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Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents

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BACKGROUND AND OBJECTIVES: The effects of endocrinological treatment on cardiovascular risk profile in transgender adolescents are unknown. In this retrospective cohort study, we aim to investigate these effects and assess obesity and dyslipidemia prevalence in transgender adolescents at 22 years compared with peers.

METHODS: Changes in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, homeostatic model assessment for insulin resistance (HOMA-IR), and lipid values during treatment, along with the prevalence of obesity and dyslipidemia at 22 years, were recorded in 71 transwomen and 121 transmen who started gonadotropin-releasing hormone agonists in their adolescence (15 years), with a subsequent addition of sex hormones (17 years).

RESULTS: In transwomen, changes in BMI (+3.0; 95% confidence interval [CI] 1.6 to 4.4), SBP (-2 mm Hg; 95% CI -7 to 3), DBP (+10 mm Hg; 95% CI 7 to 14), glucose (0.0 mmol/L; 95% CI -0.2 to 0.2), HOMA-IR (+0.6; 95% CI -0.6 to 1.9), and lipid values were similar or more favorable compared with peers. The same was true for transmen regarding changes in BMI (+2.3; 95% CI 1.7 to 2.9), SBP (+7 mm Hg; 95% CI 3 to 10), DBP (+7 mm Hg; 95% CI 5 to 10), glucose (+0.1 mmol/L; 95% CI -0.1 to 0.3), HOMA-IR (-0.2; 95% CI -0.8 to 0.3), and lipid values. At age 22, obesity prevalence was 9.9% in transwomen, 6.6% in transmen, 2.2% in ciswomen, and 3.0% in cismen.

CONCLUSIONS: Generally, endocrinological treatment in transgender adolescents is safe regarding cardiovascular risk. Because obesity is more prevalent in transgender adolescents compared with peers, body weight management should be important during the medical trajectory.

abstract

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Dr Klaver conceptualized and designed the study, contributed to data acquisition and data analysis, and drafted and revised the manuscript; Dr Wiepjes substantially contributed to the acquisition and interpretation of data and critically reviewed the manuscript; Dr van der Loos contributed to the interpretation of data and data analysis and critically reviewed and revised the manuscript; Dr Twisk contributed to the study design and data analysis and critically reviewed the manuscript; Drs de Mutsert, den Heijer, Rotteveel, and Klink conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The effect of genderaffirming hormone treatment on the cardiovascular risk profile has been studied in transgender adults, but the effects in combination with pubertal suppression by using gonadotropin-releasing hormone agonists in transgender adolescents is unknown.

WHAT THIS STUDY ADDS: This is the first study on early medical intervention in transgender adolescents examining cardiovascular risk factors in a large number of participants. Treatment with gonadotropin-releasing hormone agonists and gender-affirming hormones in transgender adolescents is generally safe regarding cardiovascular risk factors.

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Since the late 90s, transgender adolescents from the age of 12 are treated with gonadotropin-releasing hormone agonists (GnRHas) to discontinue the progression of puberty.^{1,2} Subsequently, at the age of 16, transwomen (individuals assigned male sex at birth self-identifying as women) and transmen (individuals assigned female sex at birth selfidentifying as men) can be treated with estradiol or testosterone to induce the secondary sexual characteristics of the affirmed sex.

Although first viewed as controversial,³ this approach is nowadays well accepted and endorsed by the international community of health professionals.⁴ Indeed, the psychological benefits of gender-affirming treatment of transgender adolescents have been established.⁵ One year after surgery, gender dysphoria was alleviated, psychological functioning had steadily improved, and well-being was similar to or better than that of young adults of the same age from the general population.⁵ However, few data are available on the physical outcome and safety of genderaffirming treatment.

We recently showed that body shape and body composition change toward the affirmed sex. When compared at 22 years with age-matched peers, the body shape and body composition of young adult transwomen revealed greater similarity to the body shape and body composition of their affirmed sex than to their assigned sex. In transmen, these parameters were within reference values for women and men in the general population.⁶ Also, another study revealed that at 22 years, the z score of the lumbar spine was under the pretreatment level. This implies a possible delay in or loss of peak bone mass. This was more pronounced in transwomen than in transmen. Because transwomen had a *z* score below that of the reference population before the start of GnRHa

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treatment, they may be more at risk for worse bone health than transmen.⁷

The effect of gender-affirming treatment on cardiovascular risk factors and cardiovascular events remains an issue of debate.8,9 Mortality does not seem to increase during testosterone or estradiol treatment in transgender adults.¹⁰ but there was an increase of thromboembolic incidents in transwomen treated with genderaffirming hormones (GAHs) compared with the general population.⁹ In adult transwomen and transmen, an increase in BMI was reported, with an increase in total body fat and insulin levels in transwomen and a worsening of the lipid profile in transmen.^{11–14} Besides the treatment with GAHs, the use of GnRHas has also been related to an increase in insulin resistance and lipid levels in premenopausal women.¹⁵ In addition, a study in American transgender students revealed that they were more likely to have obesity than their nontransgender peers.¹⁶ It is wellestablished that obesity is related to a higher risk for cardiovascular disease^{17,18} and cardiovascular risk factors such as dyslipidemia.¹⁹ One study in transgender adolescents revealed an increase in BMI in transmen.²⁰ Additionally, a decrease in high-density lipoprotein (HDL) cholesterol levels was seen. Blood pressure and other lipids did not change. In contrast, in transwomen, no changes were found for BMI, blood pressure, and lipid levels. However, in this study, transgender adolescents were on GAHs only and did not use GnRHas.

There is currently no insight into the potential cardiovascular side effects of treatment with GnRHas and GAHs in transgender adolescents. It is important to investigate the effects of this adolescent treatment protocol on cardiovascular risk factors to be able to make a better assessment of the risk of cardiovascular disease of adult transgender people who started treatment during adolescence. Therefore, our aim for this study was to examine the effects of treatment with GnRHas followed by the addition of GAHs on changes in cardiovascular risk factors, including BMI, blood pressure, insulin sensitivity, and lipid levels. In addition, we aimed to assess the prevalence of obesity and dyslipidemia in young adult transgender people using GAHs since adolescence compared with their peers.

METHODS

Study Design and Study Population

The medical records of all adolescents diagnosed with gender dysphoria²¹ at the Vrije Universiteit Medical Center from 1998 to December 2015 were retrospectively reviewed.²² Subjects were included (1) if they had started treatment with GnRHas before the age of 18^2 (2) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRHa or GAH treatment or within 1.5 years before or after the 22nd birthday), and (3) if, on the basis of their age, they were likely to have had at least 1 medical consultation in young adulthood (>20.5 years). During routine medical consultations, data were collected on anthropometry, laboratory measurements, and dual-energy radiograph absorptiometry. For the present study, data obtained at 3 time points were used: at the start of GnRHa treatment (mean age: 15 years), at the addition of GAHs (mean age: 17 years), and at the age of 22 years (range 20.5-23.5 years). Because of the retrospective character of the study and the large study population, necessity for informed consent was waived by the local ethics committee.²²

Treatment Protocol

The treatment protocol has been published in detail earlier.² At a minimum age of 12 and a Tanner B2 (breast) stage for girls or a Tanner G3 (genital) stage for boys, GnRHa treatment at 3.75 mg per 4 weeks subcutaneously was started. From the age of 16, GAHs were added with increasing doses to initiate pubertal development. Transwomen were prescribed 17- β estradiol (E2) orally, starting with 5 μ g/kg body weight per day, which was increased every 6 months until the maintenance dose of 2 mg per day was reached. Transmen used mixed testosterone esters (Sustanon) at 25 mg/m² body surface area per 2 weeks intramuscularly, which was increased every 6 months until the maintenance dose of 250 mg per 3 to 4 weeks was achieved. When GnRHas were started after the age of 16, GAHs were added after 3 to 6 months, with a starter dosage of 1 mg of E2 daily or 75 mg of testosterone esters intramuscularly weekly. After 6 months, dosages were increased to 2 mg of E2 daily or 250 mg of testosterone esters per 3 to 4 weeks. From the age of 18, patients were eligible for gonadectomy, whereafter GnRHa treatment was ceased. From the start of treatment, patients were advised to maintain a healthy, active lifestyle.

Anthropometry and Blood Pressure

Body height, body weight, waist circumference, and hip circumference were measured each visit. Height was measured to the nearest centimeter by using a Harpenden stadiometer. Weight was measured in underwear without shoes to the nearest 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. Office systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an electronic blood pressure monitor.

Laboratory Measurements

Fasting venous blood samples were obtained every visit. Analyses on glucose and lipids were performed by using Roche Cobas chemistry analyzers (Modular P800 or Cobas 8000; Roche Diagnostics, Mannheim, Germany). The interassay coefficients of variability were as follows: glucose, 1.1%; total cholesterol, 1.4%; HDL cholesterol, 0.9%; and triglycerides, 1.8%. The lower limit of quantification was 0.1 mmol/L for glucose, total cholesterol, and triglycerides and 0.08 mmol/L for HDL cholesterol. To measure insulin, an immunometric assay was used (Luminescence Advia Centaur; Siemens Medical Solutions Diagnostics, Malvern, PA) with an interassay CV of 7% and a lower limit of quantification of 10 pmol/L. The homeostatic model assessment for insulin resistance (HOMA-IR) provides a measure for insulin resistance. HOMA-IR is calculated as (the fasting glucose level in millimoles per liter/the fasting insulin level in milliunits per liter)/ 22.5.²³ Low-density lipoprotein (LDL) cholesterol was calculated by using the Friedewald formula.²⁴ We described the types of assays used for gonadal hormone-level measurements before.6

Statistical Analyses

Baseline data were shown as number, mean (SD), or median (interquartile range) when criteria for normality were not fulfilled. To estimate the change in cardiovascular risk factors over time, we performed linear mixed-model regression analyses with time as an independent variable. Time was treated as a categorical variable (start of GnRHa treatment, start of GAH treatment, and 22 years). Linear mixed models were used because observations were clustered within participants. To rule out selection bias, we compared changes in all cardiovascular risk factors between participants with and

without missing values. To take into account possible differences between surgical removal of the gonads and gonadal suppression by continuing GnRHa treatment, we compared changes in all cardiovascular risk factors between these 2 groups as well. By performing a regression analysis, we also examined whether the gonadal steroid levels at the age of 22, as well as the change in steroid levels from pre-GAH treatment, are related to lipids and BMI at 22 years. To show the natural course of changes in cardiovascular risk factors during adolescence in ciswomen and cismen (women and men whose gender identity matches their sex assigned at birth), references from the literature were retrieved. When possible, data from the Amsterdam Growth and Health Longitudinal Study²⁵ were used, in which indicators of body composition and cardiovascular disease were measured over a period of 15 years in men and women aged 13 to 27. From this data set, reference data for total cholesterol and HDL cholesterol were retrieved. For the other measures. when possible, reference data from Dutch population studies were used.²⁶ When Dutch reference data were not available, data from developed countries were used: blood pressure at 15²⁷ and 22 years,²⁸ glucose at 15²⁹ and 22 years,³⁰ HOMA-IR at 15³¹ and 22 years,³² LDL cholesterol at 15³³ and 22 years,³⁴ and triglycerides at 15³³ and 22 years.34

Subsequently, prevalence of obesity and dyslipidemia (high total cholesterol or low HDL cholesterol) was estimated on the basis of the predicted values of the linear mixedmodel analyses, with time as independent variable. To determine if any possibly high prevalence at 22 years was already present before treatment, we also showed the prevalence of obesity and dyslipidemia at 15 years. Ageadjusted cutoff values for obesity and

dyslipidemia were retrieved from the literature. At 15 years, obesity was defined as BMI > 28.3 in men and BMI > 29.1 in women.³⁵ A high total cholesterol level was defined as >5.2mmol/L, and a low HDL cholesterol level was defined as <1.0 mmol/L in both men and women.³⁶ At 22 years, obesity was defined as BMI > 30 in both sexes.³⁷ A high total cholesterol level was defined as >6.1 mmol/L in men and >5.9 mmol/L in women. A low HDL cholesterol level was defined as <0.9 mmol/L in men and <1.0 mmol/L in women.³⁸ Prevalence at 15 years was calculated with reference values of the birthassigned sex. Because participants had received GAHs for 5 years, prevalence at 22 years was calculated with reference values of the affirmed sex. Although the impact of karyotype cannot completely be ruled out,³⁹ there is abundant evidence of the effect of GAHs on lipid levels.⁴⁰ Therefore, we preferred to use reference values of the affirmed sex. To obtain the prevalence of obesity and dyslipidemia from the general population, the same age-adjusted cutoff values were applied to the original data set of the Amsterdam Growth and Health Longitudinal Study.

RESULTS

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In this study, 71 transwomen and 121 transmen who started GnRHa treatment at a mean age of 15 and GAH treatment at a mean age of 17 were included. General characteristics of participants are described in Table 1. The number of included persons for each visit is shown in Table 2. The comparison between changes in cardiovascular risk factors of participants with and without missing data did not reveal different results.

In Table 2, changes in cardiovascular risk factors during GnRHa treatment alone and changes after the addition of GAHs are described. In Fig 1, the changes in cardiovascular risk factors TABLE 1 General Characteristics of the Participants

	Transwomen	Transmen
No.	71	121
Age at start of GnRHa treatment, y, mean (SD)	14.6 (1.8)	15.2 (2.0)
Age at start of GAH treatment, y, mean (SD)	16.4 (1.1)	16.9 (0.9)
Ethnicity white, %	98	94
Tanner stage at start, No. ^a		
T1	0	0
T2	6	3
T3	21	8
Τ4	6	26
Τ5	34	79
Menarche, %		84
Duration of GnRHa monotherapy, y, median (IQR)	2.1 (1.0-2.7)	1.0 (0.5-2.9)
Duration of GnRHa + GAH, y, median (IQR)	3.1 (2.5–3.6)	2.3 (1.8–2.8)
Duration GAH monotherapy, y, median (IQR)	2.2 (1.1–3.1)	2.9 (1.7-3.4)
E2 level at start of GnRHa treatment, pmol/L, median (IQR)	57 (36-81)	112 (64–219)
E2 level at start of GAH treatment, pmol/L, median (IQR)	25 (20-30)	28 (23–36)
E2 level at 22 y of age, pmol/L, median (IQR)	121 (81–154)	70 (43–135)
Testosterone Level at start of GnRHa treatment, nmol/L, median (IQR)	9.1 (3.7-14.0)	1.0 (1.0–1.3)
Testosterone Level at start of GAH treatment, nmol/L, median (IQR)	1.0 (1.0-1.0)	1.0 (1.0–1.0)
Testosterone Level at 22 y of age, nmol/L median (IQR)	1.0 (0.8–1.0)	16.0 (8.8–37.0)

IQR, interquartile range; —, not applicable.

^a For 4 transwomen and 5 transmen, the Tanner stage at start was unknown.

are represented, together with changes in ciswomen and cismen. LDL cholesterol levels did not change after the addition of estradiol, whereas an increase in LDL cholesterol levels was seen in ciswomen. HOMA-IR in transwomen tended to increase after the addition of estradiol (+0.7; 95%)confidence interval [CI] -0.2 to 1.5), whereas in ciswomen, HOMA-IR did not change. DBP levels were lower than those in the reference population at start but increased during treatment in both sexes up to similar values as those in ciswomen and cismen at 22 years. Other changes in SBP, glucose, and lipid levels were similar or more favorable in transgender adolescents compared with their desired sex.

Shift tables are provided for BMI, blood pressure, glucose, HOMA-IR, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in Supplemental Tables 3 and 4.

There were no statistically significant differences between gonadectomy and continued use of GnRHas for any of the risk factors (data not shown). Additionally, both the actual sex steroid level and the change in sex steroid level from pre-GAH treatment, did not correlate significantly with BMI and lipid levels at 22 years.

At the age of 22, the prevalence of obesity was higher in transwomen (9.9%) and transmen (6.6%) than in reference men (3.0%) or reference women (2.2%). In transmen at 15 years, obesity was already more prevalent (5.0%) than in transwomen (1.4%), reference men (1.8%), or reference women (1.5%). With respect to high total cholesterol levels at 22 years, an almost similar or lower prevalence was seen in transwomen (0%) and transmen (5.3%) compared with reference men (4.4%) and reference women (6.6%). The prevalence of low HDL cholesterol levels at 22 years was slightly higher in transwomen (2.9%) compared with reference women (0.0%) (Fig 2).

DISCUSSION

In this study of 71 adolescent transwomen and 121 adolescent transmen using hormonal treatment

	Start of GnRHa Treatment, Mean (95% Cl)	22 y, Mean (95% CI)	Δ During GnRHa Treatment Alone, Mean (95% Cl)	Δ Between Start of GAH Treatment and 22 y, Mean (95% Cl)	Difference Between Transwomen or Transmen at 22 y and Ciswomen or Cismen at 22 y, Mean (95% Cl)
Transwomen					
BMI	20.2 (19.4 to 20.9)	23.2 (21.6 to 24.8)	+1.1 (0.7 to 1.5)*	+1.9 (0.6 to 3.2)**	+1.2 (0.1 to 2.2)
SBP, mm Hg	120 (116 to 123)	117 (113 to 122)	+1 (-3 to 5)	−3 (−8 to 2)	-7 (-11 to -3)
DBP, mm Hg	65 (63 to 67)	75 (72 to 78)	+4 (1 to 7)**	+6 (3 to 10)*	-3 (-6 to 0)
Glucose, mmol/L	5.0 (4.8 to 5.2)	5.0 (4.8 to 5.1)	-0.1 (-0.3 to 0.1)	+0.1 (-0.1 to 0.2)	+0.5 (-9.2 to 10.2)
Insulin, mU/L	9.5 (6.7 to 12.2)	13.0 (8.4 to 17.6)	+0.8 (-2.5 to 4.1)	+2.7 (-1.7 to 7.1)	+5.0 (3.0 to 7.0)
HOMA-IR	2.3 (1.2 to 3.4)	2.9 (1.9 to 3.9)	0.0 (-1.2 to 1.2)	+0.7 (-0.2 to 1.5)	+1.1 (0.7 to 1.6)
Total cholesterol, mmol/L	3.7 (3.5 to 3.9)	4.1 (3.8 to 4.4)	0.3 (0.2 to 0.5)*	0.1 (-0.2 to 0.4)	-0.8 (-1.1 to -0.4)
HDL cholesterol, mmol/L	1.4 (1.3 to 1.5)	1.6 (1.4 to 1.7)	+0.2 (0.1 to 0.3)*	0.0 (-0.1 to 0.2)	+0.8 (0.6 to 0.9)
LDL cholesterol, mmol/L	1.9 (1.7 to 2.1)	2.0 (1.8 to 2.3)	+0.2 (0.0 to 0.3)***	0.0 (-0.3 to 0.2)	-0.7 (-1.0 to -0.4)
Triglycerides, mmol/L	0.8 (0.7 to 0.9)	1.1 (0.9 to 1.4)	+0.1 (-0.1 to 0.2)	+0.2 (0.0 to 0.5)***	+0.1 (-0.1 to 0.3)
Transmen					
BMI	21.6 (20.9 to 22.3)	23.9 (23.0 to 24.7)	+0.9 (0.5 to 1.3)*	+1.4 (0.8 to 2.0)*	+1.5 (0.6 to 2.3)
SBP, mm Hg	120 (118 to 122)	126 (122 to 130)	+2 (-1 to 4)	+5 (1 to 9)***	−9 (−13 to −5)
DBP, mm Hg	67 (66 to 69)	74 (72 to 77)	+1 (-1 to 3)	+6 (4 to 9)*	-6 (-8 to -3)
Glucose, mmol/L	4.8 (4.7 to 4.9)	4.8 (4.7 to 5.0)	+0.1 (-0.1 to 0.2)	0.0 (-0.2 to 0.2)	+0.1 (-4.8 to 5.0)
Insulin, mU/L	9.5 (8.0 to 11.0)	8.6 (6.9 to 10.2)	+1.2 (-0.6 to 3.0)	-2.1 (-3.9 to -0.3)***	+0.6 (-0.9 to 2.1)
HOMA-IR	2.1 (1.6 to 2.5)	1.8 (1.4 to 2.2)	+0.3 (-0.2 to 0.8)	-0.5 (-1.0 to -0.1)***	+0.2 (-0.2 to 0.5)
Total cholesterol, mmol/L	3.9 (3.7 to 4.0)	4.6 (4.3 to 4.8)	+0.3 (0.2 to 0.4)*	+0.4 (0.2 to 0.6)*	+0.0 (-0.3 to 0.3)
HDL cholesterol, mmol/L	1.5 (1.4 to 1.5)	1.3 (1.2 to 1.3)	+0.1 (0.1 to 0.2)*	-0.3 (-0.4 to -0.2)*	+0.4 (0.3 to 0.5)
LDL cholesterol, mmol/L	2.1 (1.9 to 2.2)	2.6 (2.4 to 2.8)	+0.2 (0.1 to 0.3)**	+0.4 (0.2 to 0.6)*	-0.1 (-0.3 to 0.1)
Triglycerides, mmol/L	0.8 (0.7 to 0.8)	1.3 (1.1 to 1.5)	0.0 (0.0 to 0.1)	+0.5 (0.3 to 0.7)*	+0.1 (-0.1 to 0.4)

TABLE 2 Changes in BMI, SBP, DBP, Glucose, HOMA-IR, Total Cholesterol, HDL Cholesterol, LDL Cholesterol, and Triglyceride Values in Transwomen and Transmen

The number of participants with laboratory measurements at baseline were as follows for transwomen: BMI: n = 69; SBP and DBP: n = 63; glucose: n = 40; insulin: n = 40; HOMA-IR: n = 36; and total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides: n = 43. The number of participants with laboratory measurements at baseline were as follows for transmen: BMI: n = 118; SBP and DBP: n = 115; glucose: n = 78; insulin: n = 81, HOMA-IR: n = 75; and total cholesterol, HDL cholesterol, and triglycerides: n = 85. The number of participants with laboratory measurements at age 22 y were as follows for transwomen: BMI: n = 37; SBP and DBP: n = 36; glucose: n = 18; insulin: n = 12; total cholesterol: n = 21; and HDL cholesterol, LDL cholesterol, and triglycerides: n = 20. The number of participants with laboratory measurements at age 22 y were as follows for transmen: BMI: n = 55; SBP and DBP: n = 66; glucose: n = 43; insulin: n = 18; HOMA-IR: n = 18; total cholesterol: n = 44; and HDL cholesterol, LDL cholesterol, and triglycerides: n = 43.

*** P < .000.

who were followed from the start of GnRHa treatment at 15 years to the age of 22 years, we show that changes in various cardiovascular risk factors are similar to changes in cardiovascular risk factors in the general adolescent population. This results in similar or more favorable mean values in blood pressure, glucose, and lipids in young adulthood in both transwomen and transmen. Although the mean BMI of the majority of transgender people at 22 years is just slightly higher than that in ciswomen and cismen, a higher

prevalence of obesity in both young adult transwomen and transmen was found. In transmen, the pretreatment obesity prevalence was already higher compared with the general population, but the increase in prevalence (+1.6%) is comparable with cismen (+1.2%). In contrast, the increase of obesity prevalence in transwomen (+8.5%)was more remarkable compared with ciswomen (+0.7%). Thus, a subset of transwomen proved to be more prone to excessive weight gain, which may be due to numerous factors, such as a more indoor

sedentary lifestyle compared with the general population^{16,41} or dietary habits.

Transwomen tended to increase more in HOMA-IR after the addition of estradiol than ciswomen, resulting in a higher HOMA-IR value at 22 years. Possibly, this increase is due to the large increase in body fat in transwomen.⁶ This change in HOMA-IR, compared with the relatively stable values of the cis population, might be due to the fast, large changes in body composition after

^{*} P < .001. ** P < .005.



FIGURE 1

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Changes in BMI (A), SBP (B), DBP (C), glucose (D), HOMA-IR (E), total cholesterol (F), LDL cholesterol (G), HDL cholesterol (H), and triglycerides (I) during adolescence in transgender people treated with GnRHas and GAHs and in ciswomen and cismen.

the addition of GAHs, whereas body composition changes in the cis population occur more gradual during several years.⁴² Also, direct effects of GAHs on glucose metabolism in the liver or muscle might contribute to these divergent changes in HOMA-IR. $^{43-45}$

In addition, transwomen at 22 years have a more favorable lipid profile

than ciswomen, except for a higher prevalence of low HDL cholesterol levels. In addition to lower total cholesterol and LDL cholesterol levels before treatment, the addition of estradiol did not appear to increase total cholesterol and LDL cholesterol levels, whereas in ciswomen, increases in these levels were seen. In contrast, HDL cholesterol levels decreased in ciswomen but did not in transwomen. Previous studies already revealed these partial beneficial effects of estradiol on lipid levels in men⁴⁶ and in adult transwomen.¹⁴ In transmen at 22 years, lipid levels are comparable with lipid levels in cismen, except for higher HDL levels. Because both ciswomen and transmen have a more favorable HDL cholesterol level than their counterparts, one can carefully postulate a favorable genetic predisposition of HDL cholesterol levels, which may be sex chromosomal driven.47

Only 2 previous studies investigated the effects of GnRHas and GAHs on cardiovascular risk factors in transgender adolescents.^{2,48} One of these studies reported no change in lipid levels after a minimum treatment duration of 2 years in 10 transwomen and 11 transmen.² The other study, examining 16 transwomen after 3 years of GnRHa and estradiol treatment, found an increase in BMI of 0.7 and no changes in SBP.⁴⁸ This increase in BMI is consistent with our findings, although we showed a larger increase in BMI. In contrast, we showed increases in total cholesterol, LDL cholesterol, and triglyceride levels in both sexes, with a decrease in HDL cholesterol levels in transmen. Most likely, these discrepancies are due to a longer follow-up time with inherent more sex steroid exposure. Studies in adult transwomen treated with GnRHas and estradiol revealed



FIGURE 2

Age-adjusted prevalence of obesity, high total cholesterol levels, and low HDL cholesterol levels in transgender people treated with GnRHas and GAHs and in ciswomen and cismen. A, Obesity at age 15 years. B, Obesity at age 22 years. C, High total cholesterol at age 15 years. D, High total cholesterol at age 22 years. E, Low HDL cholesterol at age 15 years. F, Low HDL cholesterol at age 22 years.

increases in BMI, body fat, and HDL cholesterol levels. No changes were seen in total cholesterol, LDL cholesterol, and triglyceride levels after 12 or 24 months of treatment.^{49,50} In contrast to adulthood, adolescence is a period of development to which sex hormones partially contribute; therefore, some observed changes may not be due to the sole direct effect of the treatment with GnRHas or GAHs but are more likely to reflect body maturation beyond the secondary sexual characteristics. This is the first study on early medical intervention in transgender adolescents examining cardiovascular risk factors in a large number of participants. In addition, we present data with a long follow-up period from the start of GnRHa treatment at a mean age of 15 years until young adulthood. Our study is limited by the presence of missing data. Nevertheless, a comparison between people with and without missing data revealed similar results. Also, we could not include control groups of transmen and transwomen without hormonal treatment because it would be unethical to withhold treatment. It is conceivable that transgender people have a different lifestyle than their peers in the general population. Therefore, it is unclear to what extent changes as shown in Fig 1 are due to hormonal treatment or to other factors, such as sedentary behavior or different eating habits.

Hence, the cardiovascular risk profile in transgender persons using GnRHas and GAHs was comparable with that in the general population during treatment, except for a higher prevalence of obesity in young adulthood. Long-term studies will have to clarify whether this hormonal treatment exerts a higher risk for cardiovascular events in the future of these transgender people who started treatment in their teenaged years.

CONCLUSIONS

Treatment with GnRHas and GAHs in transgender adolescents is generally safe regarding cardiovascular risk factors. However, obesity was more prevalent in a subset of young adult transwomen and transmen compared with the young adult general population. Therefore, body weight management should be an important part of the endocrinological treatment in transgender adolescents and young adults.

ABBREVIATIONS

CI: confidence interval DBP: diastolic blood pressure E2: 17-β estradiol GAH: gender-affirming hormone GnRHa: gonadotropin-releasing hormone agonist HDL: high-density lipoprotein HOMA-IR: homeostatic model assessment for insulin resistance LDL: low-density lipoprotein SBP: systolic blood pressure

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