagues reported in 2011 that 45% of adolescents (ages 14–18 years) with gender incongruence in childhood no longer wanted to transition when they reached adolescence or adulthood.[10] In contrast, a recent study of children (ages 3–12 years) who had socially transitioned (ie, live in their identified gender) found that only 7% did not continue to identify as transgender after 5 years.[11] However, this study did not assess long-term continuation rates of gender-affirming hormone treatment in people who started treatment at a young age. Furthermore, in recent years, an increase in referrals of predominantly people assigned female at birth has been recorded; however, the reason for this is not yet clarified.[12–14]

The aim of this study was therefore to assess the proportion of people who continue gender-affirming hormone treatment in adulthood, after they started GnRHa and gender-affirming hormone treatment in adolescence according to the Dutch Protocol. Additionally, we set out to study whether timing of treatment initiation, reflected by age at first visit, age and puberty stage at start of medical treatment, duration of GnRHa monotreatment (ie, the period between start of GnRHa treatment and addition of gender-affirming hormones) were correlated with gender-affirming hormone treatment discontinuation rates. We also aimed to assess whether sex assigned at birth, year of first visit, and year in which gender-affirming hormone treatment was started were associated with discontinuation of treatment. We additionally investigated whether people who had undergone gonadectomy were more likely to continue treatment.

Methods

Study population and design

In this cohort study, we used data from the Amsterdam Cohort Of Gender dysphoria (ACOG).[15] All individuals—children, adolescents, and adults—visiting the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medical Center, Netherlands, at least once between its establishment (1972) and Dec 31, 2018, were included in the ACOG dataset. The ACOG dataset contains demographic and clinical data on all of its 8831 participants, extracted from medical records. The ACOG dataset did not include people with disorders of sex development. We included only people receiving a minimum duration of 3 months of GnRHa, which was started when younger than age of 18 years, preceding the start of gender-affirming hormone treatment (start of gender-affirming hormone treatment when younger than 18 years was not a requirement for inclusion).

Procedures and outcomes

Adolescent individuals could be medically treated at our gender identity clinic if referred by a physician, usually a general practitioner, and were diagnosed with gender dysphoria (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR 2000 or DSM-5 2013], American Psychiatric Association) by the gender identity clinic. People could start on intramuscular or subcutaneous triptorelin, a GnRHa, 3·75 mg every 4 weeks or 11·25 mg every 12 weeks when a Tanner genital stage II or higher for people assigned male at birth or Tanner breast stage II

or higher for those assigned female at birth was reached, usually around age 12 years. If gender dysphoria remained present after treatment was started, and participants met all criteria as defined by the Endocrine Society's guideline for treatment of people with gender dysphoria,[16,17] gender-affirming hormones could be added to induce puberty in eligible adolescents 16 years or older. Gender-affirming hormone treatment consists of oestrogen in people assigned male at birth, and testosterone in those assigned female at birth.[17] Over time, the Dutch Protocol was adapted, enabling adolescents who had already been treated with GnRHa for several years to start gender-affirming hormones from age 15 years. Occasionally, some people started gender-affirming hormones at a younger age than 15 years, for example to reduce growth in case a tall adult height was predicted. GnRHa was usually discontinued in people assigned female at birth when they were on the full, adult dose of testosterone. In people assigned male at birth, GnRHa treatment was continued until gonadectomy. After at least 1 year of gender-affirming hormone treatment, and at a minimum age of 18 years, people became eligible for gender-affirming surgeries. After gonadectomy, treatment with sex hormones become indicated lifelong.

The main outcome of this study was a prescription for gender-affirming hormones at the end of data collection (Dec 31, 2018), which was used as an indicator of ongoing use of gender-affirming hormones. A prescription at the end of data collection was defined in one of two ways: firstly, a gender-affirming hormone prescription in the hospital's prescription registry in 2018. However, at the gender identity clinic of the Amsterdam UMC, long-term follow-up visits are advised at least once every 3 years but some people choose to have these evaluations at another clinic and therefore might have received a prescription from clinicians elsewhere. Therefore, secondly, we (MATCvdL and CMW) linked our study population to data supplied by the national statistical office, Statistics Netherlands (Centraal Bureau voor de Statistiek; CBS) that contained information regarding all drug prescriptions reimbursed under basic health insurance. In the Netherlands health insurance covering basic medical expenses is mandatory for everyone living or working in the country. All gender-affirming hormone treatment must be prescribed by a medical doctor and is fully covered by this basic health insurance. Therefore, all gender-affirming hormones prescribed in the Netherlands are available in the CBS data. In addition, gender-affirming hormone medication is readily available at local pharmacies. It was therefore unlikely that, contrary to some other countries, gender-affirming hormones in the Netherlands are obtained through other resources after the first prescription.

Drug prescriptions in the CBS-database are classified by the Anatomical Therapeutic Chemical (ATC) system.[18] We (MATCvdL and CMW) searched for hormone prescriptions within the following subgroups: A14A, G03A, G03B, G03C, G03D, G03F, G03H, G03X, G04C, H01C, L02A, and L02B. We only searched for people for whom a prescription could not be found in the hospital's 2018 prescription registry.

Statistical analyses

We reported continuous variables as mean (SD) for normally distributed data. Non-normally distributed data were described as median with IQR. Dichotomous variables were presented as proportions. We used a Cox proportional-hazards model to analyse data. We calculated analysis time as the number of years between the start of gender-affirming hormone treatment and the first terminating event for each participant. Terminating events were either date of last found prescription in people who did not have a prescription at the end of follow-up (Dec 31, 2018) or, where no prescription was found, the date of last visit to the clinic. We censored data for people who had prescriptions at the end of the study. We also censored data of individuals who were deceased or had moved abroad at the time of death or emigration; if the date of death or emigration was not available, the date of last visit to the clinic was used.

Independent variables were sex assigned at birth, age at first visit to the clinic, age at start of GnRHa and at start of gender-affirming hormone treatment, puberty stage at start of GnRHa treatment, duration of GnRHa monotreatment, year of start of gender-affirming hormone treatment, year of first visit, and whether a gonadectomy was done. We did both a univariable analysis and a multivariable analysis. In the multivariable model, we excluded people who had already started hormone treatment elsewhere because year of first visit did not reflect their initial visit to a gender identity clinic, and this would bias the results. Individuals with missing data were also excluded from the particular analysis. The proportional-hazards assumption was tested on the basis of the Schoenfeld residuals in the multivariable model and was not met for sex assigned at birth. Therefore, we stratified the analyses by sex assigned at birth. To check for collinearity, we calculated the variance inflation factor (VIF) for each variable. A VIF greater than 10 was regarded as significant collinearity. Collinearity was found between duration of GnRHa monotreatment, and age at start of GnRHa treatment and age at start of gender-affirming hormone treatment. Duration of GnRHa monotherapy was therefore removed from the model. In the multivariable model without duration of GnRHa monotherapy, all VIF were below 10.

Except for age, which was modelled as a continuous variable, independent variables were dichotomous or categorical. Puberty stage at start of GnRHa treatment was divided into early or late puberty. For people assigned male at birth, a maximum testicular volume of 9 mL was considered early puberty, and a testicular volume above

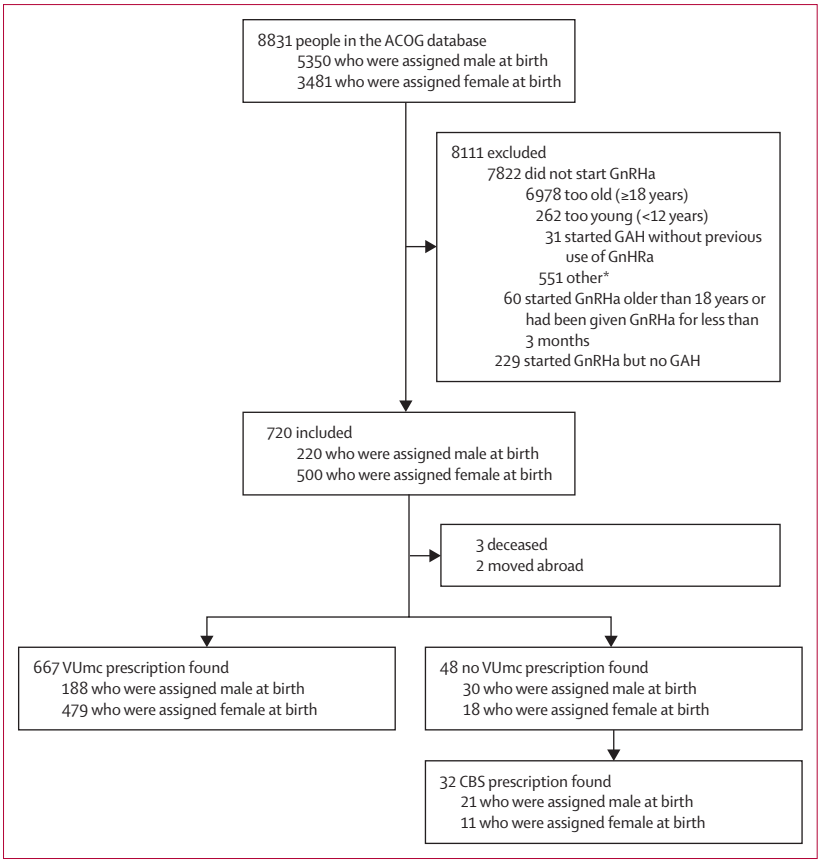


Figure 1: **Flowchart of participants**
ACOG=Amsterdam Cohort of Gender dysphoria. CBS=Centraal Bureau voor de Statistiek (Statistics Netherlands). GAH=gender-affirming hormones. GnRHa=gonadotropin-releasing hormone agonist. VUmc=Vrije Universiteit Medical Center prescription registry. *These people could still be in the diagnostic phase or were not diagnosed with gender dysphoria.

9 mL was considered late puberty. For people assigned female at birth, a Tanner breast stage II was considered early puberty, and stage III or greater was considered late puberty.

To investigate whether there was a difference in continuation of gender-affirming hormones between earlier and more recent years, year of start of gender-affirming hormones was divided in two categories (<2012 or ≥2012). We chose 2012 as the cutoff point because previous research has shown that the sharp increase in referrals of people assigned female at birth occurred around that time.[12]

Our gender identity clinic also provided care to youth who had already started medical treatment elsewhere. The initial dates of start of GnRHa and gender-affirming hormone treatment (taken from the referral letter) were registered for these people and used in the analyses. To avoid bias, these people were excluded when analysing age at first visit in our centre.

Use of CBS data is bound by strict rules to ensure anonymity. Due to low numbers, anonymity could not be guaranteed when stratifying people for both gonadectomy and sex assigned at birth. Therefore, this analysis was only done for the overall study population. We used STATA (15.1) for all data analyses.

Before initiation of the study, the local Medical Ethics Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study due to the retrospective design, and absence of interventions. The collaboration between the Amsterdam UMC, location Vrije Universiteit Medical Center, and Statistics Netherlands has been approved by the privacy officer of the Amsterdam UMC, location Vrije Universiteit Medical Center, and a lawyer from Statistics Netherlands. All data were reviewed by Statistics Netherlands to verify that the results did not contain any identifiable data.

Role of the funding source
There was no funding source for this study.

Results

In total, 720 people (529 [96%] White; 171 had missing ethnicity data) were included in this study (figure 1), of whom 220 (31%) were assigned male at birth and 500 (69%) were assigned female at birth. Their baseline characteristics are shown in table 1. Median duration of gender-affirming hormone treatment by the time of study analysis was 3·5 (IQR 1·5–7·6; range 0·1–20·0) years for people assigned male at birth, and 2·3 (1·2–4·8; range 0·0–15·5) years for those 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. Overall, 282 (59%) of all 480 eligible (ie, minimum age of 18 years and at least 1 year of gender-affirming hormone treatment) participants had gonadectomy.

Of all participants, three died and two had moved abroad during the study. For 667 (93%) of the remaining 715 individuals, we found a prescription for gender-affirming hormones consistent with the affirmed gender in the hospital's 2018 prescription registry. For an additional 32 (4%), we found a prescription in the CBS-linked database. There were 16 (2%) people for whom no prescription was found. Of these, nine were assigned male at birth (4% of all 220 people assigned male at birth) and seven were assigned female at birth (1% of all 500 those assigned female at birth). Figure 2 shows a Kaplan-Meier curve for the proportion of people prescribed gender-affirming hormones and duration of gender-affirming treatment. Of the 16 people for whom no prescription was found, 12 (75%) had undergone gonadectomy. For these individuals, no prescriptions were found for sex hormones of the sex assigned at birth either.

In the multivariable model, none of the assessed variables were correlated with finding a prescription or not. Year of start of gender-affirming hormone treatment (<2012 or ≥2012) could not be assessed because the event rate was too low in the groups starting medical treatment

in 2012 or after. All people assigned female at birth for whom a prescription was not found were in late puberty at start of GnRHa treatment. Therefore, we could not assess the association between puberty stage and finding a prescription or not finding a prescription in people assigned female at birth.

Because more people could be included in the univariable models than in multivariate models (ie, the people who had been externally referred and had already started medical treatment elsewhere were excluded from the multivariable model to avoid bias based on the year of first visit), the overall group could be assessed in the univariable models. In the univariable models, age at first visit, at start of GnRHa, and at start of gender-affirming hormone treatment were not associated with us finding a prescription or not, nor were puberty stage at start of GnRHa treatment, whether or not gonadectomy was done, year in which people first visited, or year in which gender-affirming hormone treatment was started (table 2).

Discussion

In this cohort study, we show that most people who had started medical transition with puberty suppression in adolescence followed with gender-affirming hormone treatment, continued using gender-affirming hormones in adulthood. Ongoing gender-affirming hormones use was not associated with age at first visit, nor was age at start of GnRHa treatment, age at start of gender-affirming hormone treatment, puberty stage at start of GnRHa treatment, nor gonadectomy.

In recent years, a surge of referrals of predominantly people assigned female at birth has been seen at our gender identity clinic.[12] Some people have raised concerns about gender-affirming treatment for adolescents because of poor diagnostic certainty of gender dysphoria, especially in light of the increasing demand for this treatment.[19] However, Arnoldussen and colleagues[12] have already shown that the proportion of adolescents diagnosed with gender incongruence has not changed between 2000 and 2016 at the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medical Center, suggesting that current referrals are similar with regard to gender dysphoria to those from earlier years. We have now shown that there is no difference in continuation of treatment between people who started gender-affirming hormones before 2012 and those who started treatment after 2012 in the Netherlands, corroborating Arnoldussen and colleagues'[12] statement. When assessing the association between not finding a prescription and age at first visit, at start of GnRHa treatment, and at start of gender-affirming hormone treatment, the chance of discontinuing treatment seemed to increase with older age at all these timepoints in people assigned female at birth in this Article. However, these were not statistically significant.

We were unable to find a prescription for only 2% of people in our cohort. These people might have stopped using gender-affirming hormones. There are several plausible reasons for discontinuation of treatment. There might be a lack of knowledge on the importance of continued hormone treatment after gonadectomy, or the side-effects of medication could have led to stopping of medication. Any participants with a non-binary gender identity might require only short-term medical treatment. No prescriptions for any kind of sex hormones (ie, neither for the sex assigned at birth or the experienced gender) were found, suggesting that people might not have stopped treatment because of regret of transition or change of gender identity; if people who had gonadectomy

	Overall		No prescription found	
	People assigned male at birth (n=220)	People assigned female at birth (n=500)	People assigned male at birth (n=9)	People assigned female at birth (n=7)
Age at start of GnRHa treatment, years	14·1 (13·0–16·3)	16·0 (14·1–16·9)	14·6 (13·3–15·2)	16·6 (16·5–16·9)
Early puberty at start of GnRHa treatment,	64 (30%)*	16 (3%)*	3 (33%)	0
Testicular volume at start of GnRHa treatment, mL	15 (8–20)†	NA	20 (6–22)†	NA
Menarche before GnRHa initiation	NA	335 (81%)†	NA	7 (100%)†
Monotherapy with GnRHa, years	1·7 (0·7–2·6)	0·8 (0·5–1·9)	2·4 (1·1–2·7)	0·7 (0·5–1·0)
Age at start of gender-affirming hormone treatment, years	16·0 (15·5–17·1)	16·7 (16·0–17·5)	16·0 (16·0–16·6)	17·6 (17·0–17·7)
Age at end of data collection, years	20·2 (17·9–24·8)	19·2 (17·8–22·0)	29·3 (27·8–31·2)	25·3 (19·6–26·5)
Age at last found prescription, years	NA	NA	24·6 (22·8–25·9)	20·7 (17·7–23·1)

Data are median (IQR) or n (%). Early puberty in people assigned male at birth was considered as testicular volume ≤9 mL and in people assigned female at birth considered as Tanner breast stage II. GAH=gender-affirming hormones. GnRHa=gonadotropin-releasing hormone agonist. NA=not applicable. *Data on puberty stage at start of GnRHa was missing for three people who were assigned male at birth and seven people who were assigned female at birth. †For eight people who were assigned male at birth, including two without a prescription at the end of follow-up, testicular volume was missing; for 85 people who were assigned female at birth, including one without a prescription at the end of follow-up, data on menarche were missing.

Table 1: **Characteristics of all participants**

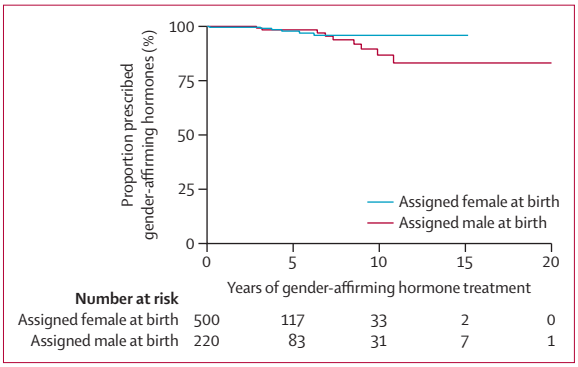


Figure 2: **Kaplan-Meier curve for proportion of people prescribed gender-affirming hormones and duration of gender-affirming hormone treatment, stratified by sex assigned at birth**

	Univariable model, overall	Univariable model, people assigned male at birth	Multivariable model*, people assigned male at birth	Univariable model*, people assigned female at birth	Multivariable model, people assigned female at birth
Age at first visit*	1·21 (0·95–1·54)	1·04 (0·76–1·41)	1·09 (0·62–1·92)	1·69 (0·97–2·93)	0·89 (0·31–2·53)
Age at start of GnRHa treatment	1·21 (0·91–1·59)	0·99 (0·67–1·45)	0·62 (0·23–1·69)	1·86 (0·97–3·56)	2·60 (0·37–18·4)
Age at start of gender-affirming hormone treatment	1·37 (0·85–2·20)	1·20 (0·67–2·16)	2·47 (0·60–10·1)	1·94 (0·89–4·26)	0·70 (0·08–6·20)
Puberty stage at start of GnRHa treatment					
Early puberty	Reference	Reference	Reference	Reference	Reference
Late puberty	0·62 (0·18–2·18)	0·62 (0·15–2·48)	0·56 (0·08–3·71)	Omitted†	Omitted†
Year of first visit*	1·03 (0·89–1·19)	0·85 (0·67–1·08)	0·83 (0·63–1·09)	1·24 (0·95–1·64)	1·09 (0·80–1·49)
Year of start of gender-affirming hormone treatment					
<2012	Reference	Reference	Reference	Reference	Reference
≥2012	0·68 (0·17–2·76)	0·90 (0·07–11·43)	Omitted‡	0·53 (0·10–2·85)	Omitted‡
Gonadectomy§					
No	Reference	..	..	..	..
Yes	0·43 (0·11–1·63)	..	..	..	..

Data are in hazard ratio (95% CI). Early puberty in people assigned male at birth was considered as testicular volume ≤9 mL and in people assigned female at birth was considered as Tanner breast stage II. GnRHa=gonadotropin-releasing hormone agonist. NA=not applicable. *External referrals excluded. †Analyses not possible because all people assigned female at birth for whom a prescription was not found were in late puberty at start of GnRHa treatment. ‡Analyses not possible because the event rate was too low in the group starting gender-affirming hormones after 2012. §Not stratified by sex assigned at birth to ensure anonymity.

Table 2: **Association between independent variables and the outcome of no prescription found**

regretted their transition they might have started treatment with sex hormones of their sex assigned at birth. A survey study by Turban and colleagues[20] found that, even among adult participants with a history of detransitioning, very few reported internal factors, including uncertainty about gender identity, as the reason for detransitioning. Alternatively a non-supportive, or even disapproving, attitude towards transitioning from an individual's environment, could have compelled participants to discontinue treatment due to social rejection.[21]

Roberts and colleagues[22] reported that, 4 years after hormone initiation, 74·4% of individuals who had started gender-affirming hormones before age 18 years continued treatment. However, it is unclear how many of these adolescents used puberty suppressing treatment before gender-affirming hormone treatment, and to what extent they underwent diagnostic evaluation before initiation of medical treatment. At our gender identity clinic, adolescents go through a meticulous diagnostic process before the start of GnRHa and gender-affirming hormone treatment. Perhaps differences in diagnostic evaluation and criteria to start treatment contribute to the discrepancy in continuation rates found between studies. In a small study from Germany,[23] the main objective of which was to assess satisfaction with transition-related care, three (9%) of 32 adolescents discontinued gender-affirming hormone treatment, none due to regret of transition. The higher proportion than in our study of discontinuation found by these authors[23] might be explained by their select and small study population. Whereas we were able to include the complete adolescent population seen at our centre, Nieder and colleagues[23] only included people who actively participated in their follow-up study. In a UK-based gender identity clinic, nine (5·1%) of 175 participants who had started gender-affirming hormones when at least age 17 years, discontinued this treatment.[24] However, this population started gender-affirming hormone treatment at a later age than our participants, without previous GnRHa treatment, and were discharged from their gender identity clinic.

Of all people for whom a prescription was not found at follow-up, 12 (75%) of 16 underwent gonadectomy and appeared to not use any sex hormones. This particular fact is troublesome as these individuals are at increased risk of complications such as osteoporosis. The proportion of people undergoing gonadectomy might be higher compared with in other countries because, in the Netherlands, gonadectomy was obligatory (until July 1, 2014) for transgender people to change their legal sex. Our findings underline the importance of careful counselling of young adults considering gonadectomy about the need for ongoing hormone treatment after gonadectomy.

To our knowledge, this study is the first to assess continuation of gender-affirming hormones in a large group of transgender individuals who started medical treatment with puberty suppression in adolescence. A valuable asset to our study is the link with a national prescription registry, yielding information on hormone use of all people who were treated at our centre. A limitation of our study is that gender-affirming hormones being prescribed does not necessarily mean that people are using the medication, possibly overestimating the number of people still using gender-affirming hormones. The results over the most recent years should be regarded with caution, as duration of follow-up is of course limited by time. This limitation by time is represented by the gradually decreasing number of people at risk with an increasing duration of gender-affirming hormone treatment in the Kaplan-Meier curve. Unfortunately, due to data limitations, we could only speculate about reasons why people might have stopped using gender-affirming hormones. Another limitation is that we were unable to do a power and sample size calculation in advance of the study because we could not find a study providing an estimation on the number of expected events in this population. Because the event rate in our study was very low, the regression analyses regarding determinants of stopping gender-affirming hormone

treatment might have been underpowered. Lastly, prescriptions might have been not recorded for people obtaining treatment outside of the regular health system. However, this would mean we overestimated the number of people stopping use of gender-affirming hormones, and would not alter the key message that the vast majority of this particular group continued using gender-affirming hormones.

Overall, 98% of people who had started gender-affirming medical treatment with puberty suppression in adolescence in this study continued gender-affirming hormones. This proportion is reassuring considering the public concern regarding regret of transition when started in adolescence. Factors associated with possibly stopping treatment were not identified; future research should identify reasons why young adults stop taking gender-affirming hormones. In the meantime, educating all young people who undergo gender-affirming treatment on the need for continued hormone treatment and on the health risks of discontinuing treatment should be a priority.

Contributors

MATCvdL contributed to conceptualisation, data curation, formal analysis, investigation, methodology, data visualisation, and writing of the Article. SEH contributed to conceptualisation, supervision, and writing of the Article. DTK contributed to conceptualisation, supervision, and writing of the Article. MdH contributed to conceptualisation, methodology, project administration, supervision, and writing of the Article. CMW contributed to conceptualisation, data curation, methodology, project administration, supervision, validation, data visualisation, and writing of the Article.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data will not be made available as this is prohibited by Statistics Netherlands to guarantee the anonymity of the people in its databases.

References

1 Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *Eur Child Adolesc Psychiatry* 1998; **7:** 246–48.

2 Delemarre-van de Waal HA, Cohen Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 2006; **155** (suppl 1)**:** S131–37.

3 Huirne JA, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; **358:** 1793–803.

4 Turban JL, Kraschel KL, Cohen IG. Legislation to criminalize gender-affirming medical care for transgender youth. *JAMA* 2021; **325:** 2251–52.

5 Courts and Tribunals Judiciaty. R on the application of Quincy Bell and A v Tavistock and Portman NHS Foundation Trust and others. Dec 1, 2020. https://www.judiciary.uk/judgments/r-on-the-application-of-quincy-bell-and-a-v-tavistock-and-portman-nhs-trust-and-others/ (accessed May 5, 2022).

6 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:** S1–259.

7 Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in referrals to a pediatric transgender clinic. *Pediatrics* 2019; **144:** e20191368.

8 Kaltiala R, Bergman H, Carmichael P, et al. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020; **74:** 40–44.

9 Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. *Arch Dis Child* 2018; **103:** 631–36.

10 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:** 499–516.

11 Olson KR, Durwood L, Horton R, Gallagher NM, Devor A. Gender identity 5 years after social transition. *Pediatrics* 2022; **150:** e2021056082.

12 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:** 803–11.

13 Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med* 2015; **12:** 756–63.

14 de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009–2016). *Arch Sex Behav* 2018; **47:** 1301–04.

15 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:** 582–90.

16 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009; **94:** 3132–54.

17 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:** 3869–903.

18 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022. https://www.whocc.no/atc_ddd_index/ (accessed May 5, 2022).

19 Laidlaw MK, Van Meter QL, Hruz PW, Van Mol A, Malone WJ. Letter to the editor: "endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline". *J Clin Endocrinol Metab* 2019; **104:** 686–87.

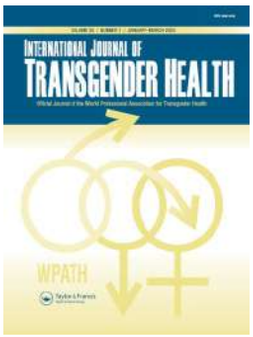
20 Turban JL, Loo SS, Almazan AN, Keuroghlian AS. Factors leading to "detransition" among transgender and gender diverse people in the United States: a mixed-methods analysis. *LGBT Health* 2021; **8:** 273–80.

21 Turban JL, Carswell J, Keuroghlian AS. Understanding pediatric patients who discontinue gender-affirming hormonal interventions. *JAMA Pediatr* 2018; **172:** 903–04.

22 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:** e3937–43.

23 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:** 632–45.

24 Hall R, Mitchell L, Sachdeva J. Access to care and frequency of detransition among a cohort discharged by a UK national adult gender identity clinic: retrospective case-note review. *BJPsych Open* 2021; **7:** e184.



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The Cass Review: Cis-supremacy in the UK's approach to healthcare for trans children

Cal Horton

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The Cass Review: Cis-supremacy in the UK's approach to healthcare for trans children

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ABSTRACT

***Background*:** Since 2016 trans people in the UK, and particularly trans children, have experienced a sustained and escalating campaign to roll back trans freedoms, rights and access to healthcare. A series of legislative, politicized and media-driven campaigns have resulted in the year-by-year worsening of access to affirmative healthcare for trans children in the UK.

***Aim*:** This study examines publications from the NHS-commissioned 'Cass Review' into children's gender services, seeking to better understand what is happening in trans children's healthcare in the UK.

***Methods*:** Inductive and deductive reflexive thematic analysis was applied to a collection of Cass Review publications related to trans children's healthcare published between January 2020 and May 2023.

***Results*:** Four concerns are presented and explored: (1) prejudice; (2) cisnormative bias; (3) pathologization; and (4) inconsistent standards of evidence. Each of these concerns impacts the Cass Review's approach to trans children's healthcare, with negative repercussions for trans children's healthcare rights and well-being.

***Discussion*:** The Cass Review itself can be understood as an example of cis-supremacy, within a cis-dominant healthcare system lacking accountability to trans communities. These findings draw attention to systemic barriers to effective healthcare policy, with relevance for trans healthcare across and beyond the UK.

KEYWORDS
Children; discrimination; gender identity; healthcare; policy; transgender; youth

Introduction

The UK is considered a hostile country for trans people especially for trans children (Madrigal-Borloz, 2023). Trans healthcare under the UK's National Health Service (NHS) has long been criticized for causing harm to trans people, with reports of pathologization, coercion and harm in NHS healthcare services (Horton, 2022d, 2022a; Pearce, 2018). Since 2016 the UK media has engaged in a sustained culture war related to trans rights, with a significant focus on trans children's healthcare (Amery, 2023; Faye, 2021; Pearce et al., 2020). Trans children's healthcare has become a topic of political interest, with politicians including the Prime Minister, the Secretary of State for Health and various Ministers for Equality questioning the validity of, or calling for the removal of access to, trans children's healthcare (Milton, 2022; Parsons, 2020; Raza-Sheikh, 2022). A 2020 legal judgment (Bell vs Tavistock, 2020), that was later overturned at appeal, called into doubt trans children's ability to consent to puberty-blocking medication. Legislative barriers to healthcare have been exacerbated by institutional responses, with NHS England responding to the original Bell court judgment by immediately suspending access to trans children's healthcare (NHS England, 2020). As a result of NHS England restrictions, no new adolescents were able to access puberty blockers from the NHS for nearly a year (Andersson, 2021), with barriers to care not removed even after the Bell judgment was overturned at appeal (Bell vs Tavistock, 2021). Within this politicized and challenging context, NHS England commissioned the 'Cass Review' into children's gender services, led by NHS pediatrician Dr Hilary Cass.

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Since the launch of the Cass Review in 2020, the situation for trans children in the UK has continued to decline (Madrigal-Borloz, 2023). In 2022 the UK Minister for Health called for clinicians to look for evidence of "*what has caused children to be trans*," citing the Cass Review to claim that "*identifying as trans*" is likely to be a response to "*child sex abuse*" (Milton, 2022). The Cass Review was cited by the British government to justify plans to exclude trans people from legislation to ban conversion therapy (British Psychological Society, 2022). The Cass Review was also cited to justify the closure of existing children's gender services for England and Wales, with services ceasing to see any new referrals 18 months before replacement services are expected to be operational (Ali, 2023). Trans healthcare professionals outside of the UK have critiqued the Cass review (Pang et al., 2022) as well as critiquing healthcare policies inspired by the Cass Review such as the NHS' 2023 draft service specification (WPATH et al., 2023).

This article offers an evidence-based analysis of key Cass Review documents, seeking to understand the positionality and approach of the Cass Review. A critical analysis of Cass Review documents is undertaken to better understand approaches to trans children's healthcare policy-making in the UK's National Health Service (NHS), with broader relevance to trans healthcare policy-making in other contexts. This effort builds from and complements a body of work analyzing trans related policy-making in different domains including in education (Horton, 2020; Omercajic & Martino, 2020) and healthcare (Linander et al., 2021; Pearce, 2018). This article is also informed by an interest in understanding the challenges trans people, and especially trans children face in the UK. The article looks to the concept of cis-supremacy to better understand how policy-making occurs in cis-dominant institutions and policy-scapes (Horton, 2023a). Cis-supremacy calls attention to the axes and forces of cis-power that actively dominate and oppress trans people, producing and perpetuating systemic and sustained injustices (Horton, 2023a). This article seeks to understand the factors that influence policy-making in one such cis-dominant institution, the UK's NHS, through examination of one discrete policy-influencing initiative, the Cass Review.

Methods

Secondary data

This article analyses a secondary dataset of NHS reports related to trans children's healthcare published since 2020. Four Cass Review reports are included: the Cass Review Terms of Reference (report 1), two Cass Review-authored stakeholder reports (reports 3–4) and the Cass Interim report (report 5). Two Cass chaired NICE reviews of evidence are also included (reports 2a and 2b). These reports are summarized in Table 1, with each report allocated a number that will be utilized for citations in the results section. Selection criteria for secondary data from the Cass Review prioritized published reports related to trans children's health care (January 2020–April 2023) and excluded letters, submissions to inquiries, submissions to draft service specifications, and blog posts. This collection of NHS documents published since 2020 constitutes an important source of information and insight on how NHS establishment stakeholders and policy-makers engage with trans children's healthcare.

Qualitative analysis

The dataset was uploaded into NVivo software and analyzed utilizing broad and unstructured inductive coding, combining qualitative document analysis (Bowen, 2009; Mackieson et al., 2019) with a critical review methodology. A critical review is inherently and intentionally subjective (Grant & Booth, 2009), bringing a reviewer's

Table 1. Summary of secondary data.

Report no.	report type	Abridged citation
Report 1	Cass Review Terms of Reference	(Cass Review, 2021b)
Report 2a and 2b	NICE evidence Review into puberty blockers (a) and hormones (b)	(National Institute for Health and Care Excellence – NICE, 2021b, 2021a)
Report 3	Online panel with primary and secondary care professionals	(Cass Review, 2021a)
Report 4	Gender specialists' questionnaire	(Cass Review, 2022a)
Report 5	Interim Report	(Cass Review, 2022b)

perspective and positionality into analysis and reflection on a body of work (Paré et al., 2015; Temple Newhook et al., 2018). I approached this analysis as a non-binary researcher, as a parent of a trans child, and with experience as a parent-service user of children's gender services in the UK. My approach to this topic is informed by a commitment to trans emancipatory research (Noel, 2016), acknowledging that trans lives are equal to cis lives, and being attentive to cisnormativity or pathologization of gender diversity. In the initial inductive coding content was reviewed and categorized into themes, drawing upon my theoretical and personal knowledge of trans healthcare, highlighting content that provided insight into the Cass Review's approach to trans children's healthcare. Initial categories were distilled into four broad themes (see Table 2), that correspond to the four key themes of the results section. For each broad theme, a thematic research question (see Table 2) was selected, with the data then taken through a second round of qualitative analysis framed by those research questions, looking for evidence and insight from the dataset to enrich and expand understanding of Cass Review approaches. This second-round of analysis applied deductive reflexive thematic analysis (Braun & Clarke, 2019), seeking data-driven answers to the four research questions, utilizing Cass Review data to enrich and expand understanding of the Cass Review's approach to trans children's healthcare.

Results

Results are presented in four broad themes: (1) prejudice; (2) cisnormative bias; (3) pathologization; and (4) inconsistent standards of evidence.

Table 2. Broad themes and research questions.

Broad theme	Research question number	Research question
Prejudice	RQ1	"How does the Cass Review engage with anti-trans prejudice?"
Cisnormative bias	RQ2	"Is there evidence of cisnormative bias within the Cass Review?"
Pathologization	RQ3	"Is there evidence of pathologization within the Cass Review"s approach?'
Inconsistent standards of evidence	RQ4	"How does the Cass Review engage with standards of evidence and decision making under uncertainty"

1/Prejudice

This section responds to the broad research question (RQ1) "How does the Cass Review engage with anti-trans prejudice?" More specifically, it seeks to examine (i) Does the Cass Review define and recognize anti-trans prejudice? (ii) Is there evidence of anti-trans or ill-informed professional views within Cass reports and how does Cass engage with such views? (iii) Does the Cass Review take steps to proactively protect trans children from anti-trans prejudice in healthcare?

Cass Review reports do not explicitly engage with the topic of anti-trans prejudice in healthcare. Reports do not cite or engage with an existing body of literature on anti-trans prejudice amongst healthcare professionals (Brown et al., 2018; Stroumsa et al., 2019). Within Cass Review reports however, quotations from interviewed healthcare professionals do display indications of potential ignorance, bias or anti-trans prejudice (see Table 3). These include healthcare professional quotes that express concern about trans children being created by peer pressure or social media, or the dismissal and belittling of trans children's identities (Table 3). All healthcare professional views, including those demonstrating ignorance, dismissiveness or hostility to trans children are presented as valid and valuable inputs to the Cass Review, with no discussion of the potential for anti-trans prejudice or ignorance amongst healthcare professionals.

One Cass Review report conducted a survey on the beliefs of a sample of healthcare professionals (Report 3). In this survey a third of interviewed healthcare professionals identified with the view that "*there is no such thing as a trans child*" (Table 3), a view that may indicate significant ignorance or anti-trans prejudice. The sample of interviewed healthcare professionals are described as "self-selecting," with the Cass Review taking no steps to exclude anti-trans professionals, despite working in a UK context of growing anti-trans prejudice (Amery, 2023; Pearce et al., 2020).

Table 3. Evidence of professional ignorance, bias or prejudice.

Category	Examples from professionals who are quoted within cass reports
Ignorance or conspiracies about transness as an externally imposed identity	"I have a concern some young people may feel pressured to believe they are gender discongruent by a powerful peer group." [Report 3, p. 37]
	"influence from external sources such as peer groups, social media, or online media such as YouTube" [Report 3, p. 37].
Belittling or dismissing trans identities	"Adult issues are being "thought about" with children who simply do not have the emotional development to be able to really think about it all." [Report 4, p. 27]
	"sometimes we get referrals for 3, 4, 5year-olds. Young children that have no true comprehension of gender identity at all." [Report 4, p. 25]
Denying the existence of trans children	"There is no such thing as a trans child. Gender dysphoria is always an indicator of another underlying problem and assessment should focus on understanding the causes of their distress." [Report 3, p. 35]. This statement, provided by the Cass Review as one of three options to describe professional views, was self-selected by 32% of interviewed healthcare professionals.

Table 4. Evidence of professional support for the non-affirmation of trans children.

Category	Examples from professionals who are quoted within Cass Reports
Challenging children on their identities	"I think it is important for a GP to gently challenge a child who presents like this" [Report 3, p. 21].
Seeking support for non-affirmative therapies	"creating a climate in which different therapeutic approaches can be discussed and developed without fear of vilification, legal action or complaints being brought. I believe the Cass Review has a role to play here." [Report 4, p. 31]

The Cass Review accepts this opinion that trans children do not exist as a valid professional viewpoint. At no point is this position or any other view recognized by the Cass Review as an indication of ignorance or prejudice. Instead, the Cass Review adopts a position where all views are welcomed and valued. The view that "there is no such thing as a trans child" is not deemed disqualifying from a professional seat at the table in designing healthcare for trans children. This approach has been noticed and critiqued by professionals from world leading healthcare services for trans children including from Australia. Professionals from Australian children's gender services wrote in the British Medical Journal that "*Cass seems keen to find a way forward that ensures 'conceptual agreement' and 'shared understanding' across all interested parties, including those who view gender diversity as inherently pathological*" (Pang et al., 2022, p. 2).

Cass Review reports include several quotations from interviewed healthcare professionals who advocate for approaches that do not accept or affirm a child's identity (see Table 4). In one quote a healthcare professional calls for trans children to be challenged on their identity (Table 4). Such professional views are presented without the Cass Review examining how a trans child would experience being probed or challenged on their identity when seeking healthcare support, with the professional's perspective centered. In another quote (Table 4) a healthcare professional expresses hope that the Cass Review will enable the practice of non-affirmative therapies "*without vilification or legal action*" (see Table 4). The exact type of non-affirmative therapy that might be subject to vilification or legal action is not defined, though the reference to legal action may relate to a long-proposed national ban on conversion therapy (Perry, 2023).

When considering references to non-affirmative or conversive clinical practice, it is important to note three points. Firstly, affirmative clinical approaches are characterized by listening to and respecting a child's individual identity, and supporting them without pre-defined expectations, whilst valuing all identities and expressions as equally valid (Hidalgo et al., 2013; Telfer et al., 2018). Secondly, conversion therapy encompasses any approaches that deny, delay or problematize a person's identity (UN Human Rights Council, 2020). Thirdly, non-affirmative practices are rarely openly labeled as conversion therapy (Ashley, 2022b). Instead conversive practices, or approaches grounded upon the rejection, pathologization or problematisation of gender diversity are commonly veiled under language of "exploratory" therapy (Ashley, 2022c). In the UK affirmative therapists have emphasized the space for gender exploration within an affirmative approach, and

have highlighted the dangers of so-called "exploratory therapy" offered by non-affirmative practitioners who do not regard trans identities as valid (TACTT, 2023). Trans healthcare policy reviews need to be aware of the potential dangers of conversive approaches, including approaches that are not openly identified as conversion therapy. Cass Review reports reference non-affirmative practice without acknowledging, defining or critiquing therapeutic practices that problematize or pathologize trans identities. Cass Review reports draw attention to the concerns of non-affirmative professionals, without recognizing the NHS' duty of care to trans children, including a responsibility to protect trans children from being harmed by conversive or pathologizing professional practice.

The Cass Review summarizes the concerns of professionals who want to provide non-affirmative therapy for trans and gender diverse children. There are many occasions where professionals seeking support for non-affirmative therapy are framed positively in Cass Review commentary.

> Participants who expressed concerns about the lack of non-affirmative or 'neutral' treatment tend to refer the child/young person to private providers. [Report 3, p. 19]

> Professionals feel unsupported to provide care that maintains a neutral approach in the face of what some participants described as an otherwise ideologically driven pathway. [Report 3, p .29]

These statements provide insight into the Cass Review's positionality. Cass Review commentary positions non-affirmative approaches as "neutral," contrasting them to affirmative approaches that are framed as "ideological." There is no recognition of the ideology underpinning approaches that deny the existence or validity of trans children. Cass Review reports do not consider the harms of approaches that deny or reject a trans child's identity (Horton, 2022c). Instead, Cass Review reports provide a sympathetic description of non-affirming professionals, centering the pressure they feel under to adopt an affirmative approach:

> Primary and secondary care staff have told us that they feel under pressure to adopt an unquestioning affirmative approach. [Report 5, p. 17]

Cass reports frame an expectation of trans positivity as an infringement on professional freedom, centering professional fears of being labeled transphobic.

> A perceived lack of freedom for professionals to take an exploratory approach or challenging approach due to perceived pressures from what some participants described as organisations taking an 'ideological stance'. [Report 3, p. 25]

> This can lead to a fear of being labelled transphobic if the professional suggests that it may be worthwhile trying to understand the possible meaning or origin of gender non-conformity in the child. [Report 3, p. 25]

Cass Review reports emphasize the concerns that some healthcare professionals hold that they might be sanctioned for their approach, presumably referencing a proposed national ban on conversion therapy:

> Fear of reprisals for professionals who take a more exploratory approach to supporting children and young people. [Report 3, p. 17]

> Some participants said they were concerned about being sanctioned by regulatory bodies if they were reported by a client who was seeking affirmation. [Report 3, p. 25]

In this last example, Cass Review commentary is referencing a hypothetical client who "*was seeking affirmation*," who might complain. The report centers a healthcare professional's concern of potential professional consequences. The Cass Review commentary does not reference the rights or well-being of the client, in this case presumably a child, who might seek redress for the harms of non-affirmative therapy. The Cass Review presents commentary on the fears of non-affirming professionals without any comment on the harms of conversion therapy, the negative impacts of transphobic professionals, or trans children's right to healthcare that is free from prejudice. Indeed, the voices of trans children harmed by interactions with transphobic healthcare professionals are noticeably absent across Cass Review publications to date. Literature outlining service user perspectives is not cited by the Cass Review (Horton, 2022d, 2022b).

The Cass Review does recognize that individual attitudes toward transness can impact on professional behavior and approach:

> Professionals' experience and position on this spectrum may determine their clinical approach. [Report 5, p. 16]

However, the review takes no steps to specifically recognize or discuss anti-trans prejudice. It does not define anti-trans prejudice, and does not recognize the scope for interviewed professionals to hold views that are impacted by prejudice or ignorance. In failing to acknowledge or understand anti-trans prejudice, it also fails to recognize that prejudice can present as good intentions, particularly framed around a rhetoric of "protecting children" (Amery, 2023; Oakley, 2023). In one report the Cass Review describes how every person on a stakeholder panel is there with the best intentions:

> There is strong professional commitment, everyone participating on the panel wants to be able to do the best for these children and young people. [Report 3, p. 41]

The Cass Review focuses on what it regards as good intentions, whilst ignoring a reality that 32% of that specific sample of healthcare professionals self-identified as denying the existence of trans children (Table 3). Denying the existence of trans children is arguably a highly ideological and prejudiced position, with the impossibility of a trans child a core tenet of "gender critical" ideology (Amery, 2023). According to Amery (2023, p. 13) "'*gender critical' activism around childhood portrays trans identity as a pernicious ideology or false belief to which children are vulnerable*." The movement against trans equality seeks to limit trans possibilities through targeting and curtailing the supports that allow trans people to exist as trans people (Owen, 2022). Denying the existence of trans children pushes trans children into a position of precarity, making it harder for trans children to be recognized and find social and institutional support as trans children (Amery, 2023). In the Cass Review, individuals who deny the existence of trans children are retained and valued as professional experts, with all healthcare professional views welcomed, included those grounded in the erasure, rejection, and problematisation of trans children.

The Cass Review emphasizes the polarization that characterizes trans children's healthcare in the UK.

> Over the last few years, broader discussions about transgender issues have been played out in public, with discussions becoming increasingly polarised and adversarial. This polarisation is such that it undermines safe debate and creates difficulties in building consensus. [Report 5, p. 26]

Here the Cass Review takes a stance that polarization is in itself a key problem in trans children's healthcare. The Cass Review discusses polarization without acknowledging the existence of anti-trans prejudice. Framing all (cis) views as equally valid and equally welcome, enables that Cass Review to frame neutrality as an appropriate starting position. Amidst a field characterized by stark polarization, the review chooses to place significant emphasis on a search for consensus:

> Recommendations of the Review and will be captured through our participative and consensus development approach. [Report 1, p. 2]

In several places in Cass Review reports, an absence of consensus is itself regarded as a significant cause for concern. The Cass Review raises concerns about puberty blockers, emphasizing a lack of consensus on "the primary purpose of puberty blockers" [Report 4, p. 11]. It references differing views on whether their aim is "*to pause puberty to allow further time to explore options (30.3%) or to alleviate or reduce distress associated with pubertal changes (21.2%)*" [Report 4, p. 27]. The Cass Review here presents different articulations on their primary purpose as a significant cause for concern, even when the presented options are overlapping and mutually compatible. Similarly, a lack of consensus on the purpose or comparator groups for evaluating affirmative healthcare is raised as a concern for both puberty blockers and gender affirming hormones.

> The first step of this involves defining the PICO (the Population being treated, the Intervention, a Comparator treatment, and the intended Outcomes).

> This of itself was challenging, with a particular difficulty being definition of the intended outcomes of puberty blockers, and suitable comparators for both hormone interventions. [Report 5, p. 35]

Here the Cass Review frames a lack of consensus on purpose or comparator groups as inherently a concern in the use of affirmative healthcare. The Cass Review fails to acknowledge the significant barriers to consensus in defining purpose, comparison group, or intended outcomes in a politicized and prejudice affected field of medicine. There is not likely to be consensus on who the target population is, or what the goal of medical intervention is, when some actors are seeking to treat, prevent or eradicate a disease, confusion or disorder, while others are seeking to maximize well-being outcomes in a minority population. There is no room for consensus between those seeking to maximize health and happiness in trans and gender diverse children, and those seeking to prevent or minimize the existence of trans children. Across Cass Review reports there are multiple indications that the Cass Review has failed to recognize, to take steps to protect trans children from the influence of anti-trans prejudice.

2/Cisnormative bias

This section addresses the research question "Is there evidence of cisnormative bias within the Cass Review?" (RQ2 see Table 2). Cisnormativity is the presumption that everyone is cisgender or should be (Keo-Meier & Ehrensaft, 2018). Serano (2016) has described cisnormativity as a societal double standard that advantages cis people. Cisnormativity permeates societies and institutions, invisible to most cis people, yet exacting harm on trans people in structures and systems that were not designed to include trans lives (Newbury, 2013). Within a cisnormative world, individuals and groups are highly likely to be influenced by cisnormative biases, which can often be unconscious or unintentional. Cisnormative bias can lead to a trans child being viewed as inherently a problem or deviation, with transness regarded as suspicious, problematic or pathological (Horton, 2022a). Cisnormative bias can lead to trans lives not being valued as equal to cis lives, with trans children's rights disregarded. This section explores the positionality of the Cass Review, examining Cass Review reports for indications of potential cisnormative bias.

In order to understand the positionality of the Cass Review, it is helpful to first examine how the Cass Review was designed and established. Dr Cass was selected to lead the process that became known as the Cass Review explicitly because she was a clinician without any knowledge or professional experience in trans children's healthcare.

> Given the increasingly evident polarisation among clinical professionals, Dr Cass was asked to chair the group as a senior clinician with no prior involvement or fixed views in this area. [Report 5, p. 35]

Wider stakeholders around Cass were likewise selected for an absence of trans specific knowledge or experience, including exclusion of those with lived experience of being trans. The original published Terms of Reference (ToR) for the Cass Review's assurance group explicitly excluded trans expertise, stating that it "*deliberately does not contain subject matter experts or people with lived experience of gender services*" [Report 1, version 1]. The current (updated) assurance group ToR is worded less clearly, yet still conveys exclusion of those with expertise or lived experience, as such individuals would naturally be expected to have an interest in the outcome of the review:

> Members are independent of NHS England and NHS Improvement and of providers of gender dysphoria services, and of any organisation or association that could reasonably be regarded as having a significant interest in the outcome of the Review. [Report 1, p. 2]

The Cass Review, by design, prioritized cis professionals with no experience in trans healthcare. Within this design there was no obvious consideration of the risk of cisnormative bias in such a leadership structure. Nevertheless, upon establishment, the Cass Review could have taken steps to actively and explicitly tackle cisnormative bias within the delivery of the Review. Indeed, such an approach could be justified as essential in a cis-led team working in trans children's healthcare (Ashley & Domínguez, 2021). However,

there is no indication that this has been done, and several indications of embedded cisnormativity.

Indications of cisnormative bias can be seen in the terms the Cass Review uses to describe trans and gender diverse children. There are multiple occasions where trans children are explicitly delegitimised and mis-gendered within Cass Review reports. In several places, trans children are defined by their assigned gender:

> The largest group currently comprises birth-registered females first presenting in adolescence. [Report 5, p. 16]

> birth-registered males presenting in early childhood. [Report 5, p. 19]

Here we see that trans children are mis-gendered and delegitimised as "*birth registered females/males*," a description that actively disregards a trans child's identity and self-knowledge. Such language is an act of disrespect and potential harm to current NHS service users including trans boys, trans girls and non-binary children. This language choice calls into question whether the Cass Review prioritizes a duty of care to trans children, including their right to have their identity respected and valued in Cass Review reports. Within the interim report the Cass Review chooses to categorize all trans boys and trans masculine adolescents under the label "*F*" and places all trans girls and trans feminine children under the label "*M*" [Report 5, p. 33]. Many current GIDS service users are trans, yet here all GIDS service users are categorized by the Cass Review as though they are cis. Categorizing all current GIDS service users as though cis can be interpreted as an indication of cisnormative bias, and arguably an exertion of cis power in a report on trans and gender diverse children. It's worth noting that this type of practice, the systemic erasure and delegitimization of trans people, falls under a definition of transphobia commonly used by trans communities in the UK (TransActual, n.d.).

Delegitimization of trans identities is not only applied to trans children. In the Cass Review's stakeholder report, interviewed professionals are listed by identity, with the report choosing to exclude adult trans professionals from the categories of "male" and "female." Instead, all trans professionals are segregated to an "other" category described as encompassing "*Other = Trans female, trans male, no gender, non-binary*" [Report 3, p. 11]. Excluding all trans people from the categories of male and female is a cisnormative approach, indicating trans people's identities are not regarded as equal to cis people's. In reports written by cis stakeholders, with no trans accountability, it can be viewed as an exercise in cis-supremacy (see discussion section), with even trans adults' genders othered and excluded.

A significant indication of cisnormative bias can be seen in the absence of recognition of the existence of trans children across all Cass Review reports. A review expected to define best practices for trans children's healthcare chooses to entirely avoid the word trans when referring to the children or adolescents who access UK Children's Gender Services. Whilst including seven references to "transgender adults," the interim report does not include even one reference to a trans child, adolescent or young person. Trans children are instead reduced to definition as "*gender questioning children and young people*" (Report 5, p. 11) or "*children and young people needing support around their gender*" (Report 5, p. 7). This framing conflates trans children, including those who have socially transitioned and are settled and confident in their affirmed identity, with children who are questioning their gender. This conflation erases the existence of trans children. The decision to erase trans children across all Cass Review reports is an indication of cisnormative bias, framing trans children's very existence as up for debate. This position can also be regarded as an act of cis-supremacy, rendering trans children invisible in a report that will determine their access to healthcare.

Cisnormative bias can also be seen in Cass Review discussions on different approaches to trans healthcare. In a Cass Review survey, healthcare professionals are asked to position themselves along a spectrum from "*cautious*" to "*affirmative*" [Report 3, p. 13]. This can be recognized as biased framing. It avoids acknowledging the existence of anti-trans and conversive approaches within the spectrum, framing "cautious" as the alternative to affirmative care. This choice to frame trans-hostile and pro-conversion

therapy views as "cautious" or "careful" is seen elsewhere in Cass Review commentary:

> some clinicians taking a more gender-affirmative approach and others emphasising the need for caution and for careful exploration of broader issues. [Report 5, p. 48]

> There is no precedent in terms of where professionals would place themselves on an ideological spectrum when it comes to their approach to the management of gender questioning children and young people… whilst a higher proportion of participants would consider themselves 'cautious', the research team was able to recruit professionals with a broad mix of views. [Report 3, p. 10]

Cass Review commentary does not include any recognition of clinical practices that are coercive or abusive. Nor does it acknowledge that anti-trans prejudice, or indeed conversion therapy, can be veiled under a banner of caution (Ashley, 2019b). The Cass Review does not examine the role of cisnormativity in making professionals uncomfortable with affirmative approaches that respect and value trans lives. The scale utilized to assess professional views seems to have been created by the Cass Review, rather than utilizing an existing tool in trans healthcare. The Cass Review scale runs from "cautious" to "affirmative," in order to assess professional viewpoints on appropriate care for trans children. The fact that this scale was deemed appropriate is an indicator of cisnormative bias. The scale enables trans-hostile professionals to list themselves under the positive banner "cautious," implying that an affirmative approach is incautious or reckless, whilst obscuring the risk inherent in denial of affirmative healthcare.

The Cass Review presents an interpretation of what it sees as the key differences between non-affirmative and affirmative approaches to trans children's healthcare:

> At primary, secondary and specialist level, there is a lack of agreement, and in many instances a lack of open discussion, about the extent to which gender incongruence in childhood and adolescence can be an inherent and immutable phenomenon for which transition is the best option for the individual, or a more fluid and temporal response to a range of developmental, social, and psychological factors. [Report 5, p. 16]

This long sentence combines several different concepts and issues. It references the nature of gender identity, factors that could influence identity, and whether identity is fixed or can be fluid or dynamic. The sentence combines these references to the concept of gender identity with discussion of discrete policy agendas. The sentence conflates specific claims (identity as inherent and rigid) with specific policy recommendations (transition may be beneficial), presupposing that transition may not be beneficial if identities are in any way socially influenced or can be evolving or fluid. These simplistic statements and assertions are provided without evidence. This interpretation arguably mischaracterizes much current trans healthcare scholarship and affirmative practice (Ashley, 2019a; Hidalgo et al., 2013; TACTT, 2023). In affirmative practice it is commonplace, for example, for gender fluidity to be respected alongside recognition of the importance of individual self-determination and support for autonomous social transition at any age (Telfer et al., 2018).

Yet here, according to the interpretation of the Cass Review, belief that identity can be socially shaped, evolving or fluid is presented as a justification for non-affirmative practice. Within Cass Review commentary, nuanced and complex questions on the nature of identity are combined and conflated with policy agendas in a way that veils more significant differences between affirmative and non-affirmative healthcare. Differences in healthcare approach are characterized as built on philosophical and metaphysical differences in understanding of gender identity. The Cass Review centers a focus on the meaning of gender, decentering acknowledgement that trans people, including trans children, exist, and have a right to equity in healthcare. This focus on the meaning of gender rather than healthcare policy and practice appears in other sections of Cass Review reports.

> At one end are those who believe that gender identity can fluctuate over time and be highly mutable… gender related distress may be a response to many psychosocial factors, the distress may resolve in later adolescence or early adulthood…. At the other end are those who believe that gender incongruence or dysphoria in childhood or adolescence is generally a

> clear indicator of that child or young person being transgender. [Report 5, p. 56]

Here the Cass Review frames disagreement between affirmative and non-affirmative approaches as one centered around "belief" on the nature of gender identity. Disagreement is presented as conceptual or philosophical, eluding more important distinctions in action and policy. Notably, the Cass Review does not examine core distinctions between affirmative and non-affirmative approaches that relate to the pathologization or celebration of gender diversity, that relate to child rights, that relate to agency or bodily autonomy, and that relate to institutional accountability to or control over marginalized communities. This framing, and its emphasis on the philosophical and conceptual draws focus away from analysis of pathologization, persecution or oppression. Approaches that control, pathologize or deny trans existence are framed through a focus on philosophical curiosities on the meaning of identity. Here the Cass Review strays from the remit of a review of effective healthcare for a minoritized population, moving from medicine into the philosophy or theory of gender. This shift from healthcare design for a minority group to philosophizing on the meaning of gender itself reveals the cis bias of the Cass team. Trans existence is not accepted as a starting point for this review into trans healthcare, instead the very meaning of gender is elevated as a clinical curiosity.

The Cass review references the polarization in trans children's healthcare (as discussed in the earlier section on prejudice), with the Cass Review presenting itself as neutral amidst this polarization, capable of building consensus. There are a number of concerns with the Cass Review seeing itself a suitable leader in the development of consensus in this polarized field. The Cass Review is a cis-led team selected for being unfamiliar with trans lives and inexperienced in trans healthcare. This inexperience and outsider status brings with it significant scope for cisnormative bias. The Cass Review has adopted a stance where all views are welcome and where anti-trans prejudice is not acknowledged or isolated, meaning a search for consensus includes stakeholders who are actively opposed to, or deny the existence of trans children. The Cass Review has adopted an approach where trans children are not explicitly recognized, with no acknowledgement of their existence let alone their right to equality in healthcare. These elements create a situation where a search for consensus holds risks for trans children. In several sections the Cass Review references the risk of ideology shaping the work of others, but without self-reflection on the likely bias of a cis outsider engaging with trans healthcare:

> there is a risk that some authors interpret their data from a particular ideological and/or theoretical standpoint. [Report 5, p. 19]

The lack of consideration of the potential for cisnormative bias amongst the Cass Review team is a significant limitation of the Cass Review. Trans healthcare is a field long impacted by the ignorance or fears of professionals who problematize trans lives (Pearce, 2018). Professionals need to take pro-active steps to overcome entrenched cisnormativity, to recognize and challenge systemic anti trans bias or fears, to welcome and respect trans people of all ages as equals.

3/Pathologization

Across Cass Review reports there are numerous examples of the problematisation of the existence of trans children. The Cass Review interim report references "*aetiology*" [Report 5, p. 56], or research into the factors that cause a trans identity. The Cass Review referencing research on etiology problematizes gender diversity. Research into the causation of trans identities has a pathologized history, running parallel to efforts to prevent or cure transness (Winters, 2011, 2022). Reference to etiology has no place in a modern depathologized healthcare system that values trans lives as equal to cis lives (Turban, 2020). This reference to seeking evidence on the causation of gender diversity contrasts strikingly with recent publications related to trans children's healthcare from countries with a more trans positive approach. The Australian Standards of Care for trans children's healthcare for example states that "*being trans or gender diverse is now largely viewed as being part of the natural spectrum of human diversity*" (Telfer et al., 2018, p. 2). The World

Professional Association for Transgender Health (WPATH)'s latest Standards of Care (version 8) chapter on children states "*childhood gender diversity is an expected aspect of general human development*" and "*childhood gender diversity is not a pathology or mental health disorder*" (Coleman et al., 2022, p. 67). Recognition of the existence and value of trans children's lives provides, in other healthcare systems, an important foundation of respect from which other data and clinical priorities are drawn. The Cass Review avoiding any such trans positive statements about the value of trans children's lives, while referencing research into 'etiology', is an indication of the pathologization of trans identities.

Research on identity fluidity at different ages is upheld as a significant research priority for a national health service.

> The more contentious and important question is how fixed or fluid gender incongruence is at different ages and stages of development, and whether, regardless of aetiology, can be an inherent characteristic of the individual concerned. [Report 5, p. 56]

Here the Cass Review presents as accepted fact that identity fluidity is an important research priority. No evidence is provided to support this presumption. There is no discussion of why this is deemed a top research priority, nor is there stipulation on who holds this view. The reader is presumed to agree with this unsupported statement. There is no consideration of whether trans communities or indeed trans children hold identity rigidity as a top research priority for their healthcare service. Presenting this as a top research priority can be seen as an indication of the problematisation of identity fluidity, with gender stability upheld as an important research question. No justification is provided on why this topic is prioritized by a National Health Service, rather than for example, research into how to improve mental and physical health in trans and gender diverse children, or efforts to enhance healthcare access and equity. Research on identity fluidity at different ages is upheld as an important research priority with no discussion or evidence on how this is relevant to healthcare outcomes. This can be seen as a pathologising research priority, with the Cass Review focusing on studying, measuring and defining trans identities, whilst disregarding priorities that ensure trans and gender diverse children receive their right to equal and respectful healthcare.

Analysis of the words used by the Cass Review can reveal underlying assumptions. In several sections the Cass Review utilizes the language of disease when referring to trans children and associated research priorities. The Cass Review references "*a rapid change in epidemiology*" [Report 5, p. 16]. The word epidemiology, with its associations with disease, presents as problematic a phenomenon (increased awareness and confidence of trans children) that could in a trans-positive report be celebrated. Framing increased confidence of trans children in the language of disease is pathologizing, inherently problematizing trans lives. Cass Review reports demonstrate no awareness of the harms of treating transness as a disease, nor any commitment to the depathologization that the NHS is meant to be adapting to under the World Health Organization's ICD-11 (as discussed further below). Cass Review usage of such language is at odds with a depathologized approach that values trans lives (Horton, 2022a).

Further evidence of a lack of commitment to depathologization can be seen in the Cass Review's approach to diagnosis. A depathologized approach would recognize trans people, including trans children, as a minoritized group who sometimes have discrete healthcare needs (Suess Schwend, 2020). Instead, the Cass Review utilizes the existence of discrete healthcare needs as justification for applying a disease diagnosis and treatment model to a minority population. In one sentence the Cass Review acknowledges that trans young people do not recognize being trans as a medical condition. However, the Cass Review immediately disregards this stance by pointing to the existence of a psychiatric diagnosis.

> Most children and young people seeking help do not see themselves as having a medical condition; yet to achieve their desired intervention they need to engage with clinical services and receive a medical diagnosis of gender dysphoria. [Report 5, p. 45]

Trans communities have historically been pathologized as holding an identity "disorder"

that requires psychiatric diagnosis (Winters, 2011). This pathologization has continued, even whilst the diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has shifted from "Gender Identity Disorder" in 1994s DSM IV (*Diagnostic and statistical manual of mental disorders, 4th ed*, 1994) to "Gender Dysphoria" in 2013s DSM V (American Psychiatric Association, 2013). The continued existence of a 2013 DSM-V psychiatric diagnosis for transness does not justify continued NHS adherence to pathologization. Indeed, global commitment to depathologization of trans identities led to the World Health Organization's reclassification of trans health in ICD-11, moving the diagnosis out from the chapter on mental and behavioral disorders (World Health Organisation, 2021). This reclassification was specifically intended to help combat a legacy of pathologization of trans identities by the medical and psychiatric establishment, with the World Health Organization recognizing that pathologization "*can cause enormous stigma*" (World Health Organization, n.d., para. 3).

There are times when the Cass Review steps close to recognizing the need to adopt a different approach to trans healthcare than a pathologized disease diagnosis, treatment and prevention paradigm. Yet, each time the Cass Review steps close to this recognition, the review turns the other way. In one paragraph the Cass Review recognizes that presenting trans identities as a clinical condition "*feels wrong*":

> We recognise that for some of those reading this report it may feel wrong to compare gender incongruence or dysphoria to clinical conditions, and indeed this approach would not be justified if individuals presenting with these conditions did not require clinician intervention. However, where a clinical intervention is given, the same ethical, professional and scientific standards have to be applied as to any other clinical condition. [Report 5, p. 54]

The fact that some trans people sometimes require specific medical interventions is deemed sufficient to justify treating transness as a clinical condition. There is no reflection on the pathologization inherent in this approach. There is also no discussion of trans children's right to equal access to healthcare, or their right not to be pathologized and problematized by their healthcare providers. In other areas of the report the Cass Review maintains that a diagnosis approach to engaging with trans children is essential, even while recognizing that gender identity is personal and cannot be externally diagnosed.

> For children and young people with gender-related distress, many people would dispute the notion that 'making a diagnosis' is a meaningful concept, arguing that gender identity is a personal, internal perception of oneself. However, there are several reasons to why a diagnostic framework is used. [Report 5, p. 59]

The concept of diagnosis is referenced in multiple areas, with a particular emphasis on clinician perspectives. In one section the Cass Review presents commentary on concerns raised by interviewed healthcare professionals:

> The majority of participants have experienced this trend where…children and young people presenting with concerns about their gender identity have self-diagnosed. [Report 3, p. 32]

Using the word "trend" in a UK NHS report to describe trans children can be considered problematic or pathologizing, resonating with a discourse (trans as a "trend") that delegitimises and harms trans children (Amery, 2023). The Cass Review then reflects on diagnosis being impeded by a lack of a blood test for being trans:

> When it comes to gender dysphoria, there are no blood tests or other laboratory tests, so assessment and diagnosis in children and young people with gender related distress is reliant on the judgements of experienced clinicians. [Report 5, p. 60]

In the above quotation, the Cass Review steps from a factual statement (there not being a blood test), to a pathologising assumption that it is therefore a clinician's responsibility to use their judgment to diagnose trans-ness. This assumption, that is not analyzed or justified, disregards affirmative approaches that recognize and respect trans people's self-knowledge. The assumption that a clinician should and can diagnose whether a child is trans, potentially contradicting and over-ruling an individual's self-understanding, feeds into a belief that a clinician ought to first rule out other possible diagnoses before

respecting a child's identity. This issue is referenced in Cass Review report discussions on the topic of "differential diagnosis."

> It is standard clinical practice to undertake a process called differential diagnosis… (establishing) the most likely diagnosis, other possible diagnoses and the reasons for including or excluding them… These considerations need to be applied to the assessment of children and young people presenting with gender-related distress. [Report 5, p. 60]

Within Cass Review reports, multiple healthcare professionals are quoted expressing concern at applying what they see as a non-clinical approach to healthcare for individuals with the disease or condition of gender distress:

> How as mental health professional do we differentiate between a child who wants to change their body, or is mentally ill and needs help, or child that has trauma and abuse? We can use detailed assessment, but we can still misdiagnose. [Report 3, p. 39]

Cis professional concerns over accepting a child's self-knowledge of their own identity are presented by the Cass Review as reasonable and appropriate clinical concerns. Cass Review reports do not consider the need to educate under-informed healthcare professionals or advocate for a depathologized understanding of trans identities. There is no examination of the potential harms and risks of a medical diagnosis approach to validating and respecting trans children's identities. The Cass Review also makes no effort to reflect upon the risks of "differential diagnosis" in a world where many medical professionals ideologically deny the existence of trans children. Instead, the Cass Review reinforces the need for applying a standard disease diagnosis and treatment approach to trans or gender diverse children. Indeed, the Cass Review shows sympathy to healthcare professionals who report feeling "under pressure" to treat trans children with respect, implicitly presenting an affirmative approach as inappropriate.

> Primary and secondary care staff have told us that they feel under pressure to adopt an unquestioning affirmative approach and that this is at odds with the standard process of clinical assessment and diagnosis that they have been trained to undertake in all other clinical encounters. [Report 5, p. 17]

Across Cass Review reports and analysis, commitment to a trans as disease paradigm is visible yet unacknowledged. Instead of acknowledging a minority population with discrete healthcare needs, the Cass Review prioritizes a disease treatment model intended to "*resolve gender related distress*" [Report 5, p. 8]. This failure to understand the purpose of trans healthcare, framing it as diagnosis, prevention and treatment of a disease, rather than supporting well-being in a minority population, flows directly into problems in the Cass Review's approach to evidence, the focus of the final theme.

4/Inconsistent standards of evidence

This section explores the Cass Review's approach to evidence and uncertainty. It examines the quality of evidence required to justify affirmative policy and practice, the level of evidence required to justify non-affirmative approaches, and how evidence informs Cass Review policy recommendations.

When reviewing existing practices in gender affirming healthcare, the Cass Review relies on two National Institute for Health and Care Excellence (NICE) evidence reviews, both chaired by Dr Cass. Dr Cass chaired reviews into the use of puberty blockers and sex hormones for trans adolescents [Report 2a and 2b]. These NICE evidence reviews, their approach to evidence, and their recommendations directly inform the wider Cass Review. Two concerns relating to these NICE evidence reviews will be outlined here. These two concerns relate to the NICE review approach to evidence, and the public communication of NICE evidence review conclusions.

The two NICE evidence reviews have been critiqued on a number of fronts. The European and World Professional Associations for Transgender Health raised written concerns about these two NICE reviews, critiquing their approach to evidence appraisal, for example critiquing their exclusion of a body of studies that combine puberty blockers with HRT (EPATH & WPATH, 2023). Parents of trans children have questioned

the exclusion from evidence review of data demonstrating the safety and effectiveness of puberty blockers when used by cis children for precocious puberty (Horton, 2023c). Other commentators have questioned the appropriateness of the critical outcomes in the NICE studies, with puberty blockers, for example, assessed by NICE on whether they lead to improvements in dysphoria or mental health rather than whether they are safe and effective in blocking puberty (Eckert, 2021). A particularly concern about the NICE evidence reviews concerns their approach to evidence quality, and their narrow focus on evidence of a specific type.

The NICE reviews adopted the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to appraisal of evidence (Guyatt et al., 2008). In the GRADE approach, evidence is designated high, moderate, low or very low quality, depending on the nature or source of the evidence (Balshem et al., 2011). "High quality" designations are reserved for evidence drawn from sources such as Randomized Control Trials (RCTs), whilst observational studies are typically considered "low" or "very low" quality evidence. The two NICE reviews, by design, prioritized a search for "high quality" evidence. They found no such "high quality" evidence, utilizing a lack of RCTs to inform their conclusion "*evidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive*" [Report 5, p. 18].

There are several significant limitations of this approach to evidence appraisal. RCTs are widely recognized as inappropriate for trans children's healthcare, with a wide range of experienced healthcare researchers, ethicists and clinicians recognizing RCTs as both infeasible and unethical in this field (Brik et al., 2020; Giordano & Holm, 2020; Horton, 2023c). Brik et al. (2020, p. 2616) notes that "*many would consider a trial where the control group is withheld treatment unethical, as the treatment has been used since the nineties and outcome studies although limited have been positive*." Parents of trans children "*felt a randomised trial in which some trans adolescents would be offered psychological therapy with an incongruent puberty instead of affirmative healthcare, was an approach that would amount to 'conversion therapy'*" (Horton, 2023c, p. 508). For reasons of feasibility and ethics no RCTs have been conducted, nor are any currently planned. Even for precocious puberty, a planned RCT into puberty blockers was unsuccessful when participants in the non-treatment arm noticed their puberty had not been blocked, and dropped out of the study in order to access puberty blockers from a different source (Mul et al., 2001). A recent article has criticized the methodological and clinical inappropriateness of RCTs in trans children's healthcare, whilst highlighting the value of observational studies in guiding clinical practice (Ashley et al., 2023). The NICE evidence reviews adopted a search strategy that centered a standard of evidence considered by many practitioners, researchers and ethicists to be inappropriate for evaluating puberty blockers and affirmative HRT.

The NICE reviews also deviated from standard GRADE guidance in their treatment of "low quality" evidence. GRADE guidance explicitly separates the appraisal of evidence quality from the development of recommendations, stating that "*low or very low quality evidence can lead to a strong recommendation*" (Balshem et al., 2011, pt. 4). GRADE guidance also clearly states that, when forming clinical recommendations, any alternative clinical approaches need to be based on "*systematic review of the impact of alternative management strategies on all patient-important outcomes*" (Balshem et al., 2011, pt. 5), drawing recommendations from appraisal of all available evidence. Lower quality studies are considered particularly valuable to inform clinical policy where multiple lower quality studies indicate the same conclusion (Balshem et al., 2011, pt. 4). In these two NICE evidence reviews, evidence from "low quality" studies, including qualitative studies or observational studies without a control arm, did not inform evidence review recommendations.

Instead of drawing policy recommendations from an appraisal of the best available evidence, the two NICE reviews prioritized only a standard of evidence that does not, and likely cannot exist in trans healthcare, resulting in the conclusion that the evidence for affirmative healthcare is "*inconclusive*." This conclusion ignores the high degree of consistency in

evidence from a significant body of "low quality" studies that attest to the important benefits of affirmative healthcare (Ashley et al., 2023). The NICE review into gender affirming hormones partially acknowledged ethical concerns associated with RCTs, proposing a route to overcome ethical barriers. The NICE report recommended that trans adolescents who are seeking affirmative healthcare, yet allocated to a study's control arm, be provided with "*close psychological support*" (Report 2b, p. 47) in place of access to affirmative hormones. No evidence is provided that psychological support whilst denied access to affirmative healthcare is an effective and ethical medical intervention for trans adolescents seeking medical transition. No evidence is provided that this is likely to result in safe or enhanced outcomes, and existing literature outlining the harms of denial of affirmative healthcare (e.g., Fisher et al., 2014) is not discussed. This indicates a double standard in the NICE Review approach to evidence-based policy in trans children's healthcare. Non-affirmative healthcare approaches such as provision of "close psychological support" are endorsed with no evidence of benefits. Affirmative healthcare, the globally recognized standard of care as endorsed by WPATH (Coleman et al., 2022), is not supported unless it can provide a standard of evidence (RCTs) that is neither feasible nor ethical.

The second major concern with the two NICE evidence reviews relates to how they are communicated to a non-specialist audience, including by the Cass Review. In healthcare communication, nuance is important when communicating about the quality of evidence (Ashley et al., 2023). A significant proportion of clinical recommendations in pediatric healthcare are unsupported by RCT standard evidence, instead relying on "lower quality" evidence (Meng et al., 2022). A review of World Health Organization recommendations found that 55% of strong recommendations relied on low or very low quality evidence (Alexander et al., 2014). "Low quality" evidence holds a specific and nuanced meaning under a GRADE approach, that can be easily misrepresented and misunderstood when used in general communication (Balshem et al., 2011). The NICE evidence review's finding of a lack of "high quality" evidence has been communicated in a way that undermines confidence in trans healthcare. The Cass Review describes evidence for trans healthcare as "*inconclusive*" across analysis and public commentary. This is presented as fact, without reference to the unsuitability of Randomized Control Trials (RCTs), and without reference to the consensus of positive impacts of affirmative healthcare found in a large body of non-RCT evidence. Multiple studies reporting benefits (Achille et al., 2020; Brik et al., 2020; Horton, 2022b; McGregor et al., 2023; Miesen et al., 2020), and no studies reporting significant harms is ignored when the Cass Review references the evidence base for trans children's healthcare:

> The disagreement and polarisation is heightened when potentially irreversible treatments are given to children and young people, when the evidence base underlying the treatments is inconclusive, and when there is uncertainty about whether, for any particular child or young person, medical intervention is the best way of resolving gender-related distress. [Report 5, p. 28]

The above paragraph does not install any confidence that trans healthcare is supported by any evidence of effectiveness. This is powerful framing in a report expected to be widely read by audiences who are not medical professionals. In the above sentence, the Cass Review utilizes language ("uncertainty," "inconclusive") to communicate risk, danger and even recklessness in the existing approach. This approach to criticizing and raising concern over established healthcare practices neglects any consideration of the risk and danger inherent in denial of healthcare that has been used for decades with significant non-RCT evidence of benefits. No evidence of harm from affirmative healthcare is provided to justify denial of such care. Instead, it is the 'polarization' and lack of consensus that justifies a shift away from the healthcare approach endorsed by global medical establishment bodies like WPATH.

The Cass Review fails to recognize the ubiquity of "controversy" in the healthcare of a highly marginalized and harassed minority group. Trans children's healthcare will always be controversial when some individuals do not recognize the validity of trans lives, when a portion of

interested stakeholders believe trans children do not or should not exist. The Cass Review does not recognize the responsibilities of healthcare professionals to center their service users, especially in the face of politicized controversy. In other countries like Australia, healthcare professionals have taken strong steps to ensure they are standing by their trans communities, including advocating for trans children's right to healthcare (Telfer et al., 2018). In the UK, the Cass Review seems to agree that controversy is itself a reason to increase barriers to healthcare. The Cass Review defines puberty blockers as a particularly controversial medication:

> The administration of puberty blockers is arguably more controversial…, because there are more uncertainties associated with their use. [Report 5, p. 37]

The Cass Review presents puberty blockers as controversial, without providing scientific evidence to justify any controversy. The global Endocrine Society recognizes their safe and effective use to temporarily block puberty in trans adolescents (Hembree et al., 2017), and they are not deemed controversial when used by cis children (Kim, 2015). No evidence is provided by the Cass Review to demonstrate that puberty blockers are ineffective or unsafe. In justifying concern over puberty blockers, the Cass Review instead asserts a series of fringe theories that are unevidenced, or outright contradicted by modern literature.

> The most difficult question is whether puberty blockers do indeed provide valuable time for children and young people to consider their options, or whether they effectively 'lock in' children and young people to a treatment pathway which culminates in progression to feminising/masculinising hormones by impeding the usual process of sexual orientation and gender identity development. [Report 5, p. 36]

The Cass Review provides no evidence to support the proposal that puberty blockers, medication routinely used by cis children with precocious puberty, cause the "locking in" of a trans identity. The Cass Review provides no evidence that forcing a trans child through an unwanted and incongruent puberty will result in deviation from a trans identity. Yet this entirely unevidenced theory is taken as sufficient evidence to elevate it to what the Cass Review calls "*the most difficult question*." This is an example of the Cass Review citing theories or views, in support of non-affirmative approaches, without evidence to substantiate these theories or approaches.

Whilst established trans-positive healthcare practices are rejected by the Cass Review without RCT standard evidence, there are a range of concepts and approaches that are accepted by Cass with little or no evidence at all. A Cass Review graphic includes the outcome "s*ettled sexuality resolves gender dysphoria*" [Report 5, p. 57]. The Cass Review is here presenting a fringe view, that settling sexuality is a root to resolving or curing gender dysphoria. This fringe view is presented as fact without any evidence at all for this claim.

In several other areas the Cass Review presents contested or outdated concepts as though they are established knowledge. This is particularly noticeable when the Cass Review references the highly disputed concept of "desistance":

> This stage of pubertal development was chosen because it was felt that although many younger children experienced gender incongruence as a transient developmental phenomenon, those who expressed early gender incongruence which continued into puberty were unlikely to desist at that stage. [Report 5, p. 31]

Here the Cass Review dismisses trans children's identities by presenting the theory of "desistance." This concept, a term drawn from criminology, has been extensively critiqued in peer reviewed literature, and is not considered a useful concept in modern healthcare (Ashley, 2022; Temple Newhook et al., 2018). The concept has also been contradicted by a body of modern research (De Castro et al., 2024; Olson et al., 2022). Nevertheless, the Cass Review is content with reference to a highly disputed theory, referring to it in several sections:

> Previous literature has indicated that if gender incongruence continues into puberty, desistance is unlikely. However, it should be noted that these older studies were not based on the current changed case-mix or the different sociocultural climate of recent years,

> which may have led to different outcomes. Having an open discussion about these questions is essential if a shared understanding of how to provide appropriate assessment and treatment is to be reached. [Report 5, p. 56]

This paragraph provides an interesting case in point on how the Cass Review approaches evidence. First the Cass Review presents, under the authority of reference to "*previous literature*" a discredited theory that puberty is relevant to "*desistance*." In this first sentence the Cass Review distorts the actual literature, inserting reference to a modern cohort and diagnosis of "gender incongruence" on studies that focused instead on gender identity disorder. The distinction is an important one, as the diagnosis of gender incongruence is intended to focus on trans children, whilst the broader category of gender identity disorder pathologized a wider range of children including those who were non-conforming cis children. Next, the Cass Review acknowledges a sub-set of the criticisms of desistance literature, avoiding reference to peer reviewed literature that has critiqued the application of desistance literature to trans children. Finally, the paragraph ends with assertion of the importance of "open discussion" of such matters. Trans healthcare scholars who have critiqued and debunked flawed and pathologizing concepts like desistance for decades are called to again debate and challenge concepts and literature that has multiple times been discredited in peer reviewed research.

The same contested research on desistance informs the Cass approach to social transition, with the professional panel report recommending denial of social transition until "*after puberty… If the Gender Dysphoria is unresolved…*" [Report 3, p. 33]. This policy position, and its suggestion of dysphoria being "resolved by puberty" relies on the same older desistance studies, predominantly on cis children, from the 1950s-2000s. A majority of this pathologizing older research was undertaken with a focus on preventing or curing gender non-conformity (Temple Newhook et al., 2018). Nonetheless this weak and discredited evidence influences significant policy recommendations, directly cited as justification for NHS England's revised service specification:

> Dr Cass has recommended that social transition be viewed as an 'active intervention'… In line with this advice, the interim service specification sets out more clearly that the clinical approach in regard to pre-pubertal children will reflect evidence that in most cases gender incongruence does not persist into adolescence… (NHS England, 2022, p. 11)

Historical studies (from the 1950s-2000s) that focused on a different cohort, that have been critiqued multiple times in peer reviewed literature, provide an extremely weak body of evidence for guiding modern healthcare (Ashley, 2022; Temple Newhook et al., 2018). Yet these low-quality historic studies, none of which focused specifically on trans children, are deemed sufficient evidence to justify denial of support for social transition. In the Cass Review approach affirmative healthcare is held to an unachievable standard of RCT evidence. Non-affirmative approaches are presented as the default position or as accepted knowledge either without citation, or with reliance on older (pre-2013) non-RCT evidence that has been critiqued multiple times in peer reviewed publications. This highlights a significant double standard that impacts on the Cass Review's approach to evidence-based policy. There is also a noticeable bias in what approaches are prioritized where evidence is limited. The Cass Review's approach, with its direct impact on NHS England policy, assumes that treating a trans child with respect and affirmation is an active intervention, requiring a high degree of evidence. The Cass Review notes:

> Social transition – this may not be thought of as an intervention or treatment, because it is not something that happens within health services. However, it is important to view it as an active intervention because it may have significant effects on the child or young person in terms of their psychological functioning. [Report 5, p. 62].

Support for affirmation of a trans child's identity is upheld as a medical "intervention" requiring high quality evidence. Rejection or non-affirmation of a child's identity is presumed the natural default position, requiring no evidence at all. Arguably, denying and rejecting a child's self-knowledge is a far greater intervention in that child's life, requiring a greater burden of

clinical proof, than simply letting each child assert and affirm their own identity. Yet the Cass Review considers acceptance of a child's identity as trans as a significant "intervention." The Cass Review's position frames rejection of a trans child's identity as neutral and benign, requiring no evidence for such a policy proposal. Accepting and embracing a trans child is viewed as more extreme and in need of "high quality" evidence. This position demonstrates extreme cisnormativity, with only cis children viewed as natural or inherently worthy of respect and acceptance. This position is also pathologizing, with acceptance of a trans identity considered a medical intervention. It is also noteworthy that the Cass Review develops recommendations cautioning against social transition without analyzing existing literature on social transition. This includes the Cass Review failing to cite or reflect upon a growing body of evidence on the known benefits of social transition for trans children (Durwood et al., 2017; Horton, 2023b, 2023d; Olson et al., 2016).

In several sections the Cass Review emphasizes the risk or significance of any affirmative medical or social interventions, whilst negating or ignoring the potential harms of nonintervention or denial of social or medical transition. Trans healthcare is referred to as comprising "challenging decisions about life-changing interventions" [Report 5, p. 18], whilst the denial of trans healthcare is not weighed as a significant or life-changing intervention. This is another example of the Cass Review centering a cisnormative perspective to evidence or decision-making. A trans person being denied affirmative healthcare and being forced through incongruent puberty is not considered "life-changing." Healthcare policies that deny access to affirmative healthcare can be justified by the Cass Review without any burden of proof that they lead to improved health or well-being outcomes. There is significant evidence of a double standard in evidence-informed policy making within the Cass Review, with affirmative approaches held to a higher standard of evidence than non-affirmative approaches.

Discussion

Within the Cass Review anti-trans prejudice is not acknowledged as a problem or a threat to trans children. Across several reports the Cass Review centers the concerns of non-affirmative professionals, including those who do not believe in the existence of trans children. The existence of anti-trans prejudice amongst healthcare professionals is well-documented in existing literature (Brown et al., 2018; Stroumsa et al., 2019) and Cass Review reports indeed provide clear indication of professional ignorance or prejudice. However, across Cass Review reports, there is no instance where professional views on trans children are identified as ill-informed or prejudiced or are rejected from inclusion in the review. Instead, the views of ignorant or pathologizing professionals seeking support for non-affirming practice with trans children are presented with sympathy. There is no parallel consideration of the rights or welfare of trans children, nor discussion of an NHS duty of care to protect trans children from being harmed by professionals who reject the validity or existence of trans lives. The Cass approach welcomes all views, including those grounded in ignorance, pathologization or denial of the existence of trans children. The Cass Review also seeks consensus in a field characterized by polarization. Those of us with expertise in this field can recognize that it is not possible, nor indeed desirable, to find consensus between advocates for trans children's equal rights, who celebrate trans children's value in this world, and individuals who deny the existence of trans children, for whom transness is a disorder or confusion in need of conversion, prevention or eradication. Policy and evidence processes in trans healthcare need to recognize the existence of anti-trans prejudice or ignorance, even amongst healthcare professionals, and take steps to protect trans healthcare users from approaches that are driven by prejudice.

The Cass Review demonstrates cisnormative bias in the erasure of trans children, and in the misgendering and delegitimization of both trans children and trans adults in Cass Review reports. The fact the report is willing to directly misgender and disrespect a portion of current service users provides some insights into the audiences that matter to the Cass Review. Erasure and misgendering of trans children is also a demonstration of cisnormativity and adultism, where child

rights and child perspectives are unrecognized, with all children defaulted to a presumed cis status. Cisnormative bias can be seen in the exclusion of trans expertise, and the marginalization of trans voices in leadership and oversight of the Cass Review. Exclusion of trans expertise is not a neutral act in a field that where lived experience and community knowledge is absolutely vital to avoiding pathologization, cisnormativity and medical harm. Exclusion of trans expertise is both indicative of the bias within the Cass Review, and explanatory for continued cisnormativity across the review and its outputs. Such exclusion of trans expertise is all too common in the UK. In a 2021 critique of a pathologizing Nuffield Council on Bioethics consultation on trans children's health (a consultation that problematized trans existence and contained no trans community leadership in design or governance) Pearce (2021, para. 10) emphasized that, in excluding trans leadership they "*are reproducing, once again, the power imbalance that has dominated trans medicine for the past two centuries*." Policy processes in trans healthcare need to take steps to reduce the impact of cisnormativity, especially in processes that are cis-led, where the risk of cisnormativity is particularly acute.

Pathologisation of gender diversity can be seen across Cass Review outputs. Entrenched cisnormativity and problematisation of transness leads to the Cass Review prioritizing the research questions about transness that trouble cis people. The Cass Review does not center trans community research priorities such as enhancing depathologized access to safe and effective healthcare for trans children. This leads the Cass Review into research priorities that are more philosophical than medical, questions on epidemiology of transness, etiology or identity persistence. The Cass Review is able to step beyond (and deprioritise) the domains of effective trans healthcare for trans children, by the Review's failure to recognize trans children as a core stakeholder group, enabling the very existence of trans children to be a valid topic of cis curiosity. Whilst the Cass Review decenters and delegitimises its core target population (trans children), their health and welfare needs are secondary to curiosity on how children came to identify as trans and whether or when they will stop.

A review of trans healthcare that excludes trans leadership or trans accountability is likely vulnerable to pathologization. The Cass Review fails to embed depathologization across its outputs, instead adopting a medicalised approach of trans-ness as something to be diagnosed, treated, prevented or cured. Avoidance of the recognition of trans children as a minority group pushes the Cass Review into a disease paradigm, seeking to treat "gender related distress." The Cass Review has two distinct options available on the topic of diagnosis. It could recognize that being trans cannot be meaningfully diagnosed by an external person. It could recognize that being trans is neither a pathology nor a problem. It could endorse affirmative approaches that start by listening to and respecting child self-knowledge of who they are, noting that affirmative approaches do not prevent an individual child from exploring or reflecting upon on their own identity, in their own time. But because the Cass Review does not endorse an affirmative approach that depathologizes transness, it is instead left tying itself in knots on the question of how a professional can diagnose a trans identity. The reality that many trans people require specific medical interventions is given as a justification for squashing transness into a disease treatment model framed in pathology-related terms of condition, diagnosis, treatment and prevention. A disease treatment model is not the only way to provide healthcare. Ashley (2022a) has drawn a comparison between trans healthcare and other healthcare services that relate to bodily autonomy, such as pregnancy and abortion healthcare. Ashley notes how those healthcare services manage to provide healthcare to a specific group, without relying upon a pathologizing and disempowering disease diagnosis and treatment model of care, prioritizing instead minority healthcare rights and bodily autonomy. The Cass Review and other trans healthcare initiatives need to recognize the harms of pathologization, and take proactive steps to embed depathologisation across their approaches and outputs.

The final section of this article examined the Cass Review's approach to evidence and dealing

with uncertainty. The NICE evidence reviews chaired by Dr Cass both utilized an approach where only evidence like RCTs are considered high quality evidence. In a field where RCTs are recognized as infeasible and unethical, in a field where "high quality evidence" does not and may never exist, we may be left to wonder, has this evidence review really served to enlighten and inform decision making in trans healthcare? Those interested in maximizing trans children's well-being would look at all available sources of evidence, and use the best quality existing evidence to inform decision making. Instead, the absence of a type of "high quality" evidence is used by the Cass Review to conclude that "*evidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive*." Such statements have legitimized the closure of current trans children's healthcare services for England and Wales, with no services currently operational. The Cass approach places so much emphasis on uncertainties, unknowns, areas without consensus and the absence of "high quality evidence" that it can be read as an argument against affirmative healthcare for trans children. A cisnormative double standard can also be seen, where evidence-based affirmative approaches are dismissed with calls for RCT standard evidence, whilst non-affirmative theories and policies are introduced and endorsed with no or limited evidence.

The Cass Review overall can be considered an example of cis-ignorance, a concept recognized in trans healthcare, where "*ignorance is not simply an absence of knowledge, but an epistemic practice in its own right*" (Mikulak, 2021, p. 827). Mikulak recognizes that "*practices of ignorance are often entangled with practices of exclusion and oppression*" (2021, p. 819). Cis-ignorance can be seen in the Cass Review's decision to exclude trans expertise, in the choice to appoint leadership without experience or knowledge, and in the valuing of insights from healthcare professionals who do not even believe in the existence of trans children. Cis-ignorance is apparent in the cisnormative framing of research questions, where research on the meaning of identity or the epidemiology of transness are perceived as important research priorities, and in the erasure of trans children from the Review's stated target group, leaving trans children's existence a topic of debate. Cis-ignorance can be seen in the citation of discredited research, forcing affirmative researchers to continually re-dispute the same literature that has been critiqued so many times, including in peer reviewed literature, preventing the field from moving forwards. Cis-ignorance can be seen in a futile search for consensus in a polarized field, setting out (with time, resources, and establishment credentials) to reach an objective of building consensus that is doomed from the start. Cis-ignorance can be seen in the dismissal of existing knowledge, framing the whole of trans healthcare as "inconclusive," "unknown" or risky, and in calls for infeasible and unethical RCT or blinded control studies. Observers may wonder whether cis-ignorance is intentional and abusive, or careless and ill-informed. Regardless of intent, it manifests as an exertion of cis power over trans communities, in a National Health Service that continues to fail to uphold trans people's rights to equality in healthcare.

The Cass Review overall can also be seen as an example of cis-supremacy in action. Elsewhere (Horton, 2023a) I have written about a theoretical framework of cis-supremacy, combining scholarship on cisnormativity, pathologization and gender minority stress with scholarship on white supremacy, centering the forces of power and cis domination that shape and constrain trans lives. Cis-supremacy calls attention to the axes and forces of cis-power that actively dominate and oppress trans people, with cis-supremacy particularly harmful in cis-dominant institutions or processes that lack trans accountability (Horton, 2023a). The Cass Review is an exemplar of cis-supremacy, and more specifically, of cis institutional dominance. This is seen in its design and leadership, with the Cass Review designed by and for cis stakeholders, led and advised by cis healthcare professionals with no knowledge or experience of trans healthcare, with no mechanisms for accountability to trans communities. This critical analysis of the Cass Review reveals four areas of concern, relating to how the Cass Review deals with prejudice, cisnormative bias, and

pathologization, and with double standards in how evidence informs policy and practice. Each of these concerns impacts on the Cass Review's approach to trans children's healthcare, with negative repercussions for trans children's healthcare rights and well-being. Actors engaged in policy development or evidence reviews in trans healthcare need to be aware of these four pitfalls that could arise in other cis-dominant policy processes.

Conclusion

The Cass Review can be understood as an exercise in cis-supremacy, in a healthcare system that lacks trans accountability. Four areas of concern are highlighted, relating to how the Cass Review deals with prejudice, cisnormative bias, and pathologization, and with double standards in how evidence informs policy and practice. Actors in trans healthcare policy and practice need to recognize these areas of concern and take steps to counter them. Initiatives in trans healthcare need to build from trans positivity and respect, including proactive recognition and celebration of trans children's lives. Initiatives like the Cass Review need to have a much greater commitment to acknowledging and upholding trans children's healthcare rights, prioritizing equity and social justice for minoritized healthcare service users.

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References

Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., & Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. *International Journal of Pediatric Endocrinology*, *2020*(1), 8. https://doi.org/10.1186/s13633-020-00078-2

Andersson, J. (2021, September 22). No trans under-17s referred for hormone treatment in last nine months despite gender clinic approval. iNews. https://inews.co.uk/news/health/transgender-young-people-nhs-hormone-treatment-puberty-blockers-transition-1205675

Alexander, P. E., Bero, L., Montori, V. M., Brito, J. P., Stoltzfus, R., Djulbegovic, B., Neumann, I., Rave, S., & Guyatt, G. (2014). World Health Organization recommendations are often strong based on low confidence in effect estimates. *Journal of Clinical Epidemiology*, *67*(6), 629–634. https://doi.org/10.1016/j.jclinepi.2013.09.020

Ali, J. (2023, February 9). Doctors warn 'NHS is failing trans people' amid row over Tavistock gender clinic. *PinkNews*. https://www.thepinknews.com/2023/02/09/tavistock-gender-clinic-closure-staff-open-letter-trans-healthcare/

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. American Psychiatric Association. https://www.psychiatry.org/psychiatrists/practice/dsm

Amery, F. (2023). Protecting children in 'gender critical' rhetoric and strategy: Regulating childhood for cisgender outcomes. *Journal of Diversity and Gender Studies*, *10*(2), 98–114. https://doi.org/10.21825/digest.85309

Ashley, F. (2019a). Homophobia, conversion therapy, and care models for trans youth: Defending the gender-affirmative approach. *Journal of LGBT Youth*, *17*(4), 361–383. https://doi.org/10.1080/19361653.2019.1665610

Ashley, F. (2019b). Watchful waiting doesn't mean no puberty blockers, and moving beyond watchful waiting. *The American Journal of Bioethics*, *19*(6), W3–W4. https://doi.org/10.1080/15265161.2019.1599466

Ashley, F. (2022). The clinical irrelevance of "desistance" research for transgender and gender creative youth. *Psychology of Sexual Orientation and Gender Diversity*, *9*(4), 387–397. https://doi.org/10.1037/sgd0000504

Ashley, F. (2022a). Adolescent medical transition is ethical: An analogy with reproductive health. *Kennedy Institute of Ethics Journal*, *32*(2), 127–171. https://doi.org/10.1353/ken.2022.0010

Ashley, F. (2022b). *Banning transgender conversion practices*. UBC Press.

Ashley, F. (2022c). Interrogating gender-exploratory therapy. *Perspectives on Psychological Science*, *18*(2), 472–481. https://doi.org/10.1177/17456916221102325

Ashley, F., & Domínguez, S. (2021). Transgender healthcare does not stop at the doorstep of the clinic. *The American*

Journal of Medicine, *134*(2), 158–160. https://doi.org/10.1016/j.amjmed.2020.09.030

Ashley, F., Tordoff, D. M., Olson-Kennedy, J., & Restar, A. J. (2023). Randomized-controlled trials are methodologically inappropriate in adolescent transgender healthcare. *International Journal of Transgender Health*, *0*(0), 1–12. https://doi.org/10.1080/26895269.2023.2218357

Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., Vist, G. E., Falck-Ytter, Y., Meerpohl, J., Norris, S., & Guyatt, G. H. (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, *64*(4), 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015

Bell vs Tavistock. (2020). *EWHC 3274 (High Court of Justice 1 December 2020)*. https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Judgment.pdf

Bell vs Tavistock. (2021). *EWCA Civ 1363 (17 September 2021)*. https://www.judiciary.uk/wp-content/uploads/2021/09/Bell-v-Tavistock-judgment-170921.pdf

Bowen, G. A. (2009). Document analysis as a qualitative research method. *Qualitative Research Journal*, *9*(2), 27–40. https://doi.org/10.3316/QRJ0902027

Braun, V., & Clarke, V. (2019). Reflecting on reflexive thematic analysis. *Qualitative Research in Sport, Exercise and Health*, *11*(4), 589–597. https://doi.org/10.1080/2159676X.2019.1628806

Brik, T., Vrouenraets, L., de Vries, M. C., & Hannema, S. E. (2020). Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. *Archives of Sexual Behavior*, *49*(7), 2611–2618. https://doi.org/10.1007/s10508-020-01660-8

British Psychological Society. (2022, June 22). Exclusion of transgender people from conversion therapy ban in the Queens Speech is deeply concerning, says BPS. *BPS.Org.Uk*. https://www.bps.org.uk/news/exclusion-transgender-people-conversion-therapy-ban-queens-speech-deeply-concerning-says-bps

Brown, S., Kucharska, J., & Marczak, M. (2018). Mental health practitioners' attitudes towards transgender people: A systematic review of the literature. *International Journal of Transgenderism*, *19*(1), 4–24. https://doi.org/10.1080/15532739.2017.1374227

Cass Review (2021a). *Online panel with primary and secondary care professionals*. Cass Review. https://cass.independent-review.uk/wp-content/uploads/2022/03/REPORT-Cass-Review-professional-panel-FINAL.pdf

Cass Review (2021b). *Terms of Reference*. https://cass.independent-review.uk/about-the-review/assurance-group/

Cass Review. (2022a). *Gender specialists questionnaire*. Cass Review. https://cass.independent-review.uk/wp-content/uploads/2022/03/Gender-specialists-questionnaire-report_FINAL.pdf

Cass Review. (2022b). *Interim Report*. The Cass Review. https://cass.independent-review.uk/publications/interim-report/

Coleman, E., Radix, A. E., Bouman, W. P., Brown, G. R., de Vries, A. L. C., Deutsch, M. B., Ettner, R., Fraser, L., Goodman, M., Green, J., Hancock, A. B., Johnson, T. W., Karasic, D. H., Knudson, G. A., Leibowitz, S. F., Meyer-Bahlburg, H. F. L., Monstrey, S. J., Motmans, J., Nahata, L., … Arcelus, J. (2022). Standards of care for the health of transgender and gender diverse people, version 8. *International Journal of Transgender Health*, *23*(Suppl 1), S1–S259. https://doi.org/10.1080/26895269.2022.2100644

De Castro, C., Solerdelcoll, M., Plana, M. T., Halperin, I., Mora, M., Ribera, L., Castelo-Branco, C., Gómez-Gil, E., & Vidal, A. (2024). High persistence in Spanish transgender minors: 18 Years of experience of the Gender Identity Unit of Catalonia. *Revista de Psiquiatría y Salud Mental*, *17*(1), 35–40. https://doi.org/10.1016/j.rpsm.2022.02.001

Diagnostic and statistical manual of mental disorders, 4th ed. (1994). (pp. xxvii, 886). American Psychiatric Publishing, Inc.

Durwood, L., McLaughlin, K. A., & Olson, K. R. (2017). Mental health and self-worth in socially transitioned transgender youth. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(2), 116–123.e2. https://doi.org/10.1016/j.jaac.2016.10.016

Eckert, A. (2021, October 17). Conclusions not so NICE: A critical analysis of the NICE evidence review of puberty blockers for children and adolescents with gender dysphoria. *Science-Based Medicine*. https://sciencebasedmedicine.org/a-critical-look-at-the-nice-review/

EPATH & WPATH. (2023). *Joint statement WPATH and EPATH re NHS puberty blocker policy*. World Professional Association for Transgender Health. https://www.wpath.org/media/cms/Documents/Public%20Policies/2023/30.10.23%20EPATH%20-%20WPATH%20Joint%20NHS%20Statement%20Final.pdf

Faye, S. (2021). *The transgender issue*. Penguin Books.

Fisher, A. D., Ristori, J., Bandini, E., Giordano, S., Mosconi, M., Jannini, E. A., Greggio, N. A., Godano, A., Manieri, C., Meriggiola, C., Ricca, V., Dettore, D., & Maggi, M. (2014). Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. *Journal of Endocrinological Investigation*, *37*(7), 675–687. https://doi.org/10.1007/s40618-014-0077-6

Giordano, S., & Holm, S. (2020). Is puberty delaying treatment 'experimental treatment'? *International Journal of Transgender Health*, *21*(2), 113–121. https://doi.org/10.1080/26895269.2020.1747768

Grant, M. J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Information and Libraries Journal*, *26*(2), 91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical Research ed.)*, *336*(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017).

Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *102*(11), 3869–3903. https://doi.org/10.1210/jc.2017-01658

Hidalgo, M. A., Ehrensaft, D., Tishelman, A. C., Clark, L. F., Garofalo, R., Rosenthal, S. M., Spack, N. P., & Olson, J. (2013). The gender affirmative model: What we know and what we aim to learn. *Human Development*, *56*(5), 285–290. https://doi.org/10.1159/000355235

Horton, C. (2020). Thriving or surviving? Raising our ambition for trans children in primary and secondary schools. *Frontiers in Sociology*, *5*, 67. https://doi.org/10.3389/fsoc.2020.00067

Horton, C. (2022a). Depathologising diversity: Trans children and families' experiences of pathologisation in the UK. *Children & Society*, *37*(3), 753–770. https://doi.org/10.1111/chso.12625

Horton, C. (2022b). Experiences of puberty and puberty blockers: Insights from trans children, trans adolescents, and their parents. *Journal of Adolescent Research*, *39*(1), 77–103. https://doi.org/10.1177/07435584221100591

Horton, C. (2022c). "I was losing that sense of her being happy"—Trans children and delaying social transition. *LGBTQ + Family: An Interdisciplinary Journal*, *18*(2), 187–203. https://doi.org/10.1080/27703371.2022.2076002

Horton, C. (2022d). 'Of course, I'm intimidated by them. they could take my human rights away': Trans children's experiences with UK gender clinics. *Bulletin of Applied Transgender Studies*, *1*(1–2), 47–70. https://doi.org/10.57814/20hf-7n94

Horton, C. (2023a). *Cis-supremacy: Experiences of trans children and families in the UK* [Doctoral]. Goldsmiths, University of London. https://research.gold.ac.uk/id/eprint/33797/

Horton, C. (2023b). "Euphoria": Trans children and experiences of prepubertal social transition. *Family Relations*, *72*(4), 1890–1907. https://doi.org/10.1111/fare.12764

Horton, C. (2023c). "I didn't want him to disappear" parental decision-making on access to puberty blockers for trans early adolescents. *The Journal of Early Adolescence*, *43*(4), 490–515. https://doi.org/10.1177/02724316221107076

Horton, C. (2023d). The importance of child voice in trans health research: A critical review of research on social transition and well-being in trans children. *International Journal of Transgender Health*, *0*(0), 1–18. https://doi.org/10.1080/26895269.2023.2295381

Keo-Meier, C., & Ehrensaft, D. (2018). *The gender affirmative model: An interdisciplinary approach to supporting transgender and gender expansive children*. American Psychological Association.

Kim, E. Y. (2015). Long-term effects of gonadotropin-releasing hormone analogs in girls with central precocious puberty. *Korean Journal of Pediatrics*, *58*(1), 1–7. https://doi.org/10.3345/kjp.2015.58.1.1

Linander, I., Lauri, M., Alm, E., & Goicolea, I. (2021). Two steps forward, one step back: A policy analysis of the swedish guidelines for trans-specific healthcare. *Sexuality Research and Social Policy*, *18*(2), 309–320. https://doi.org/10.1007/s13178-020-00459-5

Mackieson, P., Shlonsky, A., & Connolly, M. (2019). Increasing rigor and reducing bias in qualitative research: A document analysis of parliamentary debates using applied thematic analysis. *Qualitative Social Work*, *18*(6), 965–980. https://doi.org/10.1177/1473325018786996

Madrigal-Borloz, V. (2023). *End of mission statement* (Country Visit to the United Kingdom of Great Britain and Northern Ireland (24 April – 5 May 2023), pp. 1–18). UN. https://www.ohchr.org/sites/default/files/documents/issues/sexualorientation/statements/eom-statement-UK-IE-SOGI-2023-05-10.pdf

McGregor, K., McKenna, J. L., Williams, C. R., Barrera, E. P., & Boskey, E. R. (2023). Association of pubertal blockade at tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. *The Journal of Adolescent Health*, S1054–139X(23)00560-8. https://doi.org/10.1016/j.jadohealth.2023.10.028

Meng, M., Zhou, Q., Lei, W., Tian, M., Wang, P., Liu, Y., Sun, Y., Chen, Y., & Li, Q. (2022). Recommendations on off-label drug use in pediatric guidelines. *Frontiers in Pharmacology*, *13*, 892574. https://doi.org/10.3389/fphar.2022.892574

Miesen, A. I. R. v d., Steensma, T. D., Vries, A. L. C. d., Bos, H., & Popma, A. (2020). Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers. *The Journal of Adolescent Health*, *66*(6), 699–704. https://doi.org/10.1016/j.jadohealth.2019.12.018

Mikulak, M. (2021). For whom is ignorance bliss? Ignorance, its functions and transformative potential in trans health. *Journal of Gender Studies*, *30*(7), 819–829. https://doi.org/10.1080/09589236.2021.1880884

Milton, J. (2022, April 6). Health secretary Sajid Javid condemned for linking being trans to child sex abuse. *PinkNews | Latest Lesbian, Gay, Bi and Trans News | LGBTQ+ News*. https://www.pinknews.co.uk/2022/04/06/sajid-javid-conversion-therapy-ban-trans-uk/

Mul, D., Versluis-den Bieman, H., Slijper, F., Oostdijk, W., Waelkens, J., & Drop, S. (2001). Psychological assessments before and after treatment of early puberty in adopted children. *Acta Paediatrica*, *90*(9), 965–971. https://doi.org/10.1111/j.1651-2227.2001.tb01349.x

National Institute for Health and Care Excellence – NICE. (2021a). *Evidence review: Gender affirming hormones for children and adolescents with gender dysphoria*. National Institute for Health and Care Excellence (NICE); NHS England; NHS Improvement. https://cass.independent-review.uk/nice-evidence-reviews/

National Institute for Health and Care Excellence – NICE (2021b). *Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria*. National Institute for Health and Care

Excellence (NICE); NHS England; NHS Improvement. https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf

Newbury, P. (2013). *Disrupting the politics of etiquette*. https://cisnormativity.wordpress.com/2013/08/17/disrupting-the-politics-of-etiquette/

NHS England. (2020). *Amendments to service specification for gender identity development service for children and adolescents (E13/S(Hss)/E)*. https://www.england.nhs.uk/wp-content/uploads/2020/12/Amendment-to-Gender-Identity-Development-Service-Specification-for-Children-and-Adolescents.pdf?fbclid=IwAR3umsgkznshcibjUY63sV7obpVZo4NVCa5t1H9y0sHVQEaUcHosfKbsSQw

NHS England. (2022). *Interim service specification for specialist gender dysphoria services for children and young people in England (Phase 1 services)*. https://www.engage.england.nhs.uk/specialised-commissioning/gender-dysphoria-services/

Noel, L.-A. (2016). *Promoting an emancipatory research paradigm in Design Education and Practice*. DRS Biennial Conference Series.

Oakley, C. M. (2023). Curriculum censorship of LGBTQ+identity: Modern adaptation of vintage "save our children" rhetoric is still just discrimination. *Loyola University Chicago Law Journal*, *54*(2), 641–681. https://loyola-chicago-law-journal.scholasticahq.com/article/81996-curriculum-censorship-of-lgbtq-identity-modern-adaptation-of-vintage-save-our-children-rhetoric-is-still-just-discrimination

Olson, K. R., Durwood, L., DeMeules, M., & McLaughlin, K. A. (2016). Mental health of transgender children who are supported in their identities. *Pediatrics*, *137*(3), e20153223. https://doi.org/10.1542/peds.2015-3223

Olson, K. R., Durwood, L., Horton, R., Gallagher, N. M., & Devor, A. (2022). Gender identity 5 years after social transition. *Pediatrics*, *150*(2), e2021056082. https://doi.org/10.1542/peds.2021-056082

Omercajic, K., & Martino, W. (2020). Supporting transgender inclusion and gender diversity in schools: A critical policy analysis. *Frontiers in Sociology*, *5*, 27. https://doi.org/10.3389/fsoc.2020.00027

Owen, L. (2022). "Parasitically occupying bodies": Exploring toxifying securitization in anti-trans and genocidal ideologies. *Peace Review*, *34*(4), 481–494. https://doi.org/10.1080/10402659.2022.2129000

Pang, K. C., Wiggins, J., & Telfer, M. M. (2022). Gender identity services for children and young people in England. *BMJ (Clinical Research ed.)*, *377*, o825. https://doi.org/10.1136/bmj.o825

Paré, G., Trudel, M.-C., Jaana, M., & Kitsiou, S. (2015). Synthesizing information systems knowledge: A typology of literature reviews. *Information & Management*, *52*(2), 183–199. https://doi.org/10.1016/j.im.2014.08.008

Parsons, V. (2020, April 23). Liz Truss reveals 'shocking' plan to remove healthcare for trans youth, slammed as an 'extraordinary' attack on equality. *PinkNews*. https://www.pinknews.co.uk/2020/04/23/liz-truss-trans-rights-gender-recognition-act-reform-healthcare-puberty-blockers-backlash/

Pearce, R. (2018). *Understanding trans health: Discourse, power and possibility*. Policy Press.

Pearce, R. (2021, April 10). Open letter to Nuffield Council on Bioethics. *Dr Ruth Pearce*. https://ruthpearce.net/2021/04/10/open-letter-to-nuffield-council-on-bioethics/

Pearce, R., Erikainen, S., & Vincent, B. (2020). TERF wars: An introduction. *The Sociological Review*, *68*(4), 677–698. https://doi.org/10.1177/0038026120934713

Perry, S. (2023, October 19). Conversion therapy ban back on the table after backlash from MPs. *Pink News*. https://www.thepinknews.com/2023/10/19/conversion-therapy-ban-uk-rishi-sunak/

Raza-Sheikh, Z. (2022, April 6). Boris Johnson defends decision to exclude trans people from 'conversion therapy' ban. *Gay Times*. https://www.gaytimes.co.uk/life/boris-johnson-defends-decision-to-exclude-trans-people-from-conversion-therapy-ban/

Stroumsa, D., Shires, D. A., Richardson, C. R., Jaffee, K. D., & Woodford, M. R. (2019). Transphobia rather than education predicts provider knowledge of transgender health care. *Medical Education*, *53*(4), 398–407. https://doi.org/10.1111/medu.13796

Suess Schwend, A. (2020). Trans health care from a depathologization and human rights perspective. *Public Health Reviews*, *41*(1), 3. https://doi.org/10.1186/s40985-020-0118-y

TACTT. (2023). *Open letter to UKCP about their guidance regarding so-called 'gender-critical' views*. Therapists Against Conversion Therapy and Transphobia (TACTT). https://openletter.earth/open-letter-to-ukcp-about-their-guidance-regarding-so-called-gender-critical-views-c71ce5d6

Telfer, M., Kelly, F., Feldman, D., Stone, G., Robertson, R., & Poulakis, Z. (2018). Transgender adolescents and legal reform: How improved access to healthcare was achieved through medical, legal and community collaboration. *Journal of Paediatrics and Child Health*, *54*(10), 1096–1099. https://doi.org/10.1111/jpc.14124

Telfer, M. M., Tollit, M. A., Pace, C. C., & Pang, K. C. (2018). *Australian standards of care and treatment guidelines for trans and gender diverse children and adolescents*. The Royal Children's Hospital.

Temple Newhook, J., Pyne, J., Winters, K., Feder, S., Holmes, C., Tosh, J., Sinnott, M.-L., Jamieson, A., & Pickett, S. (2018). A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *International Journal of Transgenderism*, *19*(2), 212–224. https://doi.org/10.1080/15532739.2018.1456390

TransActual. (n.d.). *What is transphobia?* TransActual. https://www.transactual.org.uk/transphobia

Turban, J. (2020, October 23). The disturbing history of research into transgender identity. *Scientific American*. https://www.scientificamerican.com/article/the-disturbing-history-of-research-into-transgender-identity/

UN Human Rights Council. (2020). *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)* [Dataset]. UN HRC. https://doi.org/10.1163/2210-7975_HRD-9970-2016149

Winters, K. (2011). *Gender madness in American psychiatry: Essays from the struggle for dignity*. GID Reform Advocates.

Winters, K. (2022, January 11). From the Jurassic Clarke to the SOC8: Repsychopathologization of Trans Youth. *Trans Policy Reform*. https://transpolicyreform.wordpress.com/2022/01/11/from-the-jurassic-clarke-to-the-soc8-repsychopathologization-of-trans-youth/

World Health Organisation. (n.d.). *Gender incongruence and transgender health in the ICD*. Retrieved November 23, 2023, from https://www.who.int/standards/classifications/frequently-asked-questions/gender-incongruence-and-transgender-health-in-the-icd

World Health Organisation. (2021). *International classification of diseases for mortality and morbidity statistics (11th Revision)*. World Health Organisation. https://icd.who.int/browse11/l-m/en

WPATH, ASIAPATH, EPATH, PATHA, & USPATH (2023). *WPATH, ASIAPATH, EPATH, PATHA, and USPATH response to NHS England in the United Kingdom (UK)*. WPATH. https://www.wpath.org/media/cms/Documents/Public%20Policies/2022/25.11.22%20AUSPATH%20Statement%20reworked%20for%20WPATH%20Final%20ASIAPATH.EPATH.PATHA.USPATH.pdf?_t=1669428978