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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.

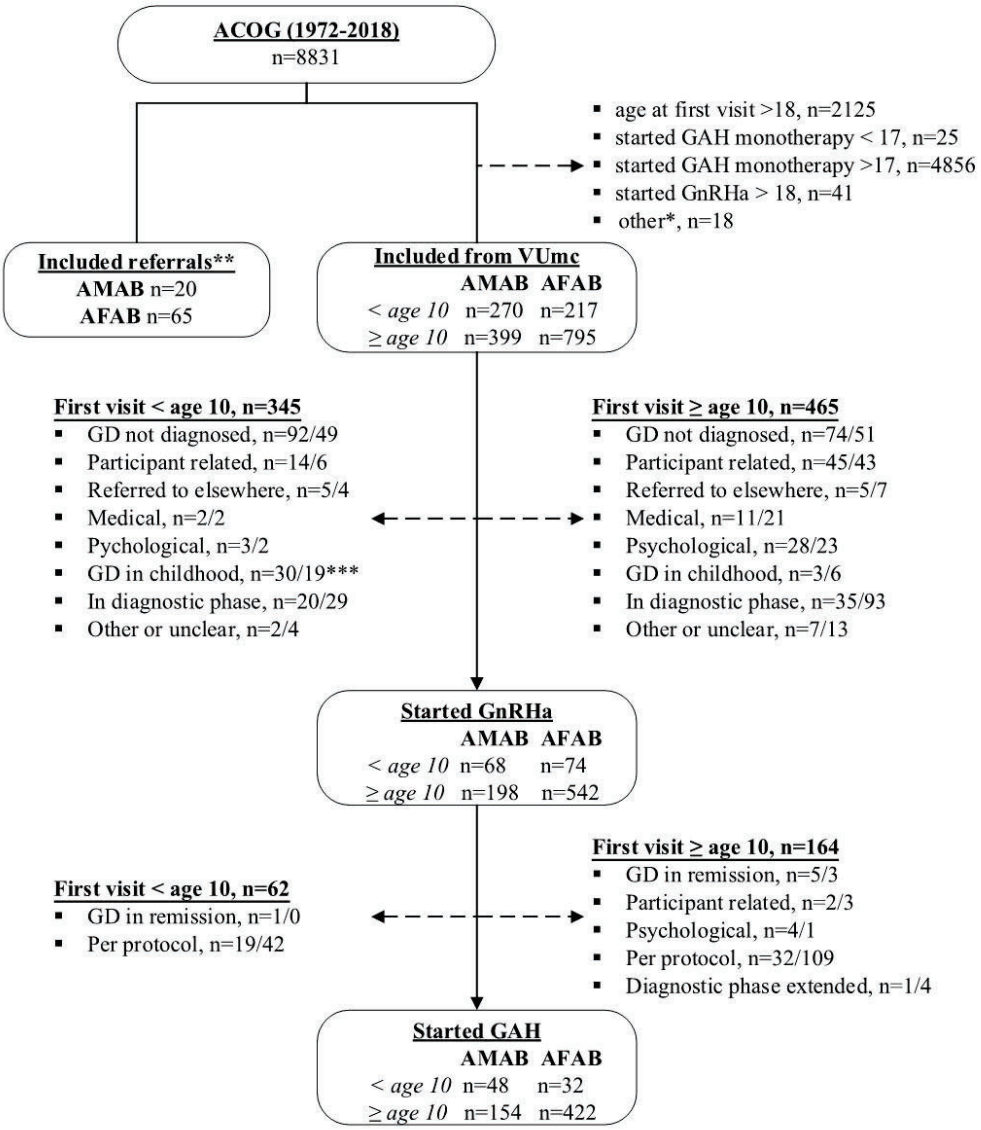

Figure 1. Flowchart of inclusion process and treatment trajectories. n = AMAB/AFAB. *Disorder of sex development, n = 6; wrongfully included, n = 1; did not follow Dutch Protocol, n = 11. **People referred from elsewhere had already started medical treatment or were referred specifically to start. ***Additionally, 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

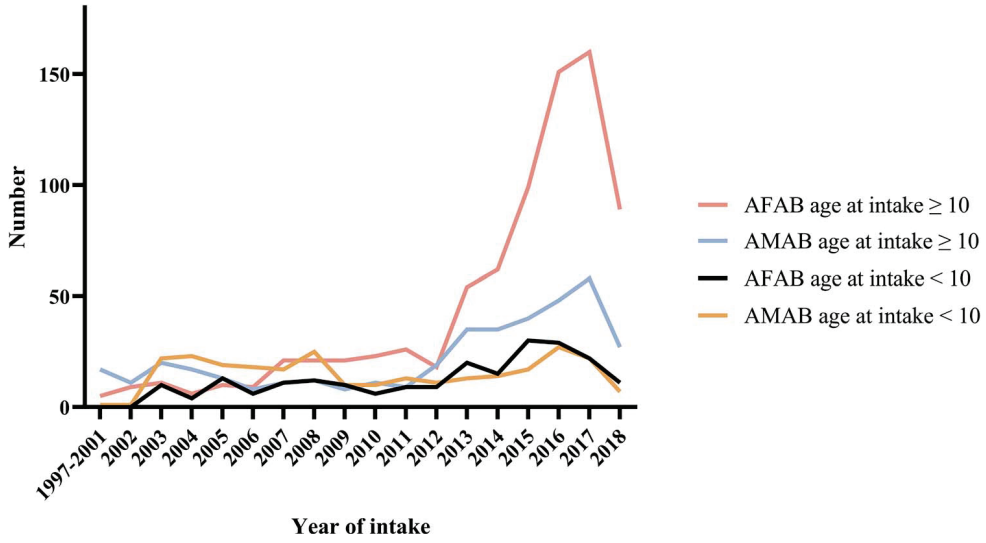

Figure 2. Number of all AMAB and AFAB seen at the VUmc gender identity clinic, stratified by age at intake. Due to a low number of visits to the gender identity clinic in the first years, 1997 to 2001 are taken together. From 2018 onward, the number of intakes was restricted because of overwhelming demand.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

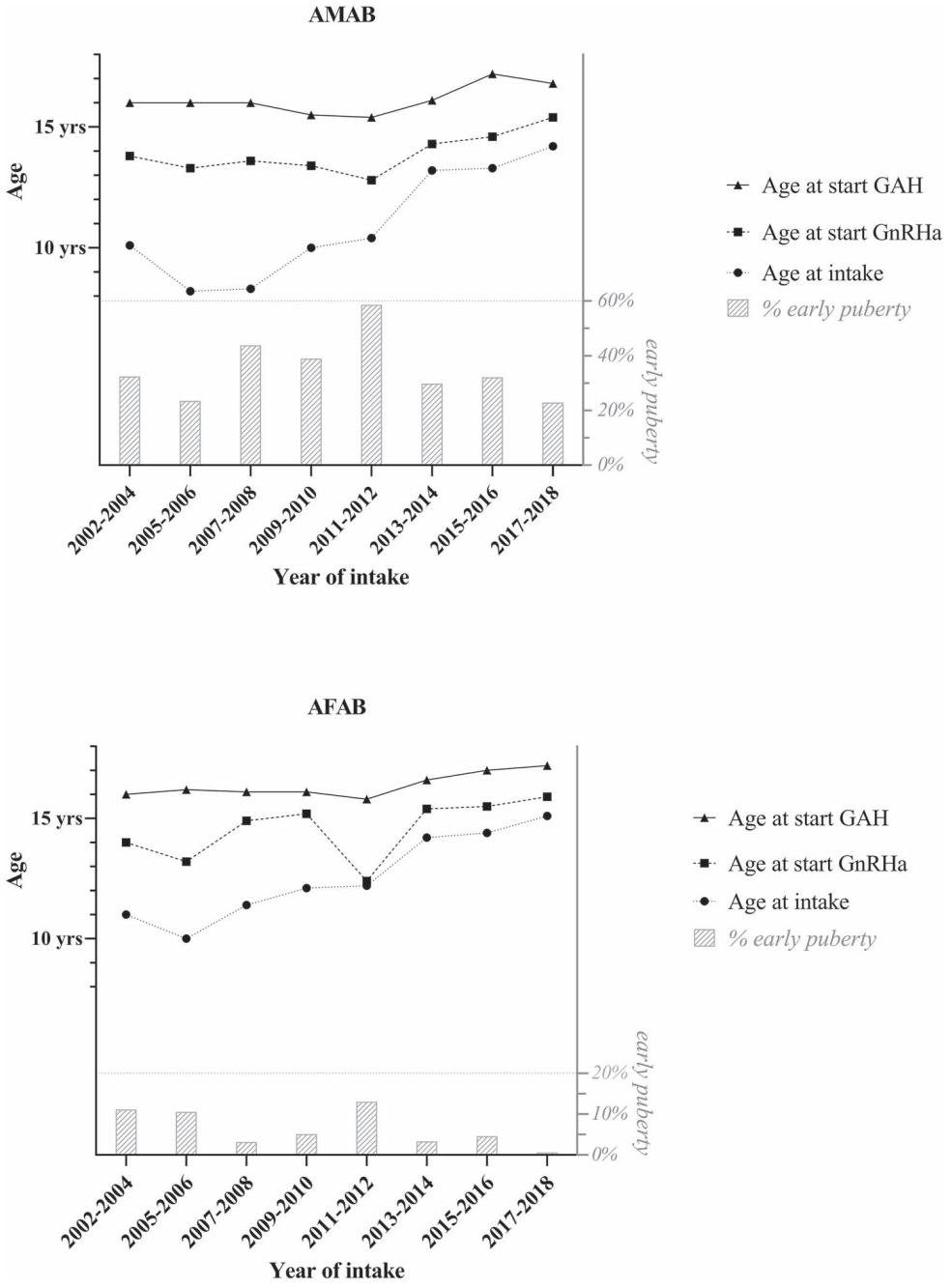

Figure 3. Trends in median age at intake, start of GnRHa and GAH treatment, and proportion of adolescents starting GnRHa in early puberty, for all people attending the gender identity clinic before age 18 years based on year of intake. Left y-axis: median age at start of GnRHa and GAH treatment. Right 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

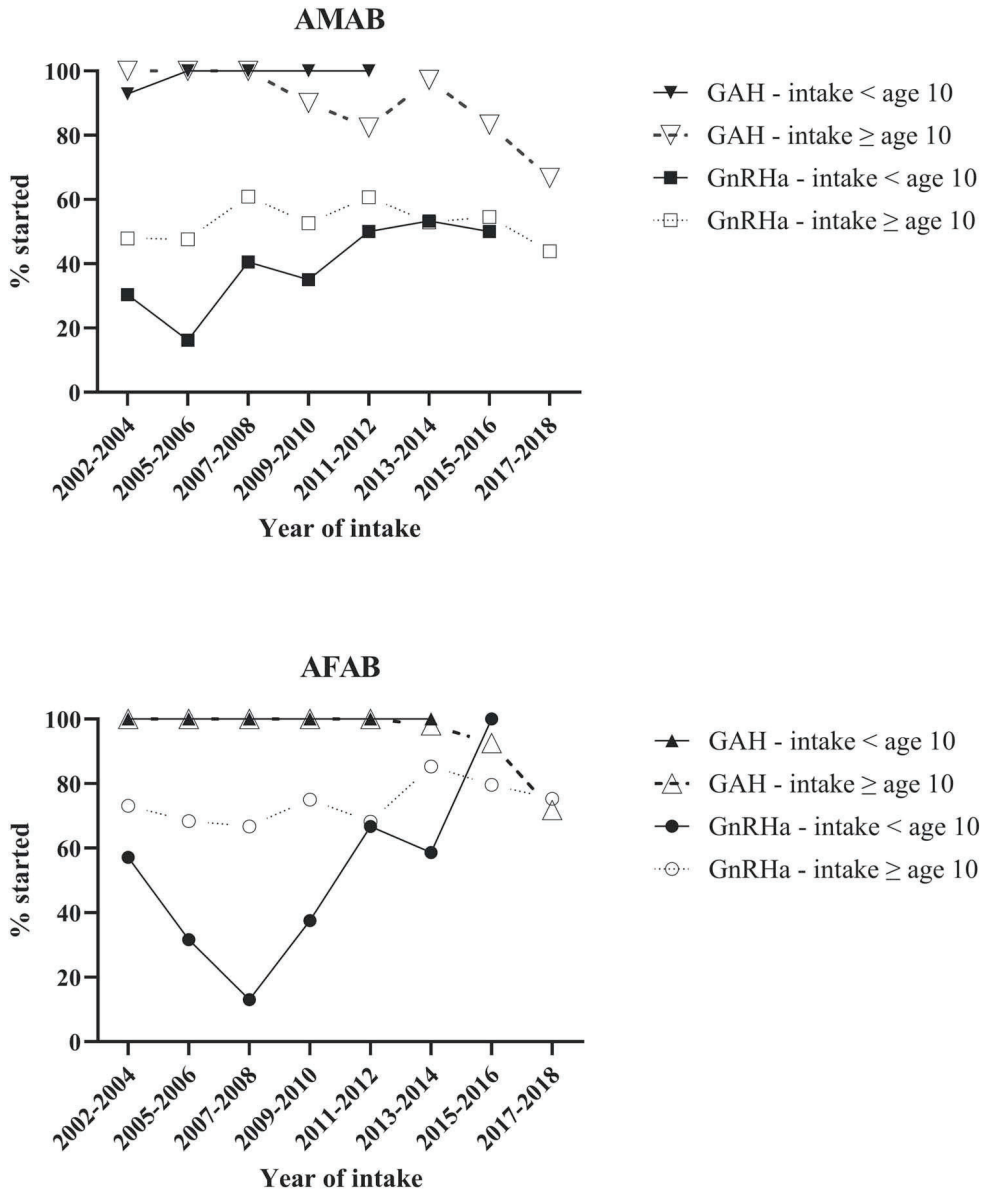

Figure 4. Percentages of people starting GnRHa and GAH treatment, stratified by age at first visit <10 or ≥10 years. In people who first visited before age 10 years, no one was eligible yet for start of GnRHa from 2017 onward. Similarly, in AMAB and AFAB, no one was eligible yet for start of GAH from 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

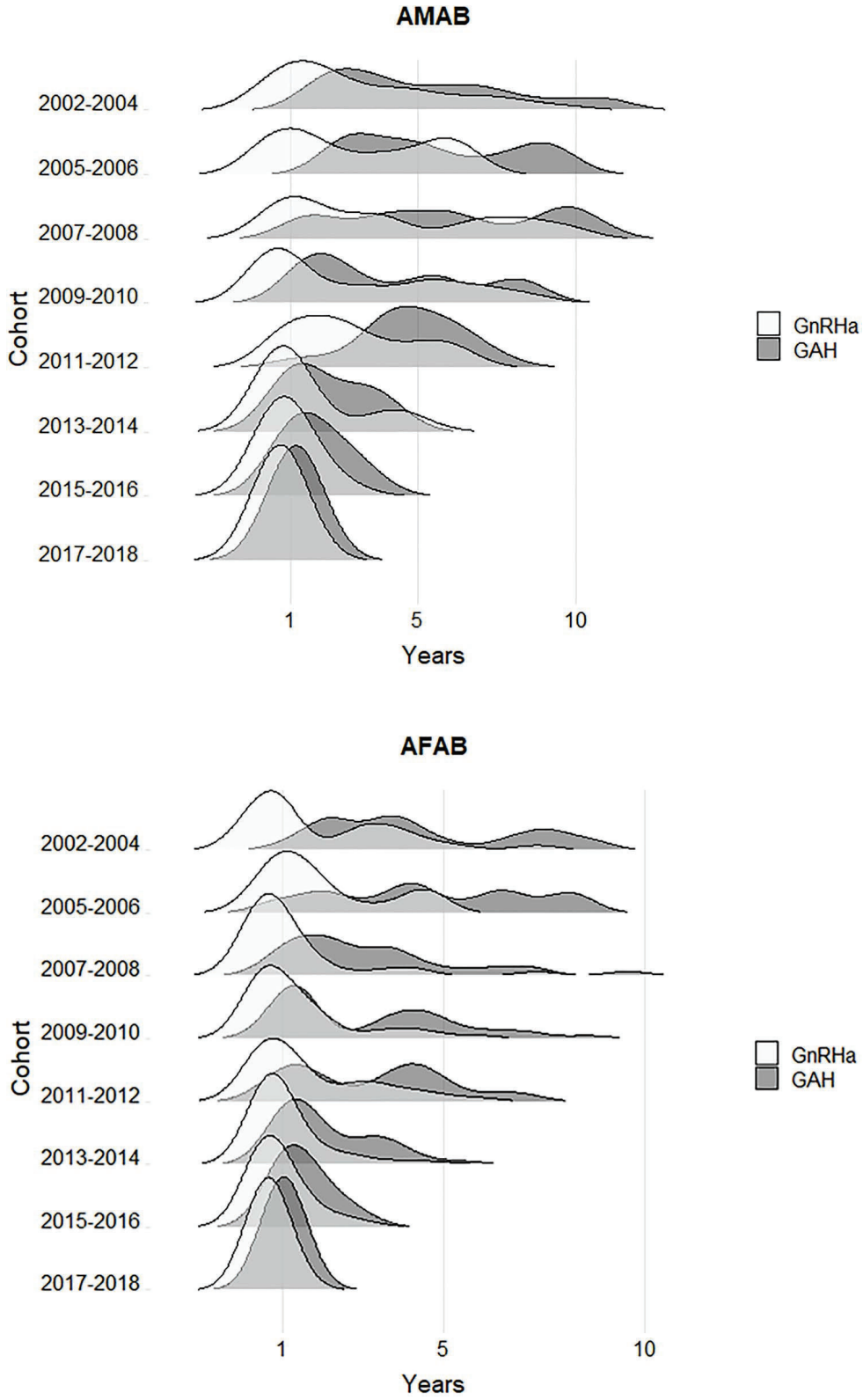

Figure 5. Time between intake and start of GnRHa and GAH treatment per cohort based on year of intake for AMAB (top) and AFAB (bottom). Follow-up is limited by the end of data collection (December 31, 2018). AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa,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

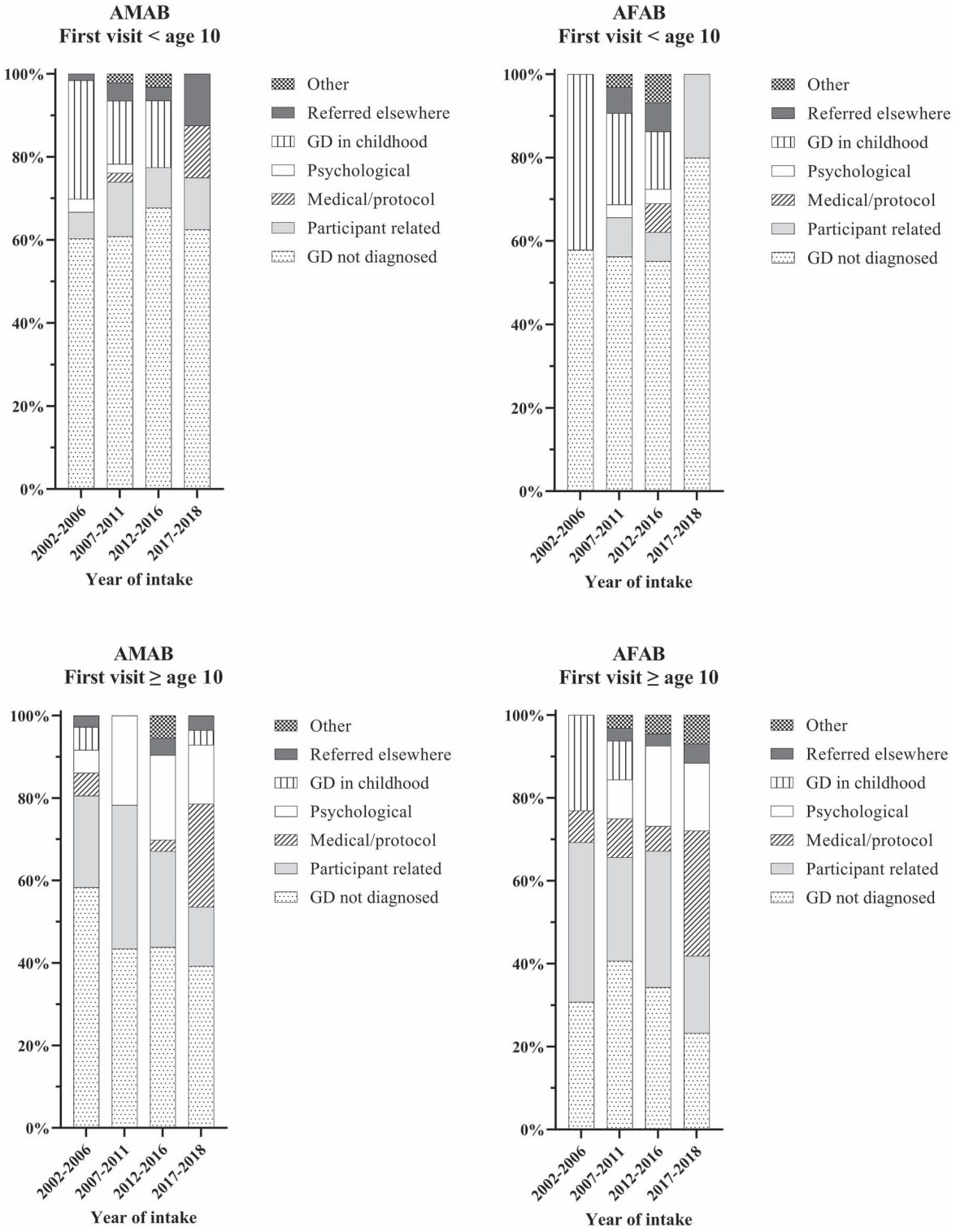

Figure 6. Reasons for not having started GnRHa for people who completed diagnostic evaluation, stratified by age at first visit <10 or ≥10 years during 4 time frames. People still in diagnostic phase: 2012-2016—age <10 years, AMAB (n = 14) and AFAB (n = 19); age ≥10 years, AMAB (n = 4) and AFAB (n = 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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Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).

WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated.

RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults. *Pediatrics* 2014;134:696–704

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KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL—Adult Behavior Checklist
ASR—Adult Self-Report
BDI—Beck Depression Inventory
BIS—Body Image Scale
CBCL—Child Behavior Checklist
CGAS—Children's Global Assessment Scale
CSH—cross-sex hormones
GD—gender dysphoria
GnRHa—gonadotropin-releasing hormone analogs
GRS—gender reassignment surgery
SHS—Subjective Happiness Scale
STAI—Spielberger's Trait Anxiety Scale
SWLS—Satisfaction With Life Scale
TPI—Spielberger's Trait Anger Scale
UGDS—Utrecht Gender Dysphoria Scale
YSR—Youth Self-Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen-Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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(Continued on last page)

Puberty Suppression Treatment for Patients with Gender Dysphoria

Patient Information and Informed Parental Consent and Assent for Minors

Your child has been diagnosed with gender dysphoria. Gender dysphoria is a term used to describe people who have significant feelings of discomfort or distress that may accompany a difference between experienced/expressed gender (gender with which they identify) and their physically assigned gender (biological sex). Gender dysphoria affects people in different ways.

This document provides information regarding treatment to suppress puberty (put puberty "on hold"). Before consenting to treatment to suppress your child's puberty with "puberty blockers", you need to be aware of the possible benefits and risks of such treatment.

After all your questions or concerns are addressed to your satisfaction, if you decide to proceed with puberty suppression for your child, you will need to initial the statements below on this form as well as sign acknowledging consent to such treatment. If there is more than one parent/legal guardian, both will have to sign. Your child will also need to sign expressing assent (approval) to treatment.

What are the benefits of suppressing puberty in adolescents with gender dysphoria?

The Endocrine Society recommends suppression of puberty for children that have the diagnosis of gender dysphoria and meet other criteria listed below. Experts in treating youth with gender dysphoria have made this recommendation on the premise that suppression of puberty may:

a) Allow for a smooth social transition to the gender role that is congruent (in harmony) with the child's gender identity, by testing persistence of the gender identity after living a "real-life experience" with the expressed gender, but before receiving irreversible hormonal or surgical treatment;
b) Possibly diminish the psychological trauma and risk of suicide often observed during the physical changes of puberty; and,
c) Avoid the need for surgery and other treatments that are required to reverse the physical effects of puberty (i.e. removal of breasts, tracheal and facial shaving, and electrolysis).

What are my other options if I do not wish to have my child undergo treatment for suppression of puberty?

Due to the high risk of anxiety, depression, self-harm and even suicide associated with gender dysphoria, psychological therapy with a mental health provider that has experience in treating youth with gender dysphoria is highly recommended regardless of whether your child undergoes suppression of puberty. No studies have been done comparing psychological therapy only (i.e., without puberty suppression treatment) versus puberty suppression treatment.

What medications are used to suppress puberty?

The main mechanism by which physical changes of puberty can be put on hold is by blocking the signal from the brain to the organs that make the hormones of puberty. These hormones are estrogen and testosterone. Estrogen is made by the ovaries. Testosterone is made by the testicles.

Medications, also called "pubertal blockers", are effective for both males and females and can be started just after the early physical changes of puberty. None of the medications have been approved by the Food and Drug Administration ("FDA") for use in adolescents with gender dysphoria, which is considered an "off label" use. However, pediatric endocrinologists (children's doctors who specialize in hormones and puberty), use these medications frequently to suppress puberty in children with precocious (early) puberty.

a. Lupron® and Histrelin are called GnRH analogs and are the most effective forms of treatment.

   - Lupron® (an "Injectable GnRH Analog") is given as a monthly or every 3-month intramuscular injection and is approved for children with precocious (early) puberty. ***With your consent, we will treat your child with an Injectable GnRH Analog.***

   - Histrelin (a "Surgical GNRH Analog") is an implant that is placed under the skin surgically, and needs to be replaced yearly to every 2 years. Histrelin is approved for children with precocious puberty with the brand name of Supprelin®, and on a slightly smaller dose, it is approved in adults with prostate cancer under the name of Vantas. However, it only comes in one dose for children which cannot be adjusted and it also requires a surgical procedure to be placed and removed, so therefore Histrelin will not be used to treat your child without additional consent.

b. Provera is a pill that needs to be taken twice a day and is approved to be used

in female adolescents with irregular menstrual bleeding. Provera was used for early puberty before Lupron® and Histrelin were available, and is less effective in suppressing puberty. Since Provera is not very effective and has a high risk of side effects, including blood clots, we will not be using any form of Provera to treat your child.

What are the anticipated effects of using an Injectable GnRH Analog to suppress puberty?

The administration of an Injectable GnRH Analog will completely or nearly completely suppress all of your child's sex hormone production and reproductive capacity. Hence, secondary sexual characteristics may recede in size (i.e., breasts will shrink in size as well as testicles) or may not further increase in size, maintaining a sexually infantile appearance. The capacity to ovulate in girls and produce sperm in boys will also be halted. Sex hormones are important for the development of muscle mass in males and for the normal thickness of bones in both males and females.

What are the requirements to receive suppression of puberty for gender dysphoria at Nemours Children's Specialty Care ("Nemours")?

In order to receive therapy to put puberty on hold at Nemours, there are specific requirements that need to be met before and during the treatment. These requirements will allow us to monitor your child's medical wellbeing as well as mental health during hormone therapy. If these requirements are not, met treatment with puberty blockers may be discontinued in the best interest and safety of your child.

Before beginning treatment with an Injectable GnRH Analog your child will need a thorough psychological and social evaluation performed by our Psychology Department. Your child also must have participated in at least 6 months of psychological therapy as confirmed in writing by your child's therapist. Additionally, your child will need to have started puberty, which varies from person to person but usually occurs at age 10.8 years in girls with breast buds, and age 11 ½ years in boys with testicular enlargement.

After proper evaluations have taken place, treatment to suppress puberty can be initiated if your child meets specific criteria recommended by the Endocrine Society, which includes ALL of the following:

1. Fulfills the current DSM or ICD criteria for gender dysphoria.
2. Has (early) pubertal changes that have resulted in an increase in gender

dysphoria.

3. Does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
4. Has adequate psychological and social support during treatment.
5. Has experienced puberty to at least Tanner stage 2, which is the first stage of puberty and refers to breast or testicle growth. This must be confirmed by a trained physician.
6. Demonstrates knowledge and understanding of the expected outcomes of suppression of puberty, future cross-sex (gender-affirming) hormone treatment, and gender affirming surgery, as well as the medical and social risks and benefits of gender reassignment.

After initiation of treatment for suppression of puberty, the following will be required:

1. Visits with the endocrinologist or adolescent medicine physician in our program every 3 months.
2. Suicide risk assessment performed by our social worker during each clinic visit every 3 months.
3. Laboratory testing every 3-4 months.
4. X-ray of the hand (bone age) once a year.
5. Bone density scan (DXA): this will allow us to monitor your child's bone density (bone strength) during treatment, since puberty blockers may decrease bone density if given for long periods of time.
6. Quarterly mental health assessment and completion of questionnaires with a member of our mental health care team. This will allow us to monitor your child's psychological wellbeing and adjustment while on puberty blockers.
7. Continued counseling with a therapist during the treatment period, with the frequency recommended by the therapist.

Both parents please initial each statement below to show that you understand the benefits, risks, and changes that may occur from giving treatment to your child to suppress his/her puberty.

<u>Effects of Treatment of Suppression of Puberty</u>

_____ _____ I understand that an Injectable GnRH Analog will be used to help temporarily

suspend or block the physical changes of puberty for my child.

_____ _____ I understand that this treatment will not change my child's genetic sex (chromosomes), and it will not change the external genitals other than secondary sexual characteristics which may recede in size (i.e., breasts will shrink in size as well as testicles) or may not further increase in size,.

_____ _____ I understand that the effect of this medication is not permanent. If my child stops treatment, in a few months my child's body will likely restart the changes of puberty at the developmental stage they were at when they started the treatment.

_____ _____ I understand that it can take several months for the medication to be effective. I understand that no one can predict how quickly or slowly my child's body will respond.

_____ _____ I understand that by taking these medications, my child's body will not be making the hormones of puberty, testosterone or estrogen. At this time, I support my child in putting on hold the hormones and the changes induced by puberty.

_____ _____ I understand that an Injectable GnRH Analog works fairly rapidly to reduce the testosterone to a very low level. This will halt the physical changes of male puberty, such as enlargement of the testicles and penis; development of muscles; development of pubic, armpit and facial hair; lowering of the voice; broadening of the shoulders and widening of the jaw; development of a male Adam's apple; sex drive, erections and ejaculations (wet dreams). An Injectable GnRH Analog will not reverse some of the changes of male development that have already happened (Adam's apple, voice changes, shoulder and jaw bone changes, and penis size). It will cause a decrease in testicular size, body hair and muscle development. It will reduce the sex drive and ability to have erections and ejaculations. While an Injectable GnRH Analog interferes with fertility, it does not affect the ability to get a sexually transmitted infection. Precautions against getting an STI must still be taken.

_____ _____I understand that an Injectable GnRH Analog works fairly rapidly to reduce the estrogen to a very low level. This will halt the physical changes of female puberty, such as enlargement of the breasts, widening of the hips; and the onset of menstrual periods. An Injectable GnRH Analog will not reverse some of the changes of female development that have already happened (breast size, width of hips). It will stop menstrual periods and cause vaginal dryness. It will reduce the sex drive. While an