et al., 2021). This compared to 0.8–1.1% of students in England (Department for Education, 2012, 2015). The association between autism and gender dysphoria is found in many populations (Socialstyrelsen, 2020; Warrier et al., 2020). Autism is known to increase the risk of suicide mortality, especially in females (Hirvikoski et al., 2016; Kirby et al., 2019; Socialstyrelsen, 2020). To some extent, therefore, the elevated suicide rate for transgender youth compared to their peers reflects the higher incidence of ASC. The same holds for other psychiatric disorders associated with gender dysphoria (Dhejne et al., 2016). Ideally, the suicide rate for patients of the GIDS would be compared to the suicide rate for patients in contact with other NHS mental health services, but the latter rate is not available.

One final caveat is that these data shed no light on the question of whether counseling or endocrinological interventions—gonadotropin-releasing hormone agonist or cross-sex hormones—affect the risk of suicide (Biggs, 2020; Turban et al., 2020). Although two out of the four suicides were of patients on the waiting list, and thus would not have obtained treatment, this is not disproportionate: the waiting list contributed nearly half of the total patient-years.

Conclusion

Data from the world's largest clinic for transgender youth over 11 years yield an estimated annual suicide rate of 13 per 100,000. This rate was 5.5 times greater than the overall suicide rate of adolescents of similar age, adjusting for sex composition. The estimate demonstrates the elevated risk of suicide among adolescents who identify as transgender, albeit without adjusting for accompanying psychological conditions such as autism. The proportion of individual patients who died by suicide was 0.03%, which is orders of magnitude smaller than the proportion of transgender adolescents who report attempting suicide when surveyed. The fact that deaths were so rare should provide some reassurance to transgender youth and their families, though of course this does not detract from the distress caused by self-harming behaviors that are non-fatal. It is irresponsible to exaggerate the prevalence of suicide. Aside from anything else, this trope might exacerbate the vulnerability of transgender adolescents. As the former lead psychologist at the Tavistock has warned, "when inaccurate data and alarmist opinion are conveyed very authoritatively to families we have to wonder what the impact would be on children's understanding of the kind of person they are…and their likely fate" (Wren, 2015).

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Declarations

Conflict of interest I acted as an expert witness (without payment) for the claimant in the case of Bell v Tavistock and Portman NHS Foundation Trust [2020] EWHC 3274.

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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

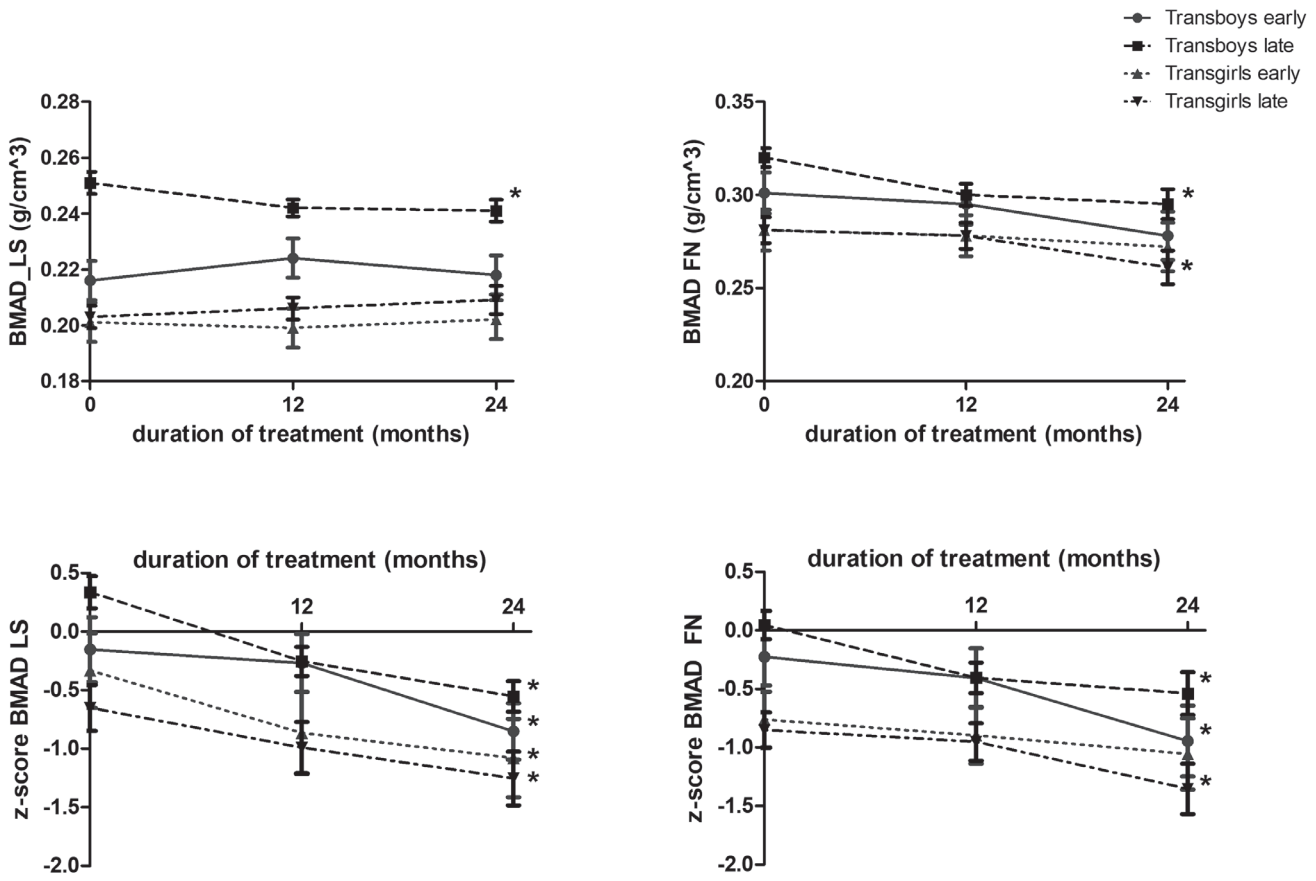

Figure 1. Estimated marginal means and standard error of the mean of BMAD prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by an asterisk. Abbreviations: BMAD: bone mineral apparent density; FM,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

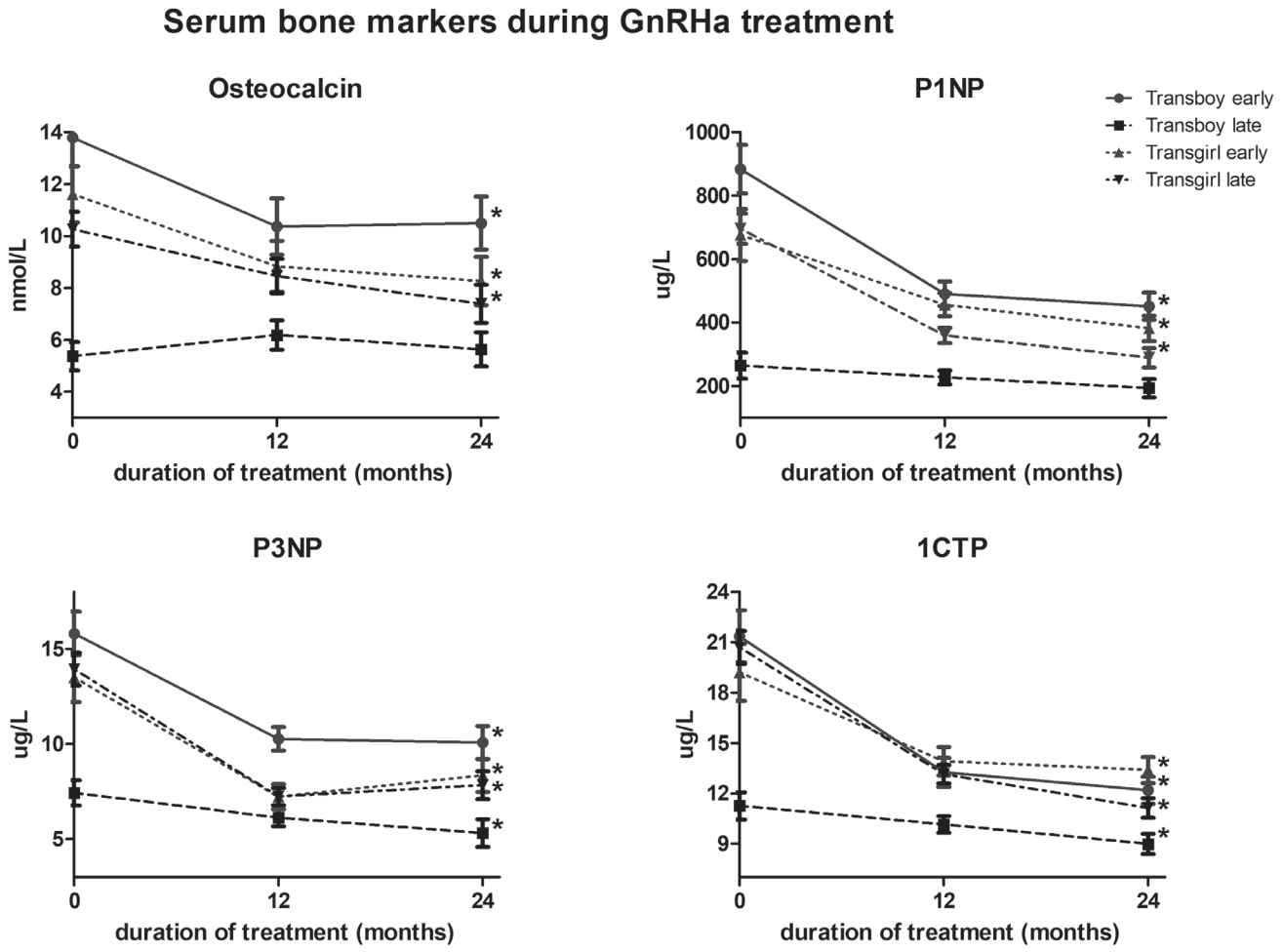

Figure 2. Estimated marginal means and negative standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by asterisk.

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

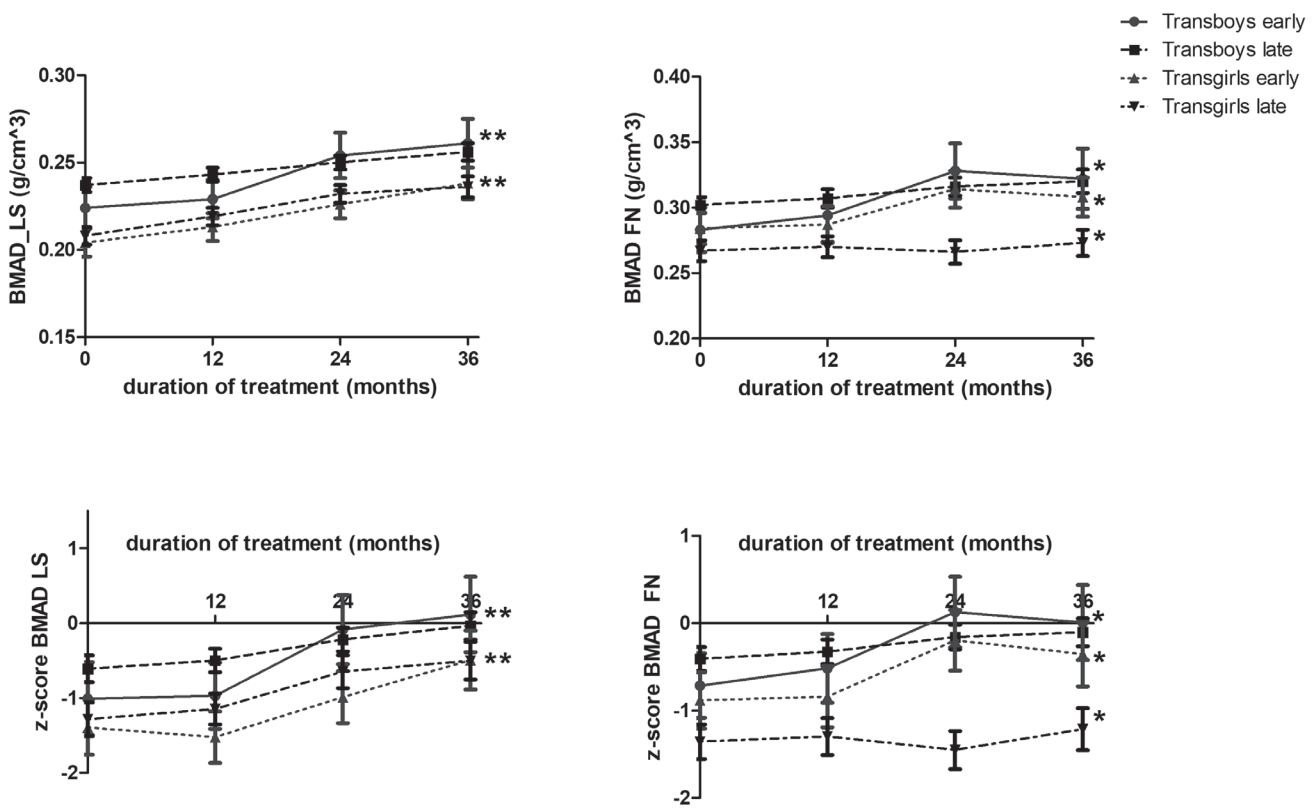

Figure 3. Estimated marginal means and standard error of the mean of BMAD prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

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).

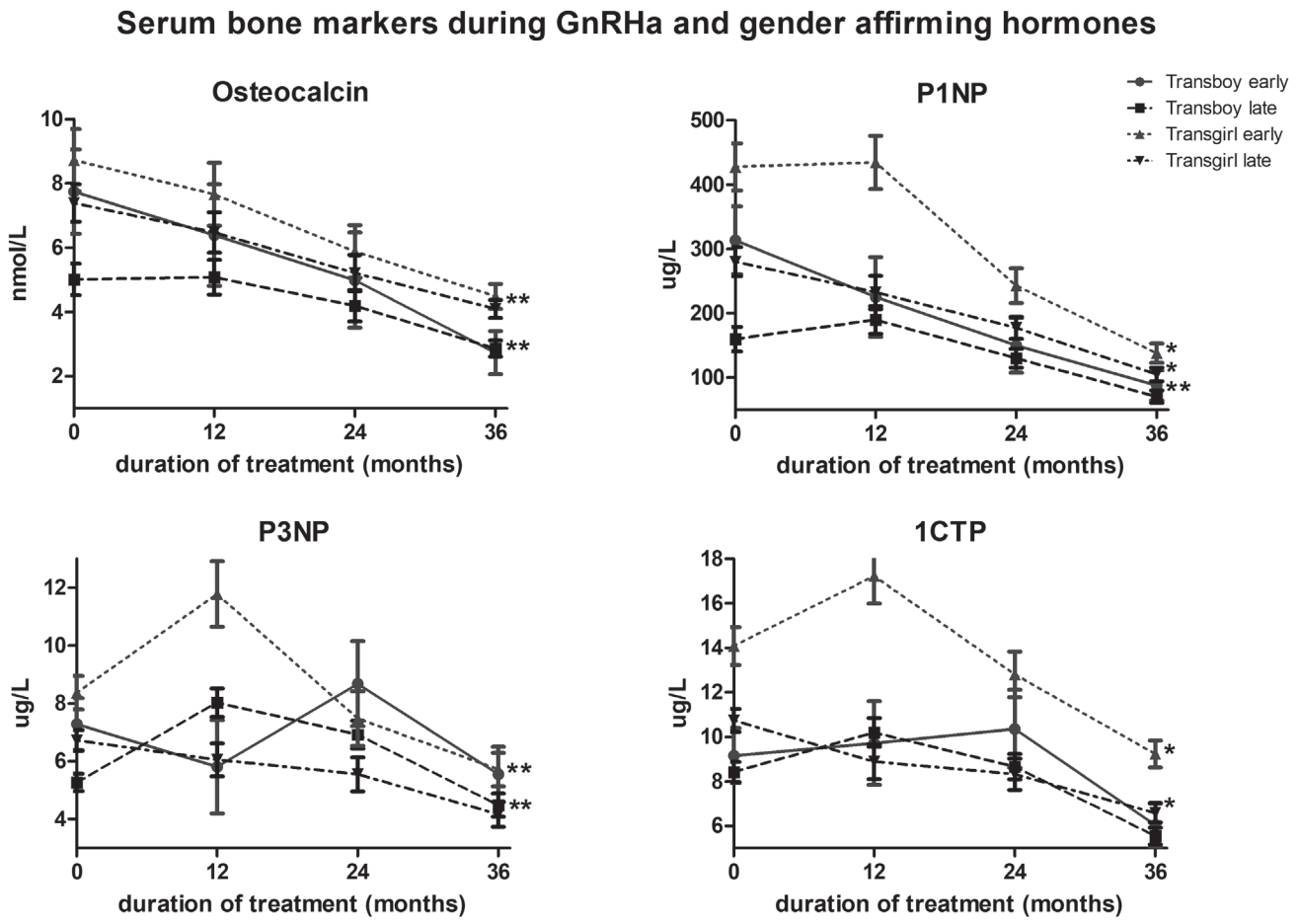

Figure 4. Estimated marginal means and standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

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/).

Additional Information

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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.

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Clinical Research Article

Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults

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Abstract

Introduction: Concerns about future regret and treatment discontinuation have led to restricted access to gender-affirming medical treatment for transgender and gender-diverse (TGD) minors in some jurisdictions. However, these concerns are merely speculative because few studies have examined gender-affirming hormone continuation rates among TGD individuals.

Methods: We performed a secondary analysis of 2009 to 2018 medical and pharmacy records from the US Military Healthcare System. We identified TGD patients who were children and spouses of active-duty, retired, or deceased military members using International Classification of Diseases-9/10 codes. We assessed initiation and continuation of gender-affirming hormones using pharmacy records. Kaplan-Meier and Cox proportional hazard analyses estimated continuation rates.

Results: The study sample included 627 transmasculine and 325 transfeminine individuals with an average age of 19.2 ± 5.3 years. The 4-year gender-affirming hormone continuation rate was 70.2% (95% CI, 63.9-76.5). Transfeminine individuals had a higher continuation rate than transmasculine individuals 81.0% (72.0%-90.0%) vs 64.4% (56.0%-72.8%). People who started hormones as minors had higher continuation rate than people who started as adults 74.4% (66.0%-82.8%) vs 64.4% (56.0%-72.8%). Continuation was not associated with household income or family member type. In Cox regression, both transmasculine gender identity (hazard ratio, 2.40; 95% CI, 1.50-3.86) and starting hormones as an adult (hazard ratio, 1.69; 95% CI, 1.14-2.52) were independently associated with increased discontinuation rates.

Discussion: Our results suggest that >70% of TGD individuals who start gender-affirming hormones will continue use beyond 4 years, with higher continuation rates in transfeminine individuals. Patients who start hormones, with their parents' assistance, before age 18 years have higher continuation rates than adults.

Key Words: transgender gender dysphoria, sex-hormones, treatment, adolescent, adult

Abbreviations: ICD, International Classification of Diseases; MHS, Military Healthcare System; TGD, transgender and gender-diverse

Approximately 1 in 250 adults or almost 1 million adults in the United States identify as transgender (1). The frequency of adults, and especially younger adults, reporting a gender-diverse identity has increased over time (1). Some persons who identify as transgender or gender-diverse (TGD) will seek treatment with gender-affirming hormones to align their bodies more closely with their gender identity (2). Medical treatment of people who identify as transgender improves body satisfaction, quality of life, and mental health (2, 3). However, many of these treatments are not entirely reversible (4).

Some adolescents or adults who take gender-affirming hormones subsequently elect to stop treatment (5, 6). Most adults who stop gender-affirming hormones report doing so for reasons unrelated to a change in gender identity, such as pressure from family, difficulty obtaining employment, or discrimination (7). Also, discontinuation of gender-affirming hormones does not necessarily represent a failure in treatment or initial decision-making. Some TGD adolescents and adults who start and then discontinue gender-affirming hormones experience use of hormones as an important part of consolidating their gender identity and experience no regret over the use of hormones despite some permanent effects (5, 7, 8). However, a portion of TGD individuals who pursue gender-affirming medical or surgical affirmation do express regret over the permanent effects of treatment (5, 9, 10). In a

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metanalysis of 7928 TGD individuals who had gender confirmation surgery, 1% expressed regret after surgery (9). The most prevalent reason for regret was psychosocial circumstances, particularly from a lack of social support or negative reactions from family and employers (9). Concerns about future regret after medical or surgical affirmation and the capacity of adolescents to provide informed assent for this treatment, with the assistance of their families, have led legislators and members of the judiciary in some locations to attempt to limit access to these interventions for youths (11-14). For example, in the United States, 16 states do not provide coverage for gender-affirming medical care through public insurance for those with incomes below the federal poverty line (Medicaid). Two states have outlawed gender-affirming care for minors, another state has taken administrative action to classify gender-affirming medical care for minors as child abuse, and 20 state legislatures are considering laws to make some or all aspects of gender-affirming medical care for minors illegal during the 2022 legislative session (13, 14). In the United Kingdom, a court ruled that gonadotropin-releasing hormone analogues could not be administered to transgender patients younger than age 16 years without obtaining a court order and suggested that older TGD adolescents should be required to obtain a court order before starting gender-affirming hormones (12).

Clinical guidelines for medical affirmation of persons who identify as TGD suggest that the rate of "de-transition" among postpubertal adolescents and adults is rare, but few studies have assessed the actual rate of treatment discontinuation (6, 7, 10). In a cross-sectional study of a self-selected sample of 27 715 TGD adults in the United States, 61.9% reported a history of social affirmation (ie, changing name, pronouns, appearance), 44.8% reported medical affirmation with hormones, and 19.5% reported surgical affirmation (7). A history of stopping affirmation and reverting to living in their sex assigned at birth for at least a little while was more common among people who only engaged in social affirmation (30.8%) than among people who had started medical (9.1%) or surgical (6.9%) affirmation (7). Among TGD adults who stopped affirmation, 82.5% reported at least 1 external factor, such as pressure from family and community or difficulty with employers as a reason to stop and 15.9% reported at least 1 internal factor, such as psychological distress and uncertainty or fluctuation in gender identity as a reason to stop. Only 5% of people who stopped affirmation reported stopping because they realized that changing gender was no longer desired. At the time of the survey, 68% of people who had discontinued affirmation had subsequently restarted (7). In a 1-year chart review of 174 adults treated at a national gender clinic in the United Kingdom, 12 (6.9%) patients discontinued medical affirmation during a 1-year period. Of these 12 patients, 4 later reengaged in gender-affirming care (6). At the Center of Expertise on Gender Dysphoria, a specialized gender clinic that provides > 95% of all gender-affirming medical and surgical care in the Netherlands, > 75% of TGD adults who started gender-affirming hormones between 1972 and 2014 had completed 1.5 years of gender-affirming hormones and met criteria for gonadectomy by the end of 2015 (10). However, this study did not assess hormone continuation rates directly.

Prior studies of treatment discontinuation rates among TGD adults undergoing medical affirmation have been limited to small samples of patients from specialized gender clinics who stopped coming in for appointments or a cross-sectional study of self-reported de-transition rates among adults who continue to identify as TGD and obtained hormonal therapy both in and outside the health care system (6, 7, 15). These studies found low levels of treatment discontinuation. The discontinuation that did occur was frequently temporary and unrelated to a change in gender identity. However, none of these studies have examined discontinuation rates among minors or assessed objective measures of medication continuation. Therefore, in the current study, we assessed the rate of treatment discontinuation after starting gender-affirming hormones among TGD adolescents and adults and identified demographic groups at higher risk of discontinuation of gender-affirming hormones. We hypothesized that gender-affirming hormone continuation rates will not differ between individuals who start hormones before or after reaching the age of legal majority.

Methods

This study is a secondary analysis of US Military Healthcare System's (MHS) medical and pharmacy billing records from October 2009 to September 2018 for family members of active-duty service members. Data were extracted from the Military Healthcare Data Repository, which includes insurance billing records of all inpatient and outpatient care and outpatient prescriptions provided to individuals enrolled in the military's health care benefit (TRICARE) both domestically and abroad at military and civilian treatment facilities.

We used the following inclusion criteria for our study:

- The patient was a child or spouse of an active duty, retired, or deceased servicemember at the time of the initial TGD-related diagnosis
- Patient had 2 or more medical encounters for a TGD-related diagnosis on different days (International Classification of Diseases [ICD] codes: ICD-9 302.6, 302.85 302.50, 302.51, 302.52, 302.53, and ICD-10 F64.0, F64.1, F64.2, F64.8, F64.9, Z87.890)
- Patient received an initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of his or her last TGD-related medical encounter
- Patient received at least 2 prescriptions for gender-affirming hormones.

We excluded active-duty servicemembers and military retirees from our analysis because servicemembers are required to obtain permission from the military service to transition while on active duty (16) and follow rules governing gender affirmation and use of gender-affirming hormones. We felt this would make them a distinctly different population from their family members and it would be inappropriate to combine them.

Use of ICD 9/10 codes to identify TGD individuals is a validated methodology. In a previous study, these codes were well-matched with clinical text notes in identification of TGD individuals (17, 18). We required patients to have 2 or more encounters with an associated TGD diagnosis to limit false-positive identifications.

We used medical and pharmacy records to identify TGD individuals who started gender-affirming hormones. We identified a TGD individual's sex assigned at birth using the sex recorded at the first encounter, for any reason, in our dataset. Then, we used pharmacy billing records to identify prescriptions and days supplied of gender-affirming hormones for both initial prescriptions and refills. We defined gender-affirming hormone prescriptions as prescriptions for testosterone issued to individuals coded as female at their first encounter and prescriptions for estrogens issued to individuals coded as male at their first encounter. We attempted to limit our sample to patients using gender-affirming hormones by requiring patients to obtain at least 2 prescriptions for gender-affirming hormones and obtain the initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of their last TGD-related medical encounter.

We collected patient age at the initial TGD-related encounter, age at the time of the first prescription for gender-affirming hormones, family role (spouse vs offspring), determined if the patient started gender-affirming hormones before or after gender-affirming health care became an officially covered military benefit for family members on September 1, 2016, and military rank of the insurance sponsor (16). We used military rank (enlisted vs officer) of the patient's insurance sponsor at the time of the last medical encounter in our dataset as a proxy for family income. Officers are required to have a 4-year college degree before military service, whereas enlisted servicemembers are only required to have a high school degree or equivalent. Officers also have a higher average base pay than enlisted servicemembers. In 2019, the average base salary for servicemembers with 10 years of military service was $48 864 for enlisted servicemembers and $86 832 for officers (19).

We used Kaplan-Meier analyses to estimate the rate of discontinuation of gender-affirming hormones after starting treatment (20). We identified patients as discontinuing their gender-affirming hormones if they failed to obtain another prescription for gender-affirming hormones more than 90 days after completing their most recent prescription. Patients were censored from further analysis if they were no longer obtaining health care in the MHS (reached the date of their most recent medical encounter in the database).

We used the log-rank test to assess the influence of sex assigned at birth, age at initiation of gender-affirming hormones (< 18 years vs 18 years of age and older), family income (officer vs enlisted insurance sponsor), family role (spouse vs offspring), and if the patient started gender-affirming hormones before or after gender-affirming care became an official TRICARE benefit on September 1, 2016 (16). We limited our analysis of the influence of official insurance coverage to the first 22 months after starting gender-affirming hormones because we only had 22 months of data after the change occurred. We also used Cox proportional hazard analysis to determine the independent influence of our demographic factors on discontinuation rates. This study was institutional review board-approved as a secondary analysis of preexisting records. Statistical significance was defined as $P < 0.05$.

Results

Of the 952 individuals in our study, 66% were assigned female at birth, 61% were ≥ 18 years old, 71% had an enlisted insurance sponsor, and 90% were children of active duty, retired, or deceased servicemembers (Table 1, Fig. 1). Patients who discontinued obtaining refills of gender-affirming hormones continued to obtain medical care in the MHS for an average of 324 days (SD, 274; range, 91-1602) after they completed their final prescription for gender-affirming hormones (Table 1). The number of patients initiating gender-affirming hormones increased during the study period, and 58% of patients had their first appointment for transgender-related care during the last 22 months of our study (September 2016-June 2018), after gender-affirming care was included as an officially covered TRICARE benefit for family members (14) (Table 1 and Fig. 2).

In our sample, 70.2% (95% CI, 63.9-76.5) of patients who started medical affirmation continued to fill prescriptions for gender-affirming hormone for at least 4 years (Fig. 1). Transfeminine individuals were more likely to continue obtaining gender-affirming hormones in the MHS than transmasculine individuals. The 4-year continuation rate for transfeminine individuals was 81.0% (95% CI, 72.0-90.0) vs 64.4% (95% CI, 56.0-72.8) for transmasculine individuals (log-rank test χ^2, 11.860) (Fig. 3). Patients who were younger than 18 years of age when starting hormones were less likely to discontinue use than patients who were 18 years of age and older. The 4-year continuation rate among people who started treatment under 18 years of age was 74.4% (95% CI, 66.0-82.8) and the rate among people who were ≥ 18 years was 64.4% (95% CI, 56.0-72.8) (log-rank test χ^2, 4.461) (Fig. 4). Family income (enlisted vs officer insurance sponsor; log-rank test χ^2, 0.013) and family member type (spouse vs child; log-rank test χ^2, 1.002) had no influence on continuation rates. Starting hormones before or after official coverage of gender-affirming medical care by TRICARE on September 1, 2016, also had no influence on continuation rates (log-rank test χ^2, 0.728).

Table 1. Sample demographics (n = 952)

Demographic group	%
Gender identity	
Transfeminine	34.1
Transmasculine	65.9
Age at Initiation of Gender-Affirming Hormones	
<18 years old	39.1
≥18 years old	60.9
Insurance sponsor rank	
Enlisted (high school or some college)	70.6
Officer (college education and beyond)	29.4
Family member type	
Dependent child	90.1
Spouse	9.9
Started gender-affirming hormones before or after approval of gender-affirming care as an official TRICARE benefit	
Before approval (October 2009-August 2016)	42
After approval (September 2016-June 2018)	58.0
	Mean ± SD (range)
Days between stopping gender-affirming hormones and last visit	324 ± 274 (91-1602)

Gender-affirming medical care became an authorized TRICARE benefit for dependents on September 1, 2016.

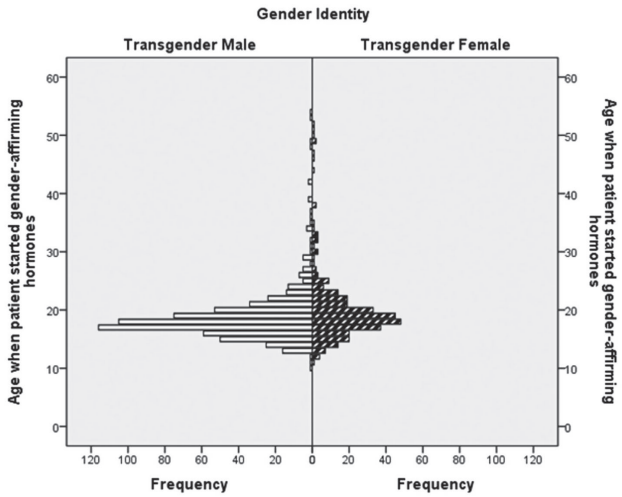

Figure 1. Age at initiation of gender-affirming hormones by sex assigned at birth.

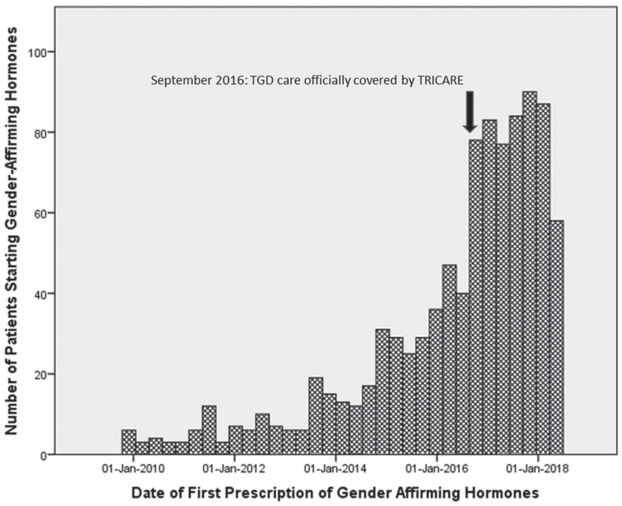

Figure 2. Incidence of gender-affirming hormone initiation over time.

In a Cox regression model containing assigned gender and age at initiation of hormones, transmasculine individuals were more than twice as likely to stop obtaining hormones in the MHS compared with transfeminine individuals (hazard ratio 2.40; 95% CI, 1.50-3.86) and people who started hormones after turning 18 years of age were more likely to stop obtaining gender-affirming hormones compared with people who started hormones before age 18 years (hazard ratio, 1.69; 95% CI, 1.14-2.52) (Table 2).

Discussion

Our study documented higher gender-affirming hormone continuation rates among transfeminine individuals and by patients who started hormones before reaching the age of legal majority in a population with universal insurance and access to low or no-cost medical and pharmaceutical care. Family socioeconomic status, family member type, and the official status of gender-affirming care as a TRICARE-covered benefit at the time the patient began taking gender-affirming hormones had no influence on continuation of gender-affirming hormones.

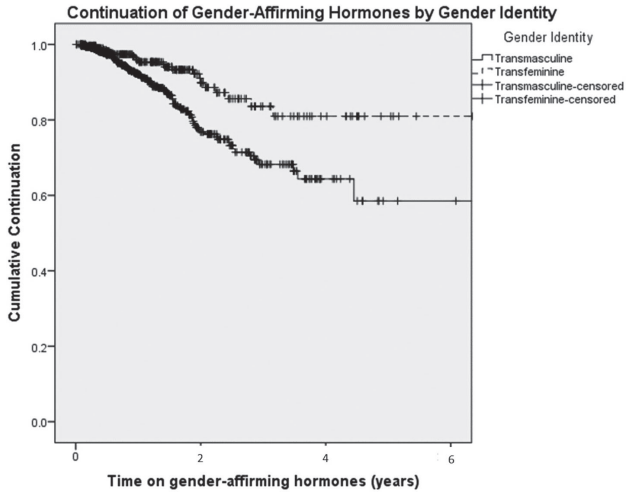

Figure 3. Continuation of gender-affirming hormones by gender identity.

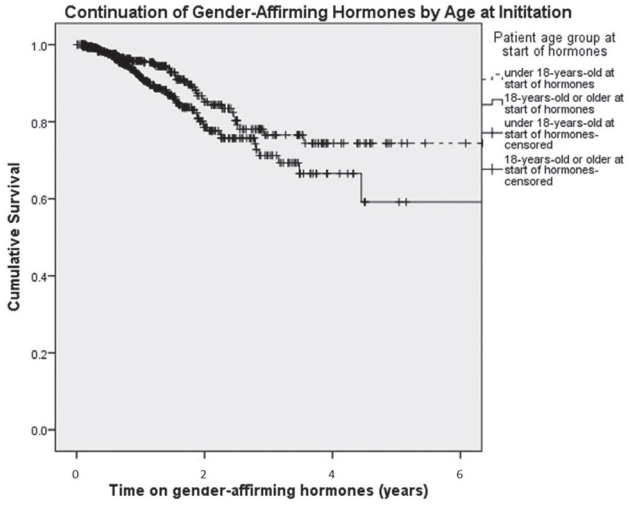

Figure 4. Continuation of gender-affirming hormones by age at initiation.

Table 2. Multivariate regression: independent association of age and gender identity on discontinuation of gender-affirming hormones

Demographic factor	Risk of discontinuing of gender-affirming hormones
Gender identity	Hazard ratio (95% CI)
Transfeminine	Reference
Transmasculine	2.40 (1.50-3.86)
Age at initiation of gender-affirming hormones	
<18 years old	Reference
≥18 years old	1.69 (1.14-2.52)

We noted a higher hormone continuation rate among TGD individuals who were younger than 18 years old at the time of first use of gender-affirming hormones compared with those who were aged 18 years and older when starting hormones. This has not been documented in previous studies.

The patients who started before turning 18 years would require parental consent for this treatment, whereas those aged 18 years and older do not. Parents who consent to use

of gender-affirming hormones likely have a higher level of support for their child's gender affirmation on average than parents who do not. Parental support plays an important role in the mental health of TGD youth (21). A prior study of adults found that lack of family support for a TGD individual's gender was associated with a history of discontinuing social or medical gender affirmation (7). Higher parental support may explain the higher continuation rate among patients who start gender-affirming hormones as minors compared with people who start as adults.

Regardless of the reason for the higher hormone continuation rate among TGD youth, this finding provides support for the idea that TGD individuals below the age of legal majority, with the assistance of their parents or legal guardians and health care providers, can provide meaningful informed assent for gender-affirming hormones and do not appear to be at a higher risk of future discontinuation of gender-affirming hormones because of their young age alone.

There was a higher gender-affirming hormone continuation rate among transfeminine individuals compared with transmasculine individuals in our study. This has not been observed in previous studies. The reasons for this difference cannot be determined using the data from this study. If confirmed in future studies, this would suggest a need to ensure routine screening of transmasculine patients for osteoporosis risk after oophorectomy, especially if this procedure occurs at a younger age.

As in a previous study, there was an increase in the number of patients presenting for gender-affirming care over time (10, 22). However, unlike previous studies, the coverage status of gender-affirming care in our study changed over time. We noted a large increase in patients presenting for care after designation of gender-affirming care as a covered benefit in the MHS.

This leads to a concern that patients and providers who were engaging in gender-affirming care in the MHS before it was officially sanctioned were different than the patients and providers who did not start engaging in gender-affirming care in the MHS until after it was officially sanctioned. However, we did not see a difference in continuation rates between these 2 groups.

The large number of adolescents in our study, the longitudinal data for TGD individuals in a naturalistic and varied clinical setting, use of objective measures of ongoing hormone use, and comparison of gender-affirming hormone use among adolescents and adults are unique strengths of our study, but there are several limitations that must be noted.

We only collected information on medication refills obtained using a single insurance plan. If patients elected to pay out of pocket for hormones, accessed hormones through nonmedical channels, or used a different insurance plan to pay for treatment before and/or after obtaining gender-affirming hormones using TRICARE insurance, we did not capture this information. This means that our findings are likely an underestimate continuation rates among transgender patients.

We attempted to address our concern about overestimating discontinuation rates by only recording cessations among patients who stopped obtaining prescriptions for gender-affirming hormones while continuing to receive medical care using TRICARE insurance for more than 90 days. We would miscategorize patients as terminations if patients elected to obtain their gender-affirming medications using alternative payment options while continuing to receive other medical care using TRICARE.

However, the medication copay for generic medications purchased using TRICARE is quite low at $0 to $3 per prescription when compared with other private insurance programs in the United States. For example, a transgender woman using TRICARE insurance would pay a total of $0 to $72 for a 1-year supply of estrogen and spironolactone. For transgender women with private insurance in the United States, the out-of-pocket expenses for gender-affirming medications would be $230 per year and $500 per year for transgender men with insurance (23). This cost difference makes it less likely that a patient would continue to use TRICARE for medical care but elect to use a different insurer to obtain gender-affirming hormones.

This study was limited by reliance on accuracy of billing data and lack of patient-level data. We cannot know why patients in our study stopped obtaining refills of gender-affirming hormones using their TRICARE insurance. Many factors inform an individual patient's desire or ability to continue obtaining refills of gender-affirming hormones including gender identity, treatment intentions, difficulty finding a provider who offers gender-affirming care, satisfaction with treatment outcomes, or social context.

In a previous study, only 16% of TGD individuals who stopped gender-affirming hormones cited a change in gender identity or mental health concerns as a reason to discontinue social or medical gender affirmation (7). Many of the individuals who reported stopping gender-affirming hormones reported subsequently restarting treatment or the intention to restart treatment (7).

The lack of patient level detail in our study makes it impossible to predict individual patient outcomes with our findings. However, our findings can still be useful to inform policy makers or legislators when assessing the risk of transgender care for minors.

A related limitation is our reliance on the gender marker at the first medical encounter as a proxy for sex assigned at birth. It is possible that this information is wrong or reflects a change in gender marker that occurred before the beginning of our study interval. We attempted to address this concern using our inclusion criteria. For example, with our inclusion criteria, we would incorrectly include a cis-male patient who was assigned male at birth, changed the sex recorded in the electronic medical record to female, received a transgender-related diagnosis at 2 different medical encounters, and then elected to fill 2 prescriptions for testosterone during the same time period he had the 2 transgender-related medical encounters. This combination would likely be a rare event and, if present, have a minimal impact on the findings of the study.

Before September 2016, gender-affirming care was not an officially covered health care benefit under TRICARE (16). Patients may have had trouble finding a TRICARE-approved clinician who would prescribe hormones or a pharmacy that would fill the prescription in their area, especially in cases where they initiated care in 1 location and then they or their family moved. However, we did not see a difference in continuation rates between patients who started hormones before or after gender-affirming care becoming an officially covered benefit.

Determining if these differences in continuation rates exist in other groups of TGD individuals and determining if there

are differences in reasons for discontinuation by gender identity or age is an important topic for future studies. Future prospective studies should investigate the rate of hormone discontinuation between transfeminine and transmasculine individuals to determine whether the same pattern of discontinuation is observed. The reasons for discontinuing treatment and whether patients anticipate restarting treatment at a future date would also be important to assess. Finally, it would be useful to prospectively assess the number of TGD individuals who experience regret after starting gender-affirming hormones and if there are any associated factors that can be used to identify patients at a higher risk of regret. This would assist clinicians in providing nuanced counseling regarding treatment options to TGD individuals before starting hormones.

Conclusion

In our study, transmasculine individuals were more likely to discontinue use of gender-affirming hormones during the first 4 years of use than transfeminine individuals. We also found that individuals who start gender-affirming hormones before reaching the age of legal majority are less likely to subsequently discontinue use when compared with individuals who start hormones after becoming a legal adult. If replicated in future studies, the improved continuation rate among patients who are not legal adults at the time of treatment should provide some reassurance to those concerned about the ability of minors to provide informed assent to use of gender-affirming hormones. A higher continuation rate among minors could also be used to inform the actions of legislators and judges who wish to prohibit gender-affirming treatment for minors to protect them from the consequences of health care decisions they make with the assistance of their parents and health care providers.

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Disclosures

The authors report no competing interests.

Data Availability

A deidentified copy of the dataset for this study is available from the authors on reasonable request

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Current Concerns About Gender-Affirming Therapy in Adolescents

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Abstract

Purpose of Review Results of long-term studies of adult transgender populations failed to demonstrate convincing improvements in mental health, and some studies suggest that there are treatment-associated harms. The purpose of this review is to clarify concerns about the rapid proliferation of hormonal and surgical care for the record numbers of youth declaring transgender identities and seeking gender reassignment procedures.

Recent Findings Systematic reviews of evidence conducted by public health authorities in Finland, Sweden, and England concluded that the risk/benefit ratio of youth gender transition ranges from unknown to unfavorable. As a result, there has been a shift from "gender-affirmative care," which prioritizes access to medical interventions, to a more conservative approach that addresses psychiatric comorbidities and psychotherapeutically explores the developmental etiology of the trans identity. Debate about the safety and efficacy of "gender-affirming care" in the USA is only recently emerging.

Summary The question, "Do the benefits of youth gender transitions outweigh the risks of harm?" remains unanswered because of a paucity of follow-up data. The conclusions of the systematic reviews of evidence for adolescents are consistent with long-term adult studies, which failed to show credible improvements in mental health and suggested a pattern of treatment-associated harms. Three recent papers examined the studies that underpin the practice of youth gender transition and found the research to be deeply flawed. Evidence does not support the notion that "affirmative care" of today's adolescents is net beneficial. Questions about how to best care for the rapidly growing numbers of gender-dysphoric youth generated an intensity of divisiveness within and outside of medicine rarely seen with other clinical uncertainties. Because the future well-being of young patients and their families is at stake, the field must stop relying on social justice arguments and return to the time-honored principles of evidence-based medicine.

Keywords Transgender · Gender dysphoria · Gender incongruence · Puberty blockers · Gender-affirming care · The Dutch protocol

Introduction

The fundamental basis for concern about "gender-affirming" interventions for adolescents, and socially transitioned children who will soon be adolescents, is how they will fare in the ensuing decades [1•]. There are significant knowledge gaps about the balance of benefits and harms as patients live their lives.

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Medicine has provided treatments for transgender-identified adolescents for over 25 years [2–6]. These treatments emerged in the late 1980s to early 1990s in large part in response to the suboptimal outcomes of transitioned adults, with the hope that early gender transition may improve outcomes [3]. Despite claims of the lifesaving nature of gender transition for adults, none of the many studies convincingly demonstrated enduring psychological benefits. The longest-term studies, with the strongest methodologies, reported markedly increased morbidity and mortality and a persistently high risk of post-transition suicide among transitioned adults [7, 8••, 9].

The lack of credible evidence of benefits of gender transition has come into focus for today's transgender-identified youth, whose numbers have sharply increased. The presentation of gender dysphoria has markedly changed in recent years [10]: the sex ratio of youth presenting in medical settings has

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reversed from primarily male to primarily female [11], with the preponderance of youth whose transgender identity emerged for the first time in adolescence and in the context of significant pre-existing mental illness and neurocognitive disorders [12]. These changes began to manifest around 2006 but became pronounced around 2014–2015 [13]. Nonetheless, many clinicians and policymakers promulgate that science long ago established the benefits of gender transition for these adolescents [14–18].

There has never been a dispute about whether medical and surgical interventions can feminize or masculinize secondary and some primary sex characteristics. For children and adolescents, the debate is not whether such transformations are possible, but "at what age can youth meaningfully consent," "upon fulfilling which criteria," and perhaps most importantly, "just because we can – should we?" [1•]. Such questions have provoked an intensity of divisiveness within and outside of medicine rarely seen with other clinical uncertainties [18–22]. This passion reflects decidedly different prioritization of *scientific evidence*, *medical ethics*, and *social values*. We elaborate on each below.

Disagreement About the Scientific Evidence

While several European countries recognized deficiencies in the evidence supporting the highly medicalized "gender-affirming" approach to treating gender-dysphoric youth [1•, 33••, 34••, 35, 36], in North America, the narrative that "gender-affirmative care has been scientifically proven" has been remarkably resilient [23••]. Its justification rests on several key assumptions misrepresented as proven facts [15, 24]:

1. The emergence of a trans identity is the result of reaching a higher level of self-awareness.
2. Whether the trans-identity emerges in very young children, older children, teens, or mature adults, it is authentic and will be lifelong.
3. All gender identity variations are biologically determined and inherently healthy.
4. The frequently co-occurring psychiatric symptoms are a direct result of gender incongruence (the so-called "minority distress" model).
5. The only way to relieve, or prevent, psychiatric problems is to alter the body at the earliest signs of puberty.
6. Psychological evaluations and attempts to address psychiatric comorbidities should only be used to support transition.
7. Attempts to resolve gender dysphoria with psychotherapy range from ineffective to harmful.
8. Gender-dysphoric youth must have unquestioning social, hormonal, and surgical support for their current gender identities and desired physical appearance.
9. All individual embodiment goals, even those that do not occur in nature, must be fulfilled to the full extent technically possible.
10. Science has proven the benefits of early gender transition, and low rates of regret and detransition further validate the practice.

These unproven or disproven assumptions [24] have created a narrative that has misled physicians, parents, and patients to conclude that meeting a young gender dysphoric individual's desired body modification goals provides the only chance for a full, successful, happy life. It has positioned invasive medical interventions for children and adolescents as a civil right, rather than as medical interventions.

The most fundamental of these assumptions are that a teenager's *transgender identity, once expressed, is permanent*; that it will cause *lifelong suffering* if no medical interventions are offered; and that "gender-affirming" *interventions are safe and effective* at improving short-term and long-term psychological outcomes. All three premises are deeply flawed, as we explain below.

Identity Development in Teenagers Is Far from Complete

Answering the question, "Who am I?" is the primary "developmental task" of adolescence [25]. Children and adolescents are too young to assume their current gender identity is permanent. Adults should know that young people's sexual orientations and gender identities fluctuate as they gain more life experiences [26].

Among the many facets of identity, the development of sexual orientation is particularly relevant as gay, lesbian, and bisexual individuals often have extended periods of suffering from gender dysphoria in their younger years [27]. The current overall crisis in mental health among youth and especially girls [28] may introduce further complexity into the identity development process. As many as 70% or more of youth who present with gender identity concerns for the first time in adolescence had psychiatric diagnoses prior to presenting with gender dysphoria [29]. The strong connection between a trans identity in adolescence and the presence of neurocognitive diagnoses [29, 30] deserves additional consideration, as individuals on the autism spectrum are often gender nonconforming. These factors may play a role in the emergence of a transgender identity as a maladaptive mechanism for understanding their distress.

The natural arc of adolescence is the eventual resolution of identity confusion and consolidation of a healthy, multifaceted identity. Problematically, every stage of "gender-affirming" care disrupts the natural course of identity development.

Goals Have Shifted from Reducing Suffering to Achieving Personal "Embodiment Goals"

For decades, gender specialists told the public that gender/sex incongruence created such suffering that these interventions are often "lifesaving." In 2022, the justification for these interventions changed. WPATH "Standards of Care 8" explicitly instructed providers to rely on the "Gender Incongruence" ICD-11 diagnosis [31], which does not require the presence of distress [32].

This recommendation came with an extensive list of medical procedures that WAPTH deems medically necessary for nonbinary patients, including the construction of a neovagina while retaining penis and testicles, and "nonbinary mastectomies" that preserve some of the female breast tissue but resize and reposition the nipple and areola to make the breast appear more masculine. Procedures ranging from "flat front" obliteration of sex organs for those with a eunuch gender identity, to uterine transplantation for male-to-female individuals wishing to pursue childbearing, are also listed as medically necessary [31, p. 136].

Although achieving body modification goals can be very satisfying to patients, clinicians should not confuse it with improved functioning in relational, sexual, educational, substance dependence, and vocational aspects of life—the domains of mental health. Nor can it be claimed to be "lifesaving."

Medical and Surgical Gender Transition Has Not Resulted in Credible Mental Health Improvements

Despite the promise that gender transition is key to ameliorating the suffering of gender-dysphoric youth, systematic reviews of evidence failed to find trustworthy evidence of such improvements. The well-known National Institute for Health and Care Excellence (NICE) reviews, commissioned by the NHS, the UK's health authority, evaluated the first two stages of medical gender transition for youth: puberty blockers and cross-sex hormones [33••, 34••]. In both reviews, the studies that reported positive findings were found to be unreliable due to poor methodology.

In the case of puberty blockers, the reviews found no evidence of improvements in key areas of mental health:

> "The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up. Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance" [33••, p. 13].

For cross-sex hormones, the review found that improvements in mental health were *highly uncertain* and had to be carefully weighed against the risks of hormonal interventions [34••]. Having conducted their own systematic review of evidence [35], the Swedish health authority came to the even starker conclusion that for most adolescents, the risks of hormones outweigh the benefits [87••]. The Finnish health authority, and the Florida health authority, came to similar conclusions after their own systematic reviews/overviews of systematic reviews [36, 37••].

Since the practice of gender-transitioning youth did not begin to be widely scaled until about 2015, the existing systematic reviews of evidence for young people are limited by very short-term follow-up. Therefore, it is informative to look at studies that followed lifelong trajectories of individuals who medically transitioned decades ago, although they represent a different demographic group (most transitioned when they were older). Unfortunately, these long-term data do not show that hormonal and surgical transitions result in lasting mental health improvements in transgender-identified individuals, and some evidence even suggests the possibility of treatment-associated harms [7, 40•].

A well-known 30-year Swedish follow-up study compared medically transitioned individuals to cisgender age-matched peers on key measures of morbidity and mortality [7]. The study found sharply elevated rates of suicide among transitioned adults (19 times higher than controls overall, and 40 times higher for female-to-male individuals [7, Table S1]) and significantly elevated all-cause morbidity and mortality, with survival curves between transitioned adults and their cisgender matched controls markedly diverging at the 10-year mark and beyond.

A more recent long-term Swedish study also failed to find that either hormones [39••] or surgery [8••, 40•] improved long-term mental health outcomes of gender dysphoric adults. Originally, the surgical outcomes showed some promise [39••]; however, the methodology was found to be deeply flawed [8••], and upon reanalysis of the surgery data, it emerged that not only did those who refrained from surgery fare no worse, but they also had half as many serious suicidal attempts [40•]. This difference did not reach the threshold of statistical significance, but the apparent doubling in serious suicide attempts among surgically transitioned individuals, as compared to gender-dysphoric controls who did not have surgery, is clinically meaningful and problematic.

Yet another long-term Dutch follow-up of transitioned individuals concluded that "suicide death risk is higher in trans people than in the general population" and that suicide deaths occurred during every stage of transitioning"—from those who were still in the evaluation phase, to those who underwent complete gender transition [41, p. 486].

Two recent US-based publications highlighted high rates of mental health problems, including depression, anxiety, substance abuse disorder, suicidality, cardiovascular disease, obesity, cancer, and sexually transmitted infections such as HIV, HPV, syphilis, and hepatitis C in community samples of adults who identify as transgender [42, 43]. Although community samples can suffer from extensive methodological problems [44], there is little debate about the high burden of physical and mental health illness in this population. The explanations offered for these health disparities focus on minority stress, discrimination, and barriers to obtaining health care including fear of mistreatment in health facilities [42, 43]. Conspicuously absent from the discussion is the possibility that the mental health of some trans persons may be intrinsically compromised.

The position that poor mental health problems are either merely co-occurring with, or a direct result of the experience of "gender incongruence"—with no acknowledgement of the possibility of reverse causation —is reinforced in the WPATH "Standards of Care 8" Assessment section for adults, which states that uncontrolled mental health problems should only rarely impede the provision of hormones and surgery [31, p. 37]. While the adolescent chapter acknowledges the difficulties of working with adolescents who have psychiatric illnesses, the focus is on controlling problems just enough to ensure that young patients can provide valid consent to gender reassignment, participate in postoperative care, and adhere to ongoing hormone treatment [31]. The predominance of pre-existing mental health problems prior to the onset of gender dysphoria in youth [29], and the implications for the future durability of a transgender identity as youth mature, is not considered. In 2022, two prominent gender specialists expressed concern that trans-identifying adolescents are too quickly diagnosed and rushed to irreversible body-modifying interventions [45, 46].

Collision of Ethical Principles

When treating transgender-identified adolescents, clinicians invariably confront three ethical principles—above all, do no harm (nonmaleficence); act in the patient's best interests (beneficence); and respect of patient autonomy [47]. These principles uncomfortably collide in the minds of many clinicians. There seems to be no simple resolution.

To avoid *harm*, clinicians conceptualize the specific physiologic, medical, social, and psychological dangers that parents and patients need to understand, attempt to avoid, or accept. Here are examples from each danger category associated with medical gender transition: sexual dysfunction and infertility [49, 50]; shortened lifespan due to increased medical morbidity [7, 51]; difficulties in romantic partnerships [52, 53]; substance abuse and addiction [54]. Advocates of the medical transition of youth point to the harms of "doing nothing" to stop natural puberty, which subjects youth to distress and necessitates more invasive procedures later in life to "undo" the irreversible effects of puberty on the body [55]. Unlike the risks of transition-associated harms which have been demonstrated, avoidance of *future harms* by undergoing a medical transition in adolescence remains at best an unproven theory. Blocking puberty at Tanner stage 2 not only removes the possibility of fertility preservation [15], but also greatly complicates future genital surgeries due to insufficient tissue [56]. The death of one of the 70 youths in the famous "Dutch study" [5] due to complications from genital surgery was likely a direct consequence of early puberty blockade [57•].

To ensure *beneficence*, clinicians need to understand the benefits of gender transition, when they appear, and the extent to which they endure over time. Initially, a high level of satisfaction is expected as desired changes such as softened skin or, conversely, facial hair appear [58••]. Surgery can further improve appearance and satisfaction, although its rate of complications is significant [59, 60], and it does not clearly improve mental health [7, 8••]. However, at some point, the interventions reach their limit. While the face, chest, and/or genitals can be surgically altered, overall skeletal size or hand size will continue to appear incongruent, and dysphoria may persist [61].

To respect patient *autonomy*, clinicians need to determine when an adolescent has the cognitive maturational capacity and life experience to consent to potentially irreversible medical and surgical interventions. However, because of the maturational capacities of children or young adolescents, it is the parents who are actually exercising the autonomy. This can be seen in families in which parents support transition and those who do not. As soon as parents consent to the first stage of gender transition, a child's future medical transition trajectory is virtually assured [62•, 63•]. While children "assent" to the interventions, recent research about the capacity of adolescents to make decisions related to future reproductive function is not reassuring [64].

Clash of Value Systems

Absent certainty about the optimal treatment of the high number of youth currently presenting with gender dysphoria [23••], decisions are made based on core values.

Those who insist that a young person has the right to receive any medical intervention they desire now, and the right to regret that intervention later, privilege *autonomy* above all else. The "patient autonomy" argument is compromised by the very young age of the many affected patients, and a common tendency among gender-affirming providers to exaggerate the benefits of the practice, while downplaying the risks and uncertainties [1•, 20].

Those who advocate for sharply curbing the practice of medical interventions in gender-diverse minors because they view the practice as a major source of iatrogenic harm, privilege the principle of *non-maleficence*.

The two positions on the issue of youth gender transition also distinctly clash over the value of *beneficence*. Each side claims they are pursuing beneficence, but sharply disagree on the solution: one side insists that the most benefit is derived by undergoing a transition as early in puberty as possible to achieve the best possible cosmetic outcomes, while the other asserts that achieving cognitive maturity, emotional stability, and obtaining life experiences (including sexual experiences) prior to making the decision to undergo irreversible transition will provide the most long-term benefit for affected individuals.

Significance of Regret and Detransition

Proponents of gender-transitioning youth insist the benefits of the practice are self-evident even if systematic reviews of evidence cannot detect them. To support their view, they quote exceedingly low regret rates of less than 1–2% [65, 66]. This implies that 98–99% of transitioned individuals are happily situated throughout their lives. This conclusion is inaccurate, for three reasons.

First, follow-up studies exploring regret and quality of life suffer from very high rates (20–60%) of loss to follow-up [67], which means the most adversely affected, including dissatisfied, sick, or deceased patients, may be lost to follow-up at a disproportionately high rate. *Second*, these rates were obtained from individuals transitioning under much different circumstances than the ones found today. They were mature adults who passed rigorous psychological screenings, which today are viewed as "discriminatory gatekeeping."

Third, and perhaps most important, is the question of how these studies defined regret. Each study's methodology differed, but generally speaking, regret has been traditionally defined very narrowly as a request for legal document change or a return to the same clinic that facilitated the original transition to start medical detransition. Even when these criteria were met, not every study would consider someone who wanted to reverse their transition as a regretter. For example, Keira Bell, arguably the most famous young adult regretter, whose case led the UK to reevaluate their approach to gender dysphoric youth, would not have been counted as a regretter in frequently-cited "low regret" studies [65]. This is because the studies required regretters to have had their gonads removed, while the only surgery Keira received was a double mastectomy.

Regret

Regret is a common, if not universal, human experience. Individuals who underwent medical transition are no exception. Regret does not preclude benefits, which typically appear first. The "honeymoon period" can last from several months to several years [68], with adverse effects emerging 8–10 years following transition [65, 69] among mature adult transitioners. Among the more recently transitioning cohorts comprised primarily of youth, there appears to be a shorter time to regret and a subsequent desire to detransition, around 3–6 years on average, with longer time to regret and detransition among biological males [70•, 71].

There are many contributing factors to regret. Many teens consenting to gender reassignment lack sexual experiences [72] and few anticipate wanting to have children in the future [64]. Later, as sexual dysfunction because of hormones, surgery, or anxiety about physical intimacy becomes a recurrent experience, regret appears. Reproductive regret can be significant, as was evident in the data presented at WPATH Symposium [73, 74••].

Strained intrafamilial bonds, inability to find a stable relationship, the experience of discrimination, need for ongoing medical care, substance use to quell anxiety and depression—matters that they may have been warned about—begin to create waves of regret. Some eventually express regret over not having had a chance to explore their concerns in psychotherapy before they transitioned [70•, 71].

There must be a hierarchy of intensity of regret related to the situations patients ultimately find themselves in. The most extreme form of regret is post-transition suicide and suicide attempts. Individuals who undergo medical detransition to restore the body to its pre-transitioned state are also high on this hierarchy. Lower on this hierarchy are those who regret their transitions but due to the irreversible changes to their bodies' anatomy and function, adaptively choose to make the best of their lives without detransitioning. Regret and acceptance can co-exist.

Detransition

Physicians providing gender transition of youth claim that they have never met a detransitioned patient. This is not

surprising: recent research with detransitioners indicated that three-quarters do not return to the treating providers to tell them about detransition [70•].

Detransition has become much more visible in recent years [70•, 71, 75–83, 84••, 85]. However, it was only recently that the rates of detransition began to be quantified. According to recent UK and US data, 10–30% of recently transitioned individuals detransition a few years after they initiated transition [82, 83, 84••]. Detransition does not invariably mean regret about the original transition. Not all detransitioned individuals have expressed regret. Those who have, are often angry at themselves for their naïve adolescent certainty and disturbed about medical professionals' unconcerned compliance with their requests. A growing number of malpractice lawsuits by regretful youth [85] is likely in the future.

The Reversal of "Gender-Affirming Care"

In the last 36 months, there has been sharply increased scrutiny of the practice of youth gender transition worldwide. Systematic reviews of evidence from Europe failed to demonstrate the hoped-for meaningful improvements in youth's mental health functioning and exposed significant risks, including demonstrated risks to bone development [33••, 34••, 35, 36].

Three different studies [1•, 57•, 74••] recently shone a spotlight on the original Dutch research [4, 5], which launched the experimental practice of pediatric gender transition into mainstream medical practices shortly after its publication. The studies argued that the Dutch research failed to demonstrate any clinically significant changes in standard measures of psychological health and that the main finding of the resolution of gender dysphoria was likely invalid due to the reversal of the scale scoring between baseline and follow-up [1•, 74••]. The Dutch research also raised serious ethical questions, as nearly all the youth in the Dutch research who were transitioned and became sterile had been same-sex attracted at baseline [57•]. Overall, the researchers deemed the Dutch studies unfit for clinical or policy decision-making due to the high risk of methodological bias [1•, 74••].

Commensurate with these conclusions, in the last 3 years, three European countries—Finland, Sweden, and England—have reversed their unquestioning belief in "affirmative care" by setting new national health policies that prioritize mental health interventions as the first and often only treatment available outside of clinical research settings [86, 87••, 88].

This reckoning has also begun in France, Australia, and the US state of Florida, and most recently, Norway [89–92]. Many US state laws have been introduced to limit or ban gender transitions of youth [93]. The reluctance of the US medical societies to recognize the apparent problems with medical "gender affirmation" of youth may have contributed to the unfortunate and preventable politicization of this complex issue.

Conclusions

Fulfilling the diagnostic criteria for gender dysphoria (DSM) or gender incongruence (ICD) in children or adolescents today does not predict its persistence in the future. Doctors may be incorrect in their assumptions about the causes, persistence, and future trajectory of adolescent gender dysphoria. The rapidly rising numbers of gender dysphoric youth treated with hormones and surgeries and the delayed onset of regret mean that the scale of possible iatrogenic harm will not be known for several years.

The evidence base for gender-affirming interventions is sparce and of very low quality. While the evidence of benefits is highly uncertain, the harms to sexual and reproductive functions are certain, and many uncertainties about the long-term health effects exist. As a result, it is hard to ethically justify continuing to use hormones and surgeries as first-line "treatment" for gender dysphoric youth.

Political arguments relying on social justice, civil rights, and freedom of expression are compelling and powerful in the public arena. Few mental health professionals would argue against these vital human rights. Nonetheless, they tend to complicate clinicians' consideration of how to respond to gender dysphoric adolescents and their families.

Parents want to know, "Where is this identity coming from?" "What about my child's previous difficulties?" and critically, "Will transition give my child the best chance for a happy and fulfilling life?" Clinicians are ethically bound to honestly represent the uncertainty of the current state of knowledge, rather than asserting that body modification is the best, safest, and most effective treatment. When a concerned family seeks our counsel, they are seeking our knowledge, not our political ideation and beliefs.

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Data Availability Data sharing is not applicable as no new data were generated or analyzed during this study.

Declarations

Conflict of Interest The authors declare no competing interests.

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