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Original Research

Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol

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Abstract

Background: Twenty years ago, the Dutch Protocol—consisting of a gonadotropin-releasing hormone agonist (GnRHa) to halt puberty and subsequent gender-affirming hormones (GAHs)—was implemented to treat adolescents with gender dysphoria.
Aim: To study trends in trajectories in children and adolescents who were referred for evaluation of gender dysphoria and/or treated following the Dutch Protocol.
Methods: The current study is based on a retrospective cohort of 1766 children and adolescents in the Amsterdam Cohort of Gender Dysphoria.
Outcomes: Outcomes included trends in number of intakes, ratio of assigned sex at birth, age at intake, age at start of GnRHa and GAH, puberty stage at start of GnRHa, proportions of adolescents starting and stopping GnRHa, reasons for refraining from GnRHa, and proportions of people undergoing gender-affirming surgery.
Results: A steep increase in referrals was observed over the years. A change in the AMAB:AFAB ratio (assigned male at birth to assigned female at birth) was seen over time, tipping the balance toward AFAB. Age at intake and at start of GnRHa has increased over time. Of possibly eligible adolescents who had their first visit before age 10 years, nearly half started GnRHa vs around two-thirds who had their first visit at or after age 10 years. The proportion starting GnRHa rose only for those first visiting before age 10. Puberty stage at start of GnRHa fluctuated over time. Absence of gender dysphoria diagnosis was the main reason for not starting GnRHa. Very few stopped GnRHa (1.4%), mostly because of remission of gender dysphoria. Age at start of GAH has increased mainly in the most recent years. When a change in law was made in July 2014 no longer requiring gonadectomy to change legal sex, percentages of people undergoing gonadectomy decreased in AMAB and AFAB.
Clinical Implications: A substantial number of adolescents did not start medical treatment. In the ones who did, risk for retransitioning was very low, providing ongoing support for medical interventions in comprehensively assessed gender diverse adolescents.
Strengths and Limitations: Important topics on transgender health care for children and adolescents were studied in a large cohort over an unprecedented time span, limited by the retrospective design.
Conclusion: Trajectories in diagnostic evaluation and medical treatment in children and adolescents referred for gender dysphoria are diverse. Initiating medical treatment and need for surgical procedures depends on not only personal characteristics but societal and legal factors as well.

Keywords: adolescents; gonadotropin-releasing hormone agonist; gender dysphoria; transgender.

Introduction

Over 20 years ago, clinicians in the Netherlands had a pioneering role in the development of medical treatment for adolescents diagnosed with gender dysphoria (GD). These adolescents are troubled by an incongruence between their experienced gender and their gender assigned at birth.[1] This may lead to the desire to obtain the physical characteristics of the experienced gender. Therefore, development of endogenous secondary sex characteristics during puberty can be distressing.

In the Netherlands, gender-affirming medical treatment was already available for transgender adults aged >18 years since 1972. Nevertheless, children and adolescents experiencing GD were devoid of treatment options until 1987, when psychologist Peggy T. Cohen-Kettenis noticed an increasing number of transgender teenagers requesting medical intervention. After careful deliberation, gender-affirming hormone (GAH) treatment was made available for thoroughly screened well-functioning young people between 16 and 18 years of age—after first-stage treatment

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with antiandrogens for assigned males at birth (AMAB) and progesterone for assigned females at birth (AFAB).[2] Thenceforth, a modest number of adolescents were treated with GAH. Around the same time, pediatric endocrinologist Henriette A. Delemarre-van de Waal treated an adolescent diagnosed with GD with a gonadotropin-releasing hormone agonist (GnRHa) to halt puberty. After following the then-current diagnostic protocol, she added GAH treatment a few years later.[3,4] Internationally, this approach of diagnostic procedure and combined treatment of GnRHa and subsequent GAH came to be known as the Dutch Protocol.[5,6]

Few studies have assessed the prevalence of GD in children and adolescents. Based on the current literature, 1.3% to 2.7% of schoolchildren self-identify as transgender or gender-nonconforming people.[7] Nevertheless, ever since the implementation of the Dutch Protocol, a rise in the number of adolescents requesting this treatment has been seen.[8-10] The protocol has become common practice in gender identity clinics throughout the Western world and has been incorporated into the Endocrine Society's guideline for the medical treatment of GD from the earliest edition and into the standards of care by the World Professional Association for Transgender Health since 1998.[11,12] However, the approach is not endorsed worldwide. For example, in Sweden the eligibility for treatment with puberty suppression in adolescents has recently been restricted.[13]

Now, the time has come to review how practice has evolved since the start of the Dutch Protocol and to evaluate the treatment trajectories in people who were treated accordingly. We set out to answer the following questions:

- Is there a trend in the number of intakes and the ratio in assigned sex at birth, as well as the age at presentation, age at the start of GnRHa, and/or age at GAH treatment in referred children and adolescents?
- Do adolescents start GnRHa earlier in puberty over the years?
- Do the proportions of adolescents starting medical treatment vary over time?
- Does the proportion of adolescents starting GnRHa differ between those who are prepubertal and pubertal at first visit?
- How many adolescents using GnRHa subsequently start GAH?
- Are there distinct differences over time in reasons for refraining from treatment?
- Does puberty stage at start of GnRHa affect the number of individuals choosing to undergo surgical gender-affirming treatment?

Last, we wanted to study trends in gender-affirming surgery being performed over time. However, a possible trend in surgery cannot be regarded separately from a change in a Dutch law in July 2014. Due to this change, people were no longer obliged to have undergone gonadectomy to change their legal sex. Therefore, we adapted the research question and investigated whether this change in law made a difference in the number of people undergoing gonadal surgery.

Methods

Study design and population

This study is part of the Amsterdam Cohort of Gender Dysphoria.[8] This cohort is composed of all people who underwent diagnostic assessment and/or medical treatment for GD (per the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition–text revision and fifth edition)[14,15] at the Center of Expertise on Gender Dysphoria of the Amsterdam UMC, location Vrije Universiteit Amsterdam (VUmc), between 1972 and December 31, 2018. The dataset contains age at intake, age at start of GnRHa and/or GAH treatment, type of hormone treatment, pubertal stage at start of GnRHa, and date of gender-affirming surgery. Data were extracted from the medical charts.

The VUmc clinic has provided mental health and medical care to transgender adults since 1972. In some cases, people close to turning 18 years old could already attend the adult gender identity clinic. Mental health care for children and adolescents was located at the University Medical Center Utrecht since 1987. If treatment was indicated, medical care was provided at the VUmc. From 2002 onward, the mental health and medical care departments have been located at the VUmc. After establishment of the gender identity clinic for children and adolescents at the VUmc around 2002, adolescents diagnosed with GD elsewhere were able to start or continue medical treatment at this center. All referrals to the gender identity clinic were added to the study cohort if they visited the gender identity clinic at least once.

To select our study population, the following inclusion criteria were applied to the Amsterdam Cohort of Gender Dysphoria: either a visit to the gender identity clinic or the start of GnRHa before the age of 18 years. There was no lower limit for age. Hence, the study sample included pubertal adolescents who followed the Dutch Protocol, as used from 1997 onward, which could include GnRHa with or without subsequent GAH, as well as prepubertal children who adopted a "watchful waiting" approach. This approach meant that the child returned to the gender identity clinic only when puberty had begun. The child was not seen in the meanwhile because medical intervention is not provided to prepubertal children at out clinic.[16] People with disorders of sex development were excluded.

People with all kinds of gender identity were included. For clarity, the terms AMAB and AFAB are used.

The entire inclusion process is shown in Figure 1.

Medical treatment protocol

The medical treatment protocol has been described comprehensively.[17] In short, adolescents diagnosed with GD and fulfilling eligibility criteria according to Hembree et al[18] could start on intramuscular or subcutaneous triptorelin (GnRHa), 3.75 mg every 4 weeks or 11.25 mg every 12 weeks, to suppress pubertal development when at least 12 years old. In addition, Tanner genital or breast stage of at least 2 was required for AMAB and AFAB to start GnRHa, respectively.

If GD persisted, adolescents were eligible for puberty induction with GAH from age ≥16 years. Over the years, the protocol was adapted so that adolescents could start GnRHa before age 12 if puberty had started, and those who had already been treated with GnRHa for several years were eligible to start GAH from age 15 years.[19] Puberty was induced with estrogen in AMAB and testosterone in AFAB according to the Endocrine Society's clinical practice guideline.[18]

After at least 1 year of GAH and a minimum age of 18 years, people became eligible for gender-affirming surgery, including gonadectomy. After gonadectomy, GnRHa is no longer indicated, while estrogen or testosterone supplementation becomes indispensable.

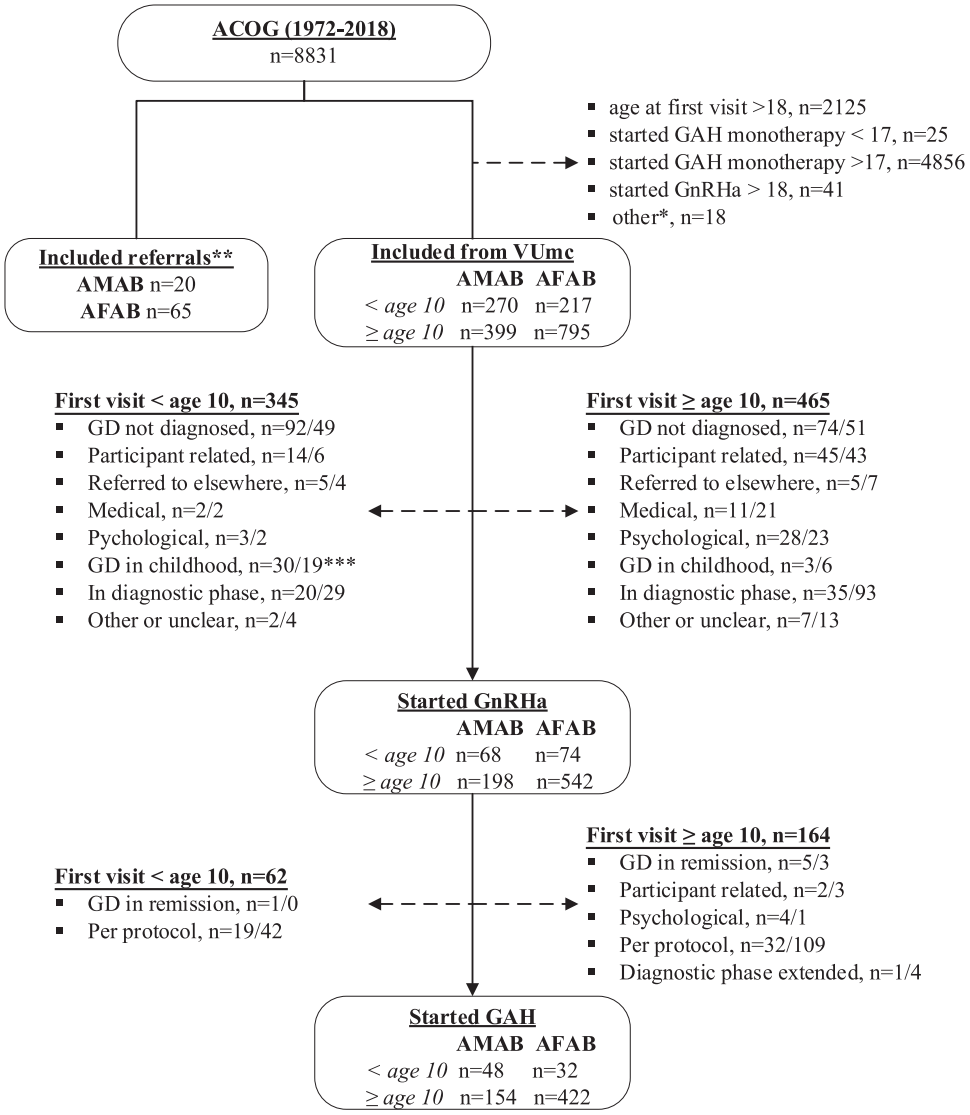

Figure 1. Flowchart of inclusion process and treatment trajectories. n = AMAB/AFAB. *Disorder of sex development, n = 6; wrongfully included, n = 1; did not follow Dutch Protocol, n = 11. **People referred from elsewhere had already started medical treatment or were referred specifically to start. ***Additionally, 34 AMAB and 28 AFAB first visiting before age 10 years were diagnosed with GD in childhood but were not yet potentially eligible for start of GnRHa at the end of data collection. ACOG, Amsterdam Cohort of Gender Dysphoria; AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist.

Pubertal development

Pubertal development according to the Tanner staging scale was assessed by a pediatric endocrinologist prior to starting GnRHa. Hence, Tanner stages were available only for adolescents who started GnRHa. Testicular volume was measured with an orchidometer.

The study population was divided into early and late puberty groups. Early puberty was defined as testicular volume ≤9 mL or maximum Tanner breast stage 2 for AMAB and AFAB, respectively. Testicular volume ≥10 mL or Tanner breast stage ≥3 was considered late puberty.

Start of GnRHa and GAH treatment

The percentage of people starting GnRHa is calculated as the number of people who started GnRHa divided by the number of people who were potentially eligible for the start of GnRHa at the end of data collection, multiplied by 100. Potential eligibility for start of GnRHa was defined as a minimum age of 12 years and at least 1 year after the first visit. Addition of this last criterion allowed for a diagnostic evaluation of at least 1 year.

Reasons for not yet starting GnRHa by the end of 2018 were extracted from the hospital chart and divided into categories (Table 1). For the percentage of people starting GAH, the denominator was composed of the number of people eligible for start of GAH based on their age and duration of GnRHa treatment (see Medical treatment protocol).

Gender-affirming surgery

The overall proportion of people undergoing gender-affirming surgery is reported. In the Netherlands, people were obliged to have undergone gonadectomy to be able to change their legal sex until a new law came into effect in July 2014. To analyze if this affected the number of people opting for gonadectomy, the proportion of people who had undergone it was calculated before and after passing of the bill. To ensure eligibility for

Table 1. Reasons for not having started GnRHa.[a]

Category	Description
1. In diagnostic phase	Participants were still in the diagnostic phase at the end of data collection.
2. Referred elsewhere for diagnostic evaluation	Participants were initially seen at our gender identity clinic but referred to another mental health care provider for diagnostic evaluation and did not return to our clinic before the end of data collection.
3. GD in childhood	Participants diagnosed with GD in childhood but not yet eligible for start of GnRHa were advised to return to our gender identity clinic at the start of puberty if GD persisted. People who did not return before end of data collection but meanwhile became potentially eligible for GnRHa belong to this category.
4. GD not diagnosed	After diagnostic assessment, a diagnosis of GD was not established.
5. Medical/per protocol	Medical reasons for not starting GnRHa were severe obesity and childhood osteoporosis, as use of GnRHa may aggravate these conditions. Also in this category are participants who had previously had an intake at our gender identity clinic before turning 18 years old but turned 18 during diagnostic evaluation and were therefore not eligible for puberty suppression.
6. Psychological	Start of GnRHa was precluded by mental health issues that required treatment first, such as severe depressive or anxiety disorders. Mental incompetence to provide informed consent for treatment was also classified under this category.
7. Participant related	Diagnostic evaluation was discontinued at request of the participant or because of not attending appointments without notice.
8. Other/unclear	

Abbreviations: GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist. [a]End of data collection: December 31, 2018.

surgery, only people meeting the criteria of age ≥18 years and at least 1 year of GAH were included in this analysis.

The majority of gender-affirming surgery in the Netherlands has been performed at the VUmc. If surgery was performed in another center, this was added to the participants' medical record and included in the Amsterdam Cohort of Gender Dysphoria database.

Statistical analyses

Characteristics are reported as mean ± SD for normally distributed data or median (IQR) for nonnormally distributed data. Dichotomous variables are presented as percentages. AMAB and AFAB were analyzed separately. To analyze trends over time, repeated analyses were done on cohorts defined by the year of first visit. Cohorts were created by 2-year intervals, except for the first 3 years, which were taken together. Reasons for not starting medical treatment were described over a 5-year time frame, except for the 2 most recent years.

Puberty stage was assessed in individuals starting GnRHa. To study whether there was a difference in the proportion of people starting GnRHa between those who were prepubertal and pubertal at their first visit, we compared those who had their first visit at age <10 and ≥10 years.

To avoid bias, participants who were diagnosed with GD elsewhere and referred to the VUmc to start treatment immediately were not included in the analyses of age at first visit and the proportion starting GnRHa and/or GAH. Similarly, people who started treatment prior to referral were left out of these analyses.

A ridgeline plot was created to visualize the distribution of years between intake and start of GnRHa and GAH.

Analyses were performed with Stata Statistical Software version 15.1 (StataCorp LLC).

Results

Overall

In total, 1766 children and adolescents visited our gender identity clinic between 1997 and 2018. The median duration of follow-up of people starting GnRHa and GAH at the VUmc was 4.6 years (IQR, 2.8-8.5; range, 0.7-18.9). Overall characteristics of this group are shown in Table 2. The number of applicants has increased over time (Figure 2). Since 2012 this increase is mainly generated by AFAB who were ≥10 years old at first visit. The overall ratio of AMAB to AFAB was 1:1.6. In earlier years the predominant proportion of referrals concerned AMAB. However, since 2009 the ratio has shifted, favoring AFAB 1:2.9 in 2018.

The overall median age at first visit was lower for AMAB than AFAB. For both groups, median age at first visit has increased from 2005 onward. Trends in the median age at first visit are shown in Figure 3.

Start of GnRHa treatment

Of all participants who went through the diagnostic evaluation process at the VUmc gender identity clinic (ie, without external referrals; n = 1681), 63% of all 1401 adolescents potentially eligible for GnRHa at the end of data collection had started GnRHa. Overall the percentage of individuals starting GnRHa was greater for AFAB (Table 2).

Out of all potentially eligible young people attending the clinic before turning 10 years old, 36% of AMAB and 53% of AFAB started GnRHa. Of all potentially eligible individuals first visiting when aged ≥10 years, 53% of AMAB and 77% of AFAB started GnRHa (Figure 4). After an initial decline, the percentage of AMAB and AFAB starting GnRHa who first visited before age 10 has increased over time. The percentage of AMAB and AFAB starting GnRHa who first visited at or over age 10 has mildly fluctuated.

Figure 5 shows that the time between first visit and start of GnRHa varies greatly due to diversity in duration of diagnostic evaluation, age, and puberty stage. For AMAB and AFAB, the median age at start of GnRHa has risen slightly over time (Figure 3), except for a temporary decrease in AFAB during 2011 to 2012. The proportion of AMAB starting GnRHa that was in early puberty has fluctuated over time. For AFAB, this proportion decreased until 2009. Except for an increase in 2011 to 2012, the percentage of AFAB who start GnRHa in early puberty has stayed relatively stable after 2009 (Figure 3).

Figure 6 shows reasons for not starting GnRHa in people who completed diagnostic evaluation. The proportion of

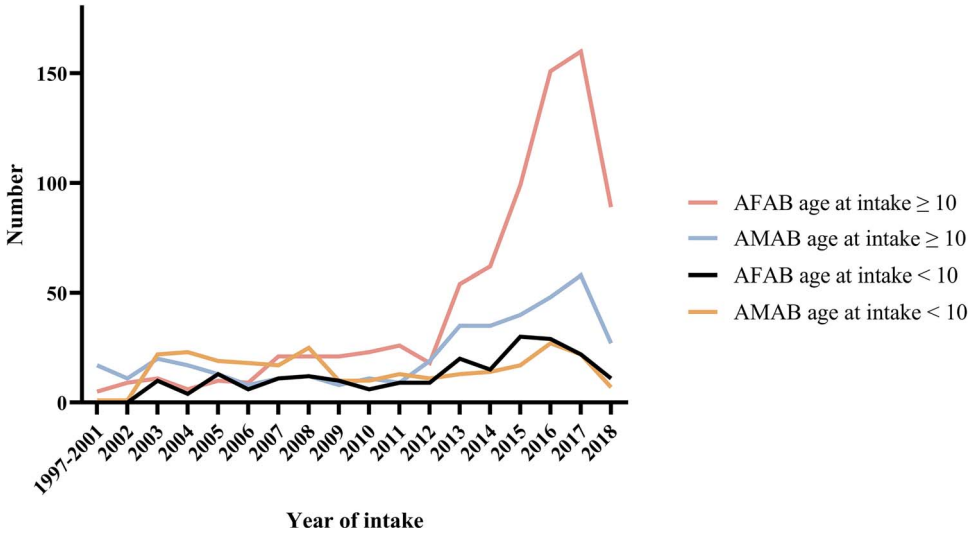

Figure 2. Number of all AMAB and AFAB seen at the VUmc gender identity clinic, stratified by age at intake. Due to a low number of visits to the gender identity clinic in the first years, 1997 to 2001 are taken together. From 2018 onward, the number of intakes was restricted because of overwhelming demand. AFAB, assigned female at birth; AMAB, assigned male at birth.

Table 2. Characteristics of pediatric population referred to VUmc gender identity clinic.[a]

	AMAB	AFAB
Total sample	689 (39)	1077 (61)
Total minus external referrals	669 (40)	1012 (60)
Age at first visit, y[b]	11.5 (8.0-15.2)	14.1 (10.5-16.0)
GnRHa		
Started GnRHa[b,c]	266 (47)	616 (73)
Age at first visit, y		
<10	68 (36)	74 (53)
≥10	198 (53)	542 (77)
Age at start of GnRHa, y	14.0 (12.8-16.1)	15.5 (12.9-16.8)
Starting GnRHa in early puberty, %[d]	34	4.6
Testicular volume at start of GnRHa, mL	12 (7-20)	NA
Menarche prior to start of GnRHa, %	NA	73[e]
Duration of GnRHa monotherapy, y	1.6 (0.7-2.6)	0.7 (0.5-1.9)
Discontinued GnRHa[b]	9 (3.4)	5 (0.8)
GAH		
Started GAH[b,f]	202 (93)	454 (93)
Age at first visit, y		
<10	48 (100)	32 (100)
≥10	154 (91)	422 (92)
Age at start of GAH, y	16.0 (15.5-17.1)	16.7 (16.0-17.5)

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist; NA, not applicable. [a] Unless stated otherwise, numbers are reported as median (IQR) or No. (%). [b] Referrals who had started hormone treatment elsewhere were excluded. [c] Percentages are based on those potentially eligible for indicated treatment. Eligible for start of GnRHa: age <10 years, AMAB (n = 191) and AFAB (n = 139); age ≥10 years, AMAB (n = 371) and AFAB (n = 700). [d] Early puberty was defined as testicular volume ≤9 mL or maximum Tanner breast stage 2 for AMAB and AFAB, respectively. [e] 21% missing. [f] Percentages are based on those potentially eligible for indicated treatment. Eligible for start of GAH: age <10 years, AMAB (n = 48) and AFAB (n = 32); age ≥10 years, AMAB (n = 91) and AFAB (n = 458).

individuals not fulfilling diagnostic criteria for GD was larger for AMAB than AFAB during all time frames. The percentage of AMAB first visiting at age <10 years who were not diagnosed with GD was stable over time. In AFAB this increased in only the most recent years. The relative number of AMAB first visiting at age ≥10 who were not diagnosed with GD showed a decreasing trend. For AFAB this fluctuated over time. A GD diagnosis was more often not present in children first visiting before age 10 than those first visiting when age ≥10 years.

The percentage of AMAB diagnosed with GD in childhood (ie, before the onset of puberty) who had not returned to the gender identity clinic despite being potentially eligible to start GnRHa was more or less stable, regardless of the age at first visit. This number showed a decreasing trend in AFAB first visiting at age <10 and ≥10 years.

The relative number of people not starting GnRHa due to medical/protocol reasons increased in both groups during the last time frame (2017-2018). A more detailed review of this subgroup showed that the majority had not started puberty suppression because they had already turned 18 years old during diagnostic evaluation and thus could start GAH directly.

No trend was found in the number of adolescents who had not started GnRHa on psychological or participant-related grounds as defined in Table 1.

Discontinuation of GnRHa treatment

Of all 266 AMAB who started GnRHa at our center, 9 (3.4%) discontinued treatment. Six (2.3%) ceased treatment because of abating GD. In 2 AMAB (0.8%), GnRHa treatment ended due to psychological or social issues hindering transition. In 1 individual (0.4%), GnRHa was discontinued due to compliance issues. Of all 616 AFAB, 5 (0.8%) broke off GnRHa. In 3 (0.5%), remission of GD led to discontinuation. In 2 (0.3%), GnRHa was suspended due to compliance issues. A temporal trend in people stopping GnRHa was not observed.

Start of GAH treatment

Of 707 eligible VUmc participants using GnRHa, 93% subsequently started GAH (Table 2). Additionally, 3 persons could

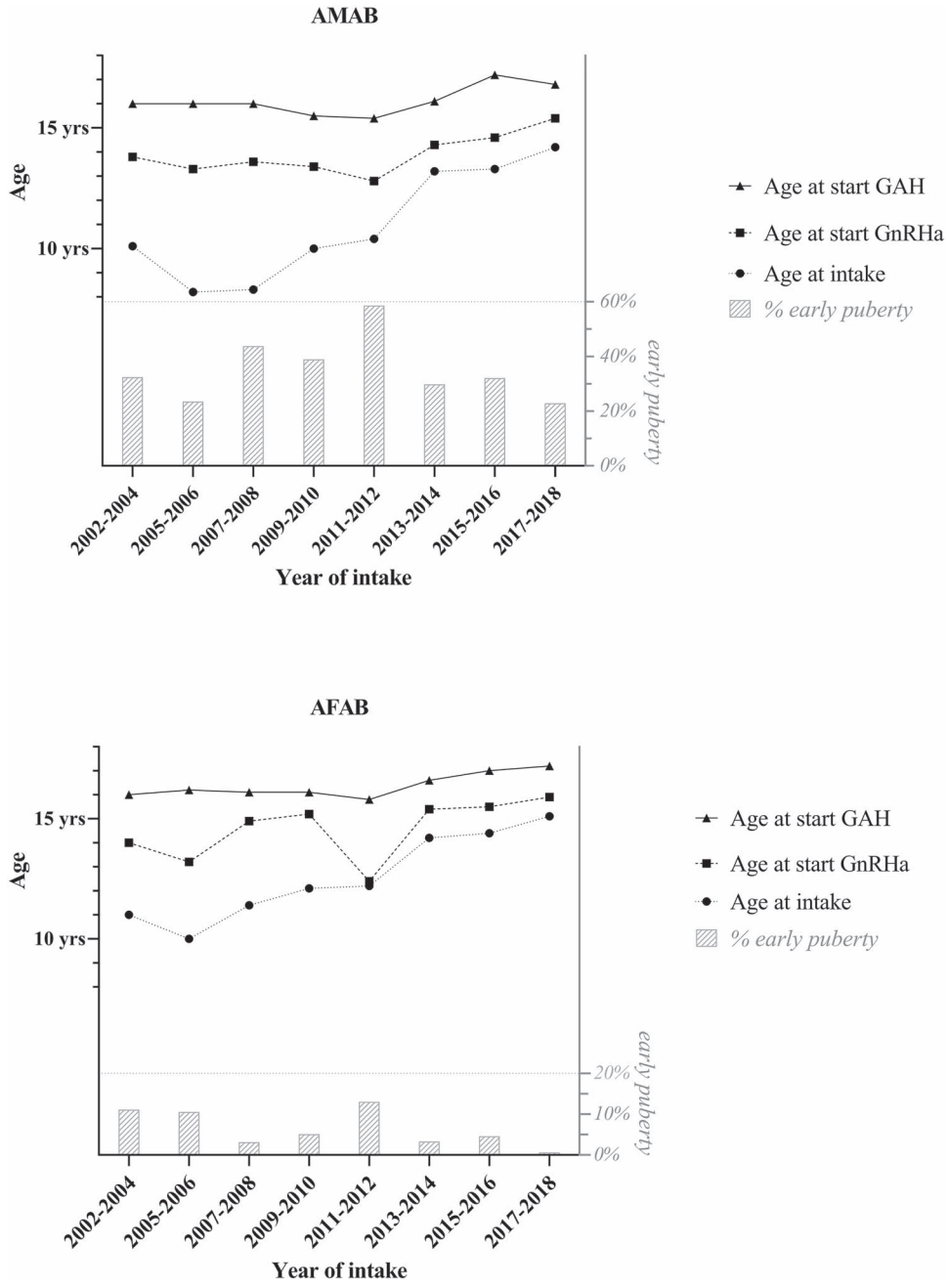

Figure 3. Trends in median age at intake, start of GnRHa and GAH treatment, and proportion of adolescents starting GnRHa in early puberty, for all people attending the gender identity clinic before age 18 years based on year of intake. Left y-axis: median age at start of GnRHa and GAH treatment. Right y-axis: percentage starting GnRHa in early puberty. The scale on the right y-axis is different for AMAB (top) and AFAB (bottom). AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

have started GnRHa but needed to start GAH directly for medical reasons.

The majority of people who had not yet started GAH did so for protocol reasons respectively. They were either too young or had not used GnRHa for the required amount of time. Otherwise, of all 266 AMAB starting GnRHa treatment, 1 (0.4%) moved abroad before a decision on starting GAH could be made. Of all 616 AFAB starting GnRHa treatment, 1 (0.2%) chose to continue GnRHa at another gender identity clinic before deciding on GAH. Of all 266 AMAB and 616 AFAB starting GnRHa treatment, psychological reasons precluded start of GAH for 2 (0.8%) and 1 (0.2%), respectively. Of all 266 AMAB and all 616 AFAB who had started GnRHa and were eligible for GAH, GAH was postponed for 1 (0.4%) and 4 (0.6%), respectively, because the diagnosis of GD had become uncertain. GnRHa was continued while the diagnostic phase was extended.

A clear trend in reasons for not starting GAH could not be found. With the exception of 2007 to 2008, the relative number of AFAB starting GAH was equal to or larger than AMAB, resulting in an overall larger proportion of AFAB who started GAH. The percentage of people starting GAH was stable for AMAB and AFAB first visiting before age 10 years. A downtrend was noted for both groups first visiting at or

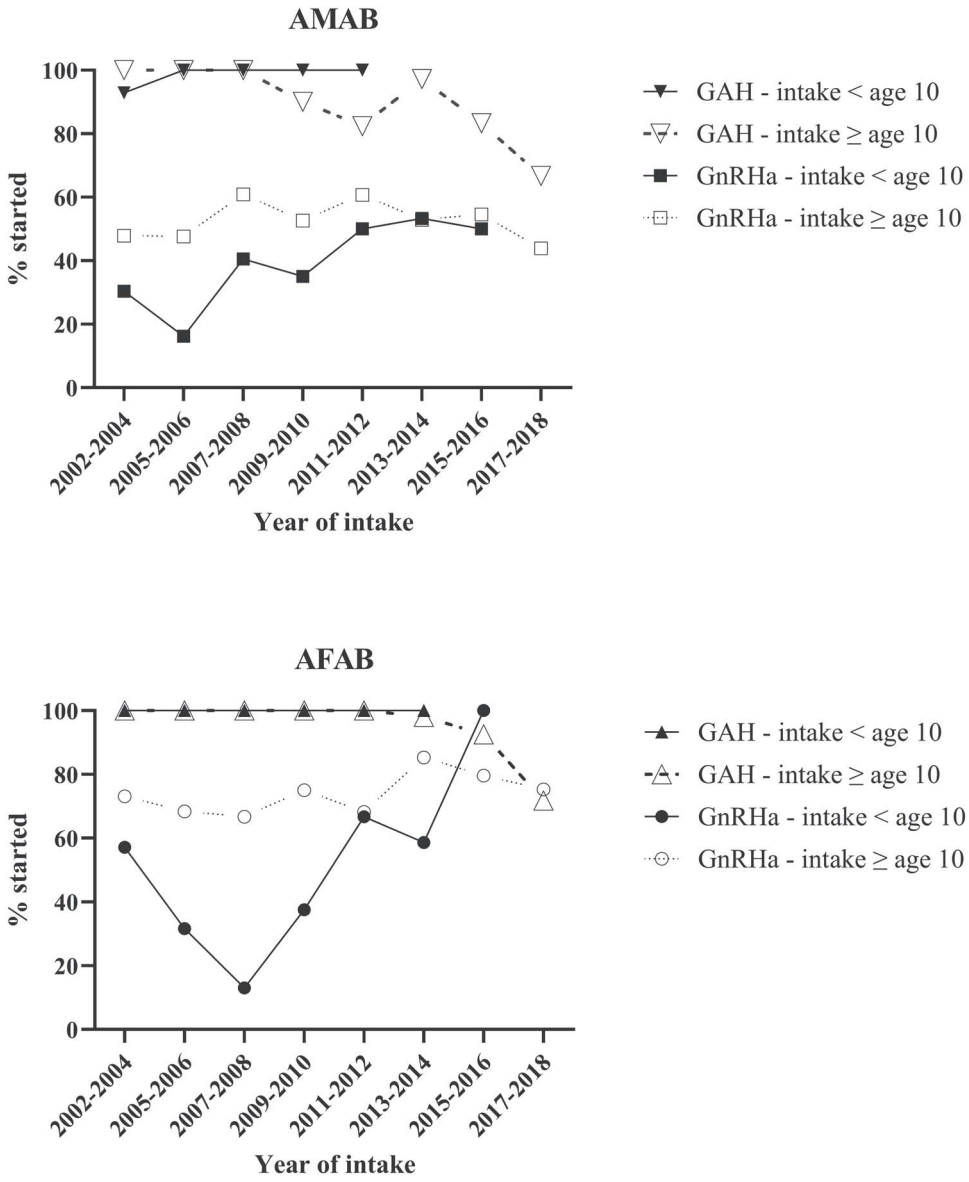

Figure 4. Percentages of people starting GnRHa and GAH treatment, stratified by age at first visit <10 or ≥10 years. In people who first visited before age 10 years, no one was eligible yet for start of GnRHa from 2017 onward. Similarly, in AMAB and AFAB, no one was eligible yet for start of GAH from 2013 and 2015 onward, respectively. AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

after age 10 (Figure 4). In parallel to a varying time between intake and start of GnRHa, time between intake and start of GAH was diverse as well (Figure 5). Until 2011, age at start of GAH in both groups was reasonably stable, but an increase was observed over the most recent years (Figure 3).

Gender-affirming surgery

In total 115 AMAB underwent gonadectomy. Until July 2014, 69 were eligible for gonadectomy based on age and duration of treatment, of whom 58 (84%) proceeded with surgery. Three did not opt for gonadectomy at all, and 8 underwent gonadectomy after July 2014. From July 2014 until the end of data inclusion, 93 AMAB became eligible for gonadectomy, of whom 49 (53%) had this operation.

Gonadectomy was performed in 189 AFAB. Before July 2014, 104 were eligible for gonadectomy. Of these, 78 (75%) underwent surgery before July 2014. Nine did not opt for gonadectomy at all. The remaining 17 underwent gonadectomy after July 2014. Of the 249 AFAB who became eligible for gonadectomy after July 2014, 94 (38%) had this operation. The remaining 155 have not (yet) had a gonadectomy.

Table 3 provides an overview of all gender-affirming surgery performed and the proportion of people undergoing it. Additionally, the percentage of people undergoing surgery stratified by puberty stage at start of GnRHa is shown.

Discussion

This article describes trends in trajectories of children and adolescents who were referred for GD in the oldest and largest European gender identity clinic. We provide answers to questions regarding the number and ratio of assigned sex at birth of people first visiting, the age at first visit and at

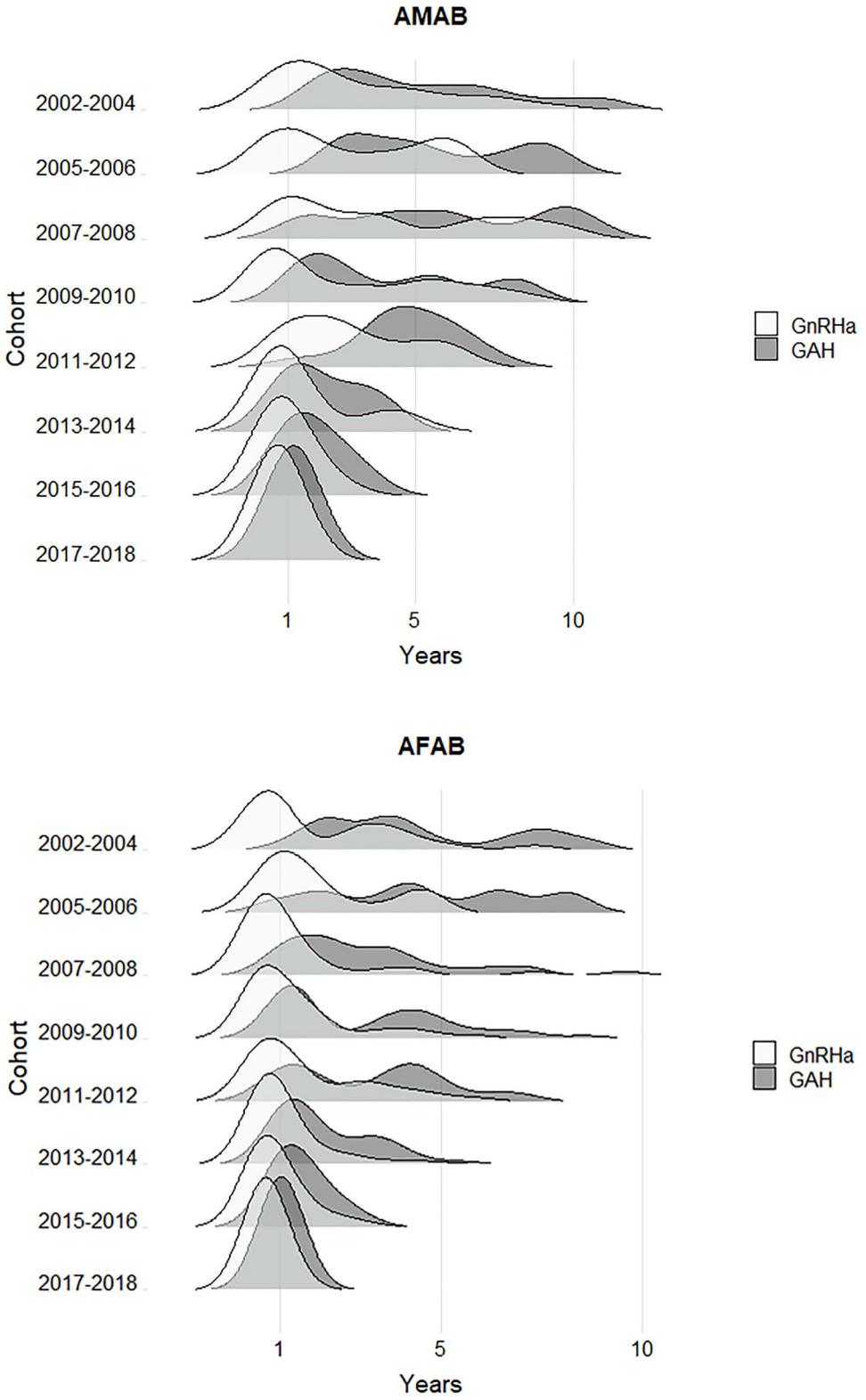

Figure 5. Time between intake and start of GnRHa and GAH treatment per cohort based on year of intake for AMAB (top) and AFAB (bottom). Follow-up is limited by the end of data collection (December 31, 2018). AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

start of medical treatment, trends in proportions of people starting and stopping medical treatment, differences over time in the puberty stage of people starting GnRHa, reasons for not starting treatment, and proportions of people undergoing gender-affirming surgery.

In a recent study, Arnoldussen et al reported on a subset of our participants but included only adolescents who were already potentially eligible for GnRHa and/or GAH, instead of all data from the start of the Dutch Protocol, including prepubertal children, thus making it difficult to compare

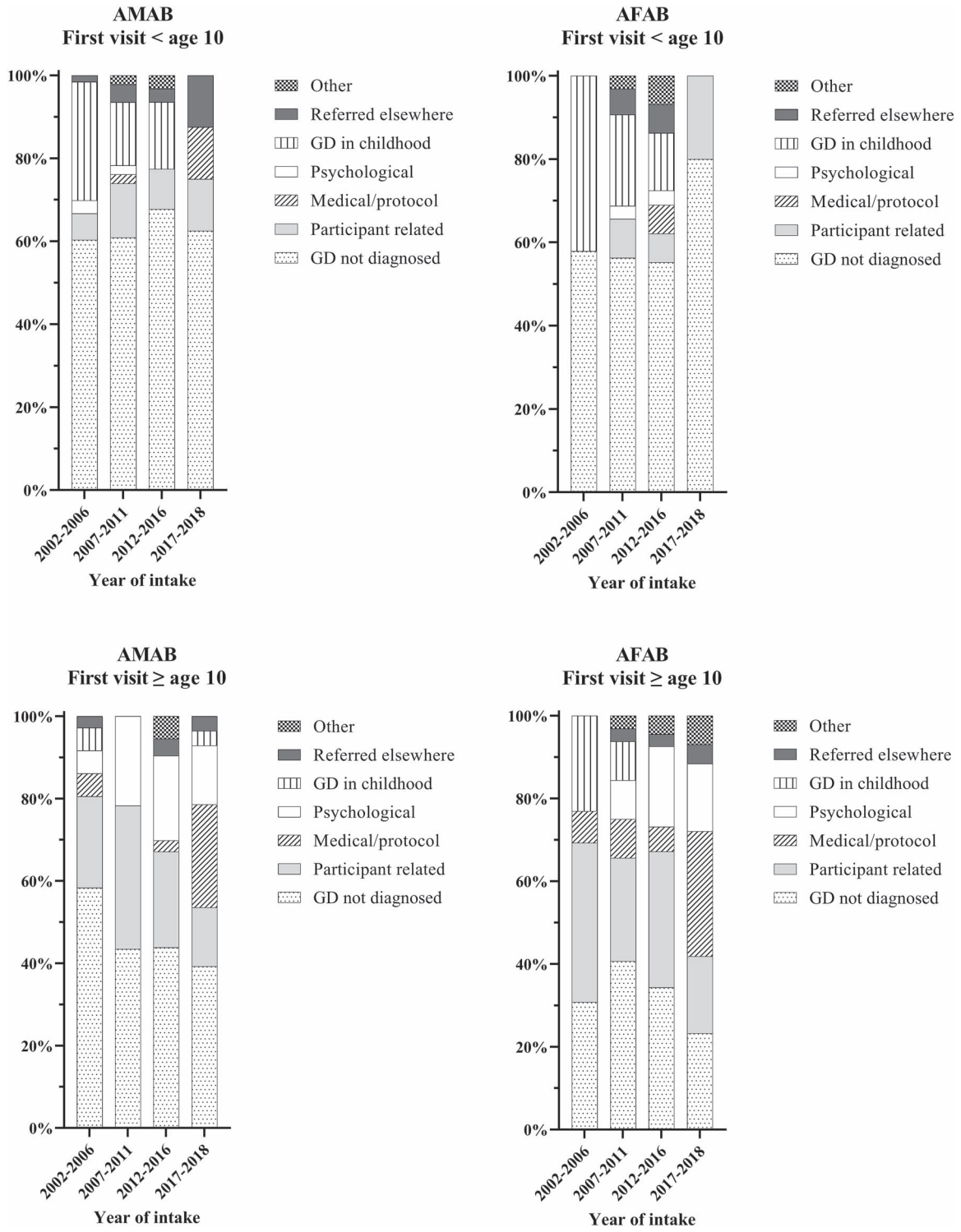

Figure 6. Reasons for not having started GnRHa for people who completed diagnostic evaluation, stratified by age at first visit <10 or ≥10 years during 4 time frames. People still in diagnostic phase: 2012-2016—age <10 years, AMAB (n = 14) and AFAB (n = 19); age ≥10 years, AMAB (n = 4) and AFAB (n = 6); 2017-2018—age <10 years, AMAB (n = 6) and AFAB (n = 10); age ≥10 years, AMAB (n = 31) and AFAB (n = 87). AFAB, assigned female birth; AMAB, assigned male at birth; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist. Categories are explained in Table 1.

outcomes.[10] Additionally, the previous study put more focus on the adolescents' psychological functioning, while we provided data on reasons for refraining for medical intervention and puberty stage at start of GnRHa.

The number of people seen at our clinic has rapidly increased over the last years, a phenomenon that has become familiar not only in our center.[20-23] Until 2007 the ratio of AMAB to AFAB referred to our center tipped toward AMAB. Yet, this ratio clearly shifted after 2009, tipping toward AFAB from then on. This shift seems to have occurred because the increase in referrals is steeper for AFAB than AMAB and has been observed before.[9,21,24-26] An explanation that has been

Table 3. People undergoing gender-affirming surgery overall and stratified by puberty stage at start of GnRHa.

		Started GnRHain, No. (%)	
	No. (%)	**Early puberty**	**Late puberty**
AMAB			
Sample	162[a]	35	120
Orchiectomy	115 (71)	26 (74)	82 (68)
Vaginoplasty	112 (69)	26 (74)	79 (66)
Breast augmentation	21 (13)	4 (11)	12 (10)
Adam's apple reduction	3 (1.9)	0	3 (2.5)
Voice feminization surgery	3 (1.9)	0	3 (2.5)
Facial feminization surgery	6 (3.7)	0	6 (5.0)
AFAB			
Sample	353[a]	9	336
Mastectomy	280 (79)	3 (33)	265 (79)
Hysterectomy	193 (55)	9 (100)	177 (53)
Salpingo-oophorectomy	190 (54)	9 (100)	175 (52)
Colpectomy	58 (16)	3 (33)	54 (16)
Metoidioplasty/phalloplasty	37 (10)	1 (11)	35 (10)

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; GnRHa, gonadotropin-releasing hormone agonist. [a]Percentages are based on the number of people potentially eligible for gender-affirming surgery. Puberty stage missing in 7 AMAB and 8 AFAB.

mentioned is that in most Western cultures, it is more widely accepted for AFAB to come out as trans men, as opposed to AMAB longing for a more feminine appearance.[24] However, a conclusive explanation has yet to be found.

Unfortunately, the increase in applicants has resulted in a considerable waiting time to access transgender care. This might explain why the age at which people had their first appointment has been rising over the recent periods for AMAB and AFAB. From 2002 onward, AMAB presented at a younger age as compared with AFAB. This finding was not in line with the previously mentioned study[10] on a subset of this cohort, most likely due to different inclusion criteria as indicated, but it has been noted by others.[27] It might be that AMAB experience gender dysphoric feelings at an earlier age, but this thought is not supported by a study that found no statistically significant difference in age of first experiencing feelings of GD between AMAB and AFAB.[28] Otherwise, it is likely that AMAB with gender-variant behavior are more rapidly considered deviant from the societally accepted standard and that professional care is sought at younger ages than for their AFAB counterparts.

A slight increase in median age at start of GnRHa was found for AMAB and AFAB. In general, AFAB started GnRHa at a later age and more often than AMAB. This is in line with an earlier study on the trajectories of people starting GnRHa.[29] The difference in age at start of treatment is most likely a reflection of older age at presentation in AFAB. A not-yet-elucidated drop in age at start of GnRHa was seen during 2011 to 2012, most outspoken in AFAB.

The proportion of AMAB starting GnRHa in early puberty was larger than in AFAB. This may be related to the sex difference in age of onset of puberty, as AMAB are known to enter puberty at a later age than AFAB. Adding to this, AMAB already presented at an earlier age, thereby enabling this group to start GnRHa at an earlier age and thus amplifying the difference in puberty stage at start of GnRHa.

The difference between AMAB and AFAB in the relative number of people starting GnRHa is remarkable. It seems to be partly due to the fact that GD is absent in a larger percentage of AMAB than AFAB, which is line with previous findings.[30] It may be that GD is more severe in AFAB, as indeed found in studies by Olson et al.[31] Alternatively, this might be related to sociocultural acceptance of gender-variant behavior as well. Altogether, the primary explanation underlying this finding is complex, and more compelling arguments need to be identified.

The majority of adolescents (93%) using GnRHa go on to start with GAH. This finding may imply that GnRHa treatment is used as a start of transition rather than an extension of the diagnostic phase. Only a few individuals (1.6%) discontinued GnRHa. The main reason for discontinuing GnRHa was remission of GD. Previous research suggests that the period between the ages of 10 to 13 years is pivotal for continuation or resolution of GD.[32] Since nearly all participants started GnRHa after turning 13 and underwent a thorough diagnostic assessment before treatment was started, it is likely that most people starting GnRHa experienced sustained GD. Still, one cannot exclude the possibility that starting GnRHa in itself makes adolescents more likely to continue medical transition.[33,34] This percentage of 1.6% is lower than that found at a Scottish pediatric endocrinology service, where among the 79 young people who had started GnRHa, 6 (8%) discontinued treatment.[35] Yet, the sample size of 79 is markedly smaller than that in our study. A Dutch study that assessed trajectories in 143 young people diagnosed with GD found that 3.5% of all young people discontinued GnRHa treatment because the desire for gender-affirming treatment had abated.[29] A recent study at the Gender Identity Development Service in England showed that of 431 young people consenting to the start of GnRHa, 30 (7%) did not start or eventually stopped GnRHa.[36] However, some of these might have received further care at private clinics. Therefore, as put forward by the authors themselves, it is difficult to compare these data with outcomes from our gender identity clinic. A complementary study reporting on the reasons for discharge from the Gender Identity Development Service demonstrated that between 2008 and 2021, 49 (4%) out of 1089 young people stopped GnRHa because they identified with their gender assigned at birth.[37]

Age at start of GAH increased over time in parallel with age at start of GnRHa, probably as an unfortunate result of waiting lists. The indicated difference in age at presentation

and start of GnRHa between AMAB and AFAB did not affect age at start of GAH, as this was largely similar in both groups. Overall AFAB were more likely to start GAH. Although the difference was small, it was observed particularly from 2011 onward. This was also noticed in previous research.[30]

In the recent years, the proportion of participants visiting after age 10 years who started GAH has decreased. These numbers may have increased when reexamined at a later time, as Figure 5 shows that GAH may still be pursued many years after starting GnRHa. However, it might be that treatment trajectories have changed over time, with more adolescents not desiring GAH in the recent years or possibly taking more time to consider GAH while using GnRHa.

Overall, more AMAB opted for gender-affirming genital surgery than AFAB. Masculinizing gender-affirming genital surgery is a challenging, high-risk procedure,[38,39] which may explain why only a modest number of AFAB chose to undergo it. Otherwise, the AFAB group might consist of a greater number of people with a nonbinary gender identity not seeking masculinizing genital surgery. However, considerations for choosing genital surgery were beyond the scope of this study.

A very clear distinction was found in the relative number of participants undergoing gonadectomy before and after July 2014. This is likely a result of the "transgender law" that took effect at that time. It emphasizes that this kind of legislation can lead to people undergoing irreversible procedures, with far-reaching consequences and for nonintrinsic motives, and should be abolished. Yet, due to the long waiting lists for gender-affirming surgery, it is possible that the number of people undergoing gonadectomy after July 2014 will still increase. Considering the finding that an increasing number of trans people want to keep their reproductive organs in situ while on GAH, it is important that nationwide screening programs (eg, for cervix carcinoma) be brought to their attention during medical check-ups. Furthermore, future research should focus on the long-term effects of this approach.

The size of our study population, originating from the oldest and largest pediatric gender identity clinic in the Netherlands, is a valuable asset to this study. This population can serve as a representative of young people diagnosed with GD receiving health care in the Netherlands according to the Dutch Protocol. The long time span in this study is unprecedented.

We are aware of some limitations to our study. As these results originate from 1 center that followed 1 diagnostic and treatment protocol, the results may be different for centers following a different treatment approach. Due to the retrospective design, data might be lacking. Caution needs to be taken when interpreting results from the most recent years. Although the percentages of people starting GnRHa and GAH are calculated per the number of people who met the criteria for initiation of treatment, the calculated proportions in the most recent years are likely an underestimation. Many might have started treatment after data collection ended. The proportion of participants from the 2017-2018 cohort who start GnRHa in early puberty may well increase when reviewed in the future. Many prepubescent participants have not yet had time to enter puberty and start treatment as the age at intake was relatively low for AMAB and AFAB. Although great care was taken to complete participants' medical history, some might have undergone gender-affirming surgery elsewhere and beyond our knowledge, thereby underestimating numbers on this operation.

Conclusion

This study confirmed a steep increase of referrals to our gender identity clinic and a change in sex ratio predominantly propelled by an influx of older AFAB, which are still only partly understood. A substantial proportion of children first visiting before age 10 years did not meet criteria for a GD diagnosis, underlining the need for an individualized diagnostic approach. Novel findings are that detransition was very rare and that the majority of people starting GnRHa continued with subsequent GAH. This provides ongoing support for medical interventions in gender-diverse adolescents. Last, as such a striking difference was found in the number of people undergoing gonadectomy before and after July 2014—coinciding with the "transgender law" coming into effect—it seems reasonable to suggest that certain legislation affected the choices made regarding gonadectomy and might have motivated people to undergo medical procedures for nonintrinsic reasons.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997;**36**:263–271.
3. Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *Eur Child Adolesc Psychiatry*. 1998;**7**:246-248.
4. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011;**40**:843–847.
5. Delemarre-van de Waal HA, Cohen Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol*. 2006;**155**:S131–S137.
6. Shumer DE, Spack NP. Paediatrics: transgender medicine—long-term outcomes from "the Dutch model." *Nat Rev Urol*. 2015;**12**:12-13.
7. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and distribution of transgender and gender nonconforming populations: a narrative review. *Endocrinol Metab Clin North Am*. 2019;**48**:303–321.
8. Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med*. 2018;**15**:582–590.

9. de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). *Arch Sex Behav*. 2018;**47**:1301–1304.
10. Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? *Eur Child Adolesc Psychiatry*. 2020;**29**:803–811.
11. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, *et al*. Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;**94**:3132-3154.
12. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people, 5th version. 1998. https://www.wpath.org/publications/soc.
13. Socialstyrelsen. Care of children and adolescents with gender dysphoria. 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth edition, text revision. ed. American Psychiatric Association; 2000.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth edition. American Psychiatric Association; 2013.
16. de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex*. 2012;**59**:301–320.
17. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;**100**:E270–E275.
18. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;**102**:3869-3903.
19. de Vries AL, Klink D, Cohen-Kettenis PT. What the primary care pediatrician needs to know about gender incongruence and gender dysphoria in children and adolescents. *Pediatr Clin North Am*. 2016;**63**:1121–1135.
20. Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in referrals to a pediatric transgender clinic. *Pediatrics*. 2019;**144(5):e20191368**.
21. Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry*. 2020;**74**:40-44.
22. Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. *Arch Dis Child*. 2018;**103**:631–636.
23. Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender dysphoria in Israel: increasing referral and fertility preservation rates. *Endocr Pract*. 2020;**26**:423–428.
24. Aitken M, Steensma TD, Blanchard R, *et al*. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med*. 2015;**12**:756-763..
25. Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports? *Horm Res Paediatr*. 2018;**89**:434–441.
26. Steensma TD, Cohen-Kettenis PT, Zucker KJ. Evidence for a change in the sex ratio of children referred for gender dysphoria: data from the Center of Expertise on Gender Dysphoria in Amsterdam (1988-2016). *J Sex Marital Ther*. 2018;**44**:713–715.
27. Spack NP, Edwards-Leeper L, Feldman HA, *et al*. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;**129**:418–425.
28. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry*. 2016;**21**:108-118.
29. Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. *Arch Sex Behav*. 2020;**49**:2611–2618.
30. Wagner S, Panagiotakopoulos L, Nash R, *et al*. Progression of gender dysphoria in children and adolescents: a longitudinal study. *Pediatrics*. 2021;**148(1):e2020027722**.
31. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J Adolesc Health*. 2015;**57**:374–380.
32. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;**16**:499–516.
33. Richards C, Maxwell J, McCune N. Use of puberty blockers for gender dysphoria: a momentous step in the dark. *Arch Dis Child*. 2019;**104**:611–612.
34. Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early medical treatment of children and adolescents with gender dysphoria: an empirical ethical study. *J Adolesc Health*. 2015;**57**:367–673.
35. McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr*. 2021;**180**:2969–2976.
36. Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child*. Published online July 28, 2022. https://doi:10.1136/archdischild-2022-324283.
37. Butler G, Adu-Gyamfi K, Clarkson K, *et al*. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child*. Published online July 28, 2022. https://doi:10.1136/archdischild-2022-324302.
38. Frey JD, Poudrier G, Chiodo MV, Hazen A. A systematic review of metoidioplasty and radial forearm flap phalloplasty in female-to-male transgender genital reconstruction: is the "ideal" neophallus an achievable goal? *Plast Reconstr Surg Glob Open*. 2016;**4**:e1131.
39. Veerman H, de Rooij FPW, Al-Tamimi M, *et al*. Functional outcomes and urological complications after genital gender affirming surgery with urethral lengthening in transgender men. *J Urol*. 2020;**204**:104–109.