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## Puberty suppression with hormonal treatment in adolescent trans people is safe regarding cardiovascular risk profile

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## ABSTRACT

### Context

The effects of endocrinological treatment in transgender adolescents on their cardiovascular risk profile is unknown.

### Objective

To investigate the effects of endocrinological treatment on cardiovascular risk factors and to assess the prevalence of obesity and dyslipidemia at 22 years, compared to peers.

### Design

Retrospective cohort study

### Setting

Tertiary referral center for gender dysphoria.

### Participants & intervention

71 transwomen and 121 transmen who started gonadotropin-releasing hormone agonists in their adolescence (15 years) with subsequent addition of sex hormones (17 years).

### Main outcome measures

Change in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, insulin resistance (HOMA-IR), and lipids during treatment from a mean age of 15 years to 22 years and the prevalence of obesity and dyslipidemia at 22 years.

### Results

In transwomen, changes in BMI (+3.0 kg/m<sup>2</sup>, 95%CI 1.6;4.4), SBP (-2 mmHg, 95%CI -7;3), DBP (+10 mmHg, 95%CI 7;14), glucose (0.0 mmol/l, 95%CI -0.2;0.2), HOMA-IR (+0.6, 95%CI -0.6;1.9), and lipids were similar or more favorable compared with peers. Same as for changes in transmen in BMI (+2.3 kg/m<sup>2</sup>, 95%CI 1.7;2.9), SBP (+7 mmHg, 95%CI 3;10), DBP (+7 mmHg, 95%CI 5;10), glucose (+0.1 mmHg, 95%CI -0.1;0.3), HOMA-IR (-0.2, 95%CI -0.8;0.3), and lipids. At 22, obesity prevalences were 9.9% in transwomen and 6.6% in transmen, compared to 2.2% in ciswomen, and 3.0% in cismen.

## Conclusions

Generally, endocrinological treatment in transgender adolescents can be considered safe concerning cardiovascular risk. Because obesity is more prevalent in both young adult transwomen and transmen compared with peers, body weight management should be an important part of the medical trajectory.

## INTRODUCTION

Since the late 90s, transgender adolescents from the age of 12 years are treated with gonadotropin releasing hormone agonists (GnRHa) to discontinue the progression of puberty<sup>1,2</sup>. Subsequently, at the age of 16 years, transwomen (individuals assigned male at birth self-identifying as female) and transmen (individuals assigned female at birth self-identifying as male) can be treated with estradiol or testosterone treatment to induce the secondary sexual characteristics of the affirmed sex.

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

We recently showed that, during endocrinological treatment, body shape and body composition change towards values of the affirmed sex. When compared at 22 years to age-matched peers, it was found that in young adult transwomen, body shape and body composition showed greater similarity to their affirmed sex than to their assigned sex. In transmen, these parameters were within reference values for women and men in the general population<sup>6</sup>. In addition, it was shown that at age 22 the Z-score of the lumbar spine was under 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 prior to the start of GnRHa a Z-score below reference population, they may be more at risk of worse bone health than transmen<sup>7</sup>.

The effect of gender affirming treatment on cardiovascular risk factors and cardiovascular events remains an issue of debate<sup>8,9</sup>. Mortality does not seem to increase during testosterone or estradiol treatment in transgender adults<sup>10</sup>, but there was an increase of thromboembolic incidents in transwomen treated with gender affirming hormones, compared with the general population<sup>9</sup>. In adult transwomen and transmen using gender affirming hormones, 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<sup>11-14</sup>. Besides the treatment with gender affirming hormones, also the use of GnRHa has been related to

an increase in insulin resistance and lipids in premenopausal women<sup>15</sup>. Further, a study in 53 American transgender college students showed that they were more likely to be obese than their non-transgender peers<sup>16</sup>, although it was not reported whether they received hormonal treatment or not. It is well-established that obesity is related to a higher risk for cardiovascular disease<sup>17,18</sup>, and cardiovascular risk factors such as dyslipidemia<sup>19</sup>.

There is currently no insight in the potential cardiovascular side-effects of treatment with GnRHa and gender affirming hormones in transgender adolescents. It is important to investigate the effects of this adolescent treatment protocol on cardiovascular risk factors in order to be able to make a better assessment of the risk of cardiovascular disease of adult trans people who started treatment during adolescence. Therefore the aim of our study is to examine the effects of treatment with GnRHa followed by the addition of gender affirming hormones on changes in cardiovascular risk factors such as BMI, blood pressure, insulin sensitivity and lipids. Further, we aimed to assess the prevalence of obesity and dyslipidemia in young adult trans people using hormonal treatment since adolescence and to compare this with their peers.

## METHODS

### Study design and study population

The medical records of all adolescents diagnosed with gender dysphoria<sup>20</sup> at the VU University Medical Center from 1998 until December 2015 were retrospectively reviewed<sup>21</sup>. Subjects were eligible for inclusion when 1) they had started treatment with GnRHa before the age of 18 as described below<sup>2</sup>, 2) whole body dual-energy X-ray absorptiometry (DXA) was performed at least once during treatment (4 months before or after start GnRha or GAH, or within 1.5 year before or after the 22<sup>nd</sup> birthday) and 3) based on their age were likely to have had at least one medical consultation in young adulthood (>20.5 years). During routine medical consultations data were collected on anthropometry, laboratory measurements, and whole body dual-energy X-ray absorptiometry. For present study, data obtained at three time points were used: start GnRHa (mean age: 15 years), addition of gender affirming hormones (GAH) (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<sup>21</sup>.

### Treatment protocol

The treatment protocol, also referred to as the Dutch protocol, has been published in detail earlier<sup>2</sup>. At a minimum age of 12 years and a B2 (breast) stage for girls or a Tanner G3 (genital) stage for boys, GnRHa 3.75 mg per 4 weeks subcutaneously was started. From the age of 16 years, gender affirming hormones were added with increasing doses to initiate pubertal development. Transwomen were prescribed 17 $\beta$ -estradiol (E2) orally, starting with 5 microgram/kg body weight per day which was increased with 5 microgram/kg per day every six months until the maintenance dose of 2 mg per day was reached. Transmen used initially mixed testosterone (T) esters (Sustanon®) 25 mg/m<sup>2</sup> body surface area per 2 weeks intramuscular (im) which was increased with 25 mg/m<sup>2</sup> every 6 months until the maintenance dose of 250 mg per 3-4 weeks was achieved. When GnRHa were started after the age of 16, gender affirming hormones were added after 3-6 months with a start dosage of 1 mg 17 $\beta$ -estradiol daily or 75 mg Sustanon® im weekly. After 6 months, dosages were increased to 2 mg 17 $\beta$ -estradiol daily in transwomen and Sustanon® 250 mg per 3-4 weeks in transmen. From the age of 18 years, patients were eligible for gonadectomy, after which GnRHa treatment was ceased. From the start of treatment, patients were advised to maintain a healthy lifestyle with sportive activities and an adequate calcium intake to prevent bone loss.

### Anthropometry and blood pressure

Body height, body weight, waist circumference, and hip circumference were measured at each visit. Body height was measured to the nearest centimeter using a Harpenden stadiometer. Body weight was measured in underwear without shoes to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Office systolic blood pressure and diastolic blood pressure were measured with an electronic blood pressure monitor.

### Laboratory measurements

Fasting venous blood samples were obtained at every visit. Analyses on glucose and lipids were performed using Roche Cobas chemistry analyzers (Modular P800 or Cobas 8000, Roche Diagnostics, Mannheim, Germany). The inter-assay CVs were as follows: glucose 1.1%, total cholesterol 1.4%, HDL cholesterol 0.9%, and triglycerides 1.8%. The lower limit of quantification (LOQ) was as follows: glucose 0.1 mmol/L, total cholesterol 0.1 mmol/L, HDL cholesterol 0.08 mmol/L, and triglycerides 0.1 mmol/L. To measure insulin, an immunometric assay was used (Luminescence Advia Centaur, Siemens Medical Solutions Diagnostics, USA) with an inter-assay CV of 7% and a LOQ of 10 pmol/L. The homeostatic model assessment provides a measure for insulin resistance (HOMA-IR) and is widely used in literature<sup>22</sup>. HOMA-IR is calculated as  $\text{HOMA-IR} = (\text{fasting glucose in mmol} / \text{fasting insulin in mU/L}) / 22.5$ <sup>23</sup>. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula<sup>24</sup>.

### Statistical analyses

STATA 13.1 (StataCorp, College Station, TX, USA) was used for statistical analyses. Baseline data were shown as a number, mean (standard deviation), 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 independent variable. Time was treated as a categorical variable (start GnRHa, start GAH, and 22 years) and represented by dummy variables. Linear mixed models were used because observations were clustered within participants. In order to rule out selection bias, we compared changes in all cardiovascular risk factors between participants with and without missing values. In order 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 literature were retrieved. When possible, original data from the Amsterdam Growth and Health Longitudinal Study (AGHLS)<sup>25</sup> were used, a longitudinal study performed in the Netherlands, which measured

indicators of body composition and cardiovascular disease over a period of 15 years in men and women aged 13 to 27 years. From this original data set, reference data for total cholesterol and HDL cholesterol could be retrieved. For the other measures, when possible, reference data from Dutch population studies were used (BMI)<sup>26</sup>. When Dutch reference data were not available, reference data from developed countries were used: for blood pressure at 15 years<sup>27</sup> and 22 years<sup>28</sup>, for glucose at 15 years<sup>29</sup> and 22 years<sup>30</sup>, for HOMA-IR at 15 years<sup>31</sup> and 22 years<sup>32</sup>, for LDL cholesterol at 15 years<sup>33</sup> and 22 years<sup>34</sup>, and for triglycerides at 15 years<sup>33</sup> and 22 years<sup>34</sup>.

Subsequently, prevalences for obesity and dyslipidemia (high total cholesterol or low HDL cholesterol) were estimated based on the predicted values of the linear mixed models analyses with time as independent variable. To determine whether any possibly high prevalences at 22 years were already present prior to treatment, we also show prevalences of obesity and dyslipidemia at 15 years (start of GnRHa). Age-adjusted cut-off values for obesity and dyslipidemia were retrieved from literature. At 15 years, obesity was defined as BMI >28.3 kg/m<sup>2</sup> in men, and BMI >29.1 kg/m<sup>2</sup> in women<sup>35</sup>. High total cholesterol was defined as >5.2 mmol/l and low HDL cholesterol as <1.0 mmol/l in both men and women<sup>36</sup>. At 22 years, obesity was defined as BMI >30 kg/m<sup>2</sup> in both sexes<sup>37</sup>. High total cholesterol was defined as >6.1 mmol/l in men and >5.9 mmol/l in women, whereas low HDL cholesterol was defined as <0.9 mmol/l in men and <1.0 mmol/l in women<sup>38</sup>. Prevalences at 15 years were calculated with reference values of the at birth assigned sex. Because the participants had received gender affirming hormones for 5 years, prevalences at 22 years were calculated with reference values of the affirmed sex. Although the impact of the karyotype cannot completely be ruled out<sup>39</sup>, there is abundant evidence of the effect of gender affirming hormones on lipid levels<sup>40</sup>. Therefore, we preferred to use reference values of the affirmed sex. To obtain prevalences of obesity and dyslipidemia from the general population, the same age-adjusted cut-off values were applied to the original data set of the AGHLS.

## RESULTS

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

**Table 1.** General characteristics of the participants.

	TRANSWOMEN	TRANSMEN
Number (n=)	71	121
Age at start of GnRHa (years)	14.6 (1.8)	15.2 (2.0)
Age at start of GAH (years)	16.4 (1.1)	16.9 (0.9)
Ethnicity (% caucasian)	98	94
Tanner stage at start (n=)*		
T1	0	0
T2	6	3
T3	21	8
T4	6	26
T5	34	79
Menarche (%)	-	84
Duration of GnRHa monotherapy (yr)	2.1 (1.0-2.7)	1.0 (0.5-2.9)
Duration of GnRHa + GAH (yr)	3.1 (2.5-3.6)	2.3 (1.8-2.8)
Duration GAH monotherapy (yr)	2.2 (1.1-3.1)	2.9 (1.7-3.4)
E2 level at start GnRHa (pmol/L)	57 (36-81)	112 (64-219)
E2 level at start GAH (pmol/L)	25 (20-30)	28 (23-36)
E2 level at 22 years of age (pmol/L)	121 (81-154)	70 (43-135)
T level at start GnRHa (nmol/L)	9.1 (3.7-14.0)	1.0 (1.0-1.3)
T level at start GAH (nmol/L)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
T level at 22 years of age (nmol/L)	1.0 (0.8-1.0)	16.0 (8.8-37.0)

Data are shown as means (standard deviation) for age at start of GnRHa and age at start of GAH. Data are shown as median (+interquartile range) for duration of treatment, E2 levels and T levels. GnRHa: gonadotropin releasing hormone agonists, GAH: gender affirming hormones, E2: estradiol, T: testosterone.

\*Of 4 transwomen and 5 transmen Tanner stage at start was unknown.

### Changes in BMI, blood pressure, glucose, HOMA-IR, and lipids

In Table 2, changes in cardiovascular risk factors during GnRHa treatment alone and changes after the addition of GAH are described. In Figure 1, the changes in cardiovascular risk factors are visually represented, together with changes in ciswomen and cismen. LDL cholesterol did not change after the addition of estradiol, while an increase in LDL cholesterol was seen in ciswomen. HOMA-IR in transwomen tended to increase after the addition of estradiol (+0.7, 95% CI -0.2;1.5), while in ciswomen HOMA-IR did not change. Diastolic blood pressure was lower than the reference population at start, but increased during treatment in both sexes, up to similar values as ciswomen and cismen at 22 years. Other changes in BMI, systolic blood pressure, glucose, and lipids were similar or more favorable in transgender adolescents compared with their desired sex.

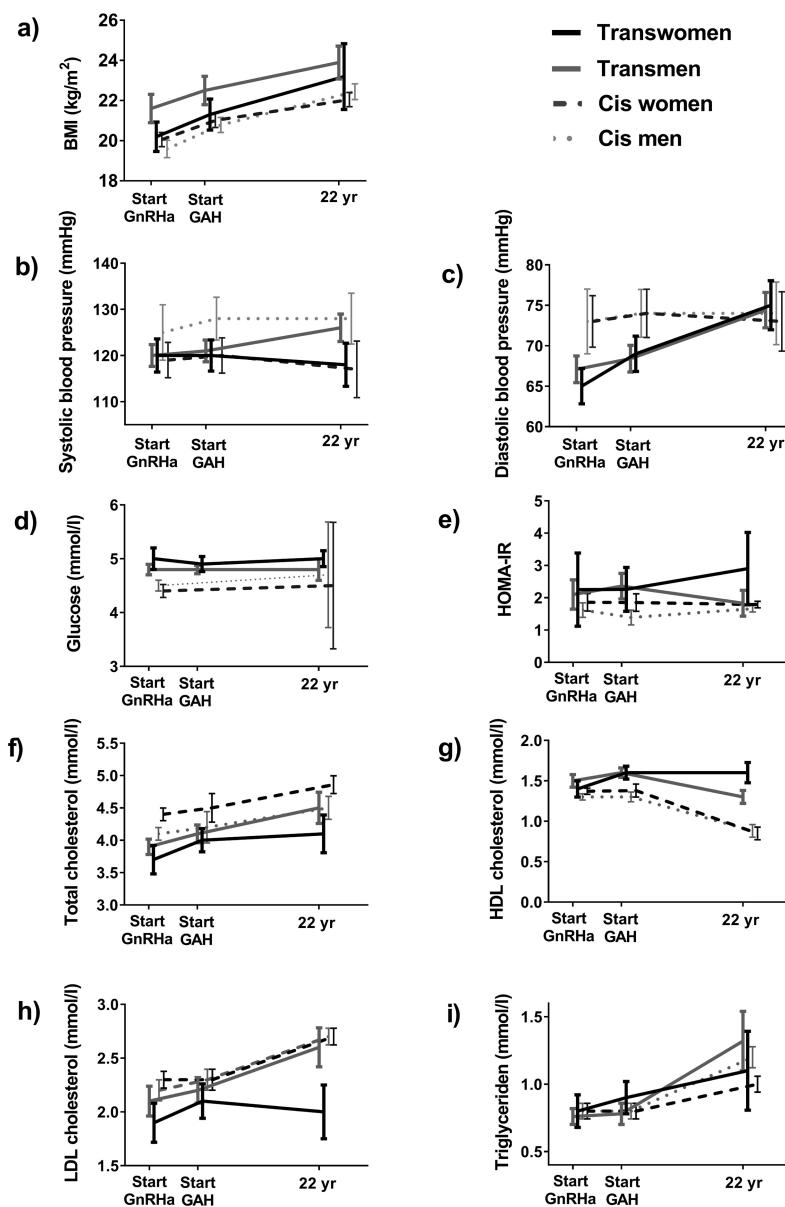
### Prevalence of obesity and dyslipidemia

At the age of 22 years, 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 (start GnRHa), 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 to reference men (4.4%) and reference women (6.6%). The prevalence of low HDL cholesterol at 22 years was slightly higher in transwomen (2.9%) compared to reference women (0.0%) (Figure 2).

**Table 2.** Changes in BMI, total body fat, systolic blood pressure, diastolic blood pressure, glucose, HOMA-IR, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in transwomen and transmen.

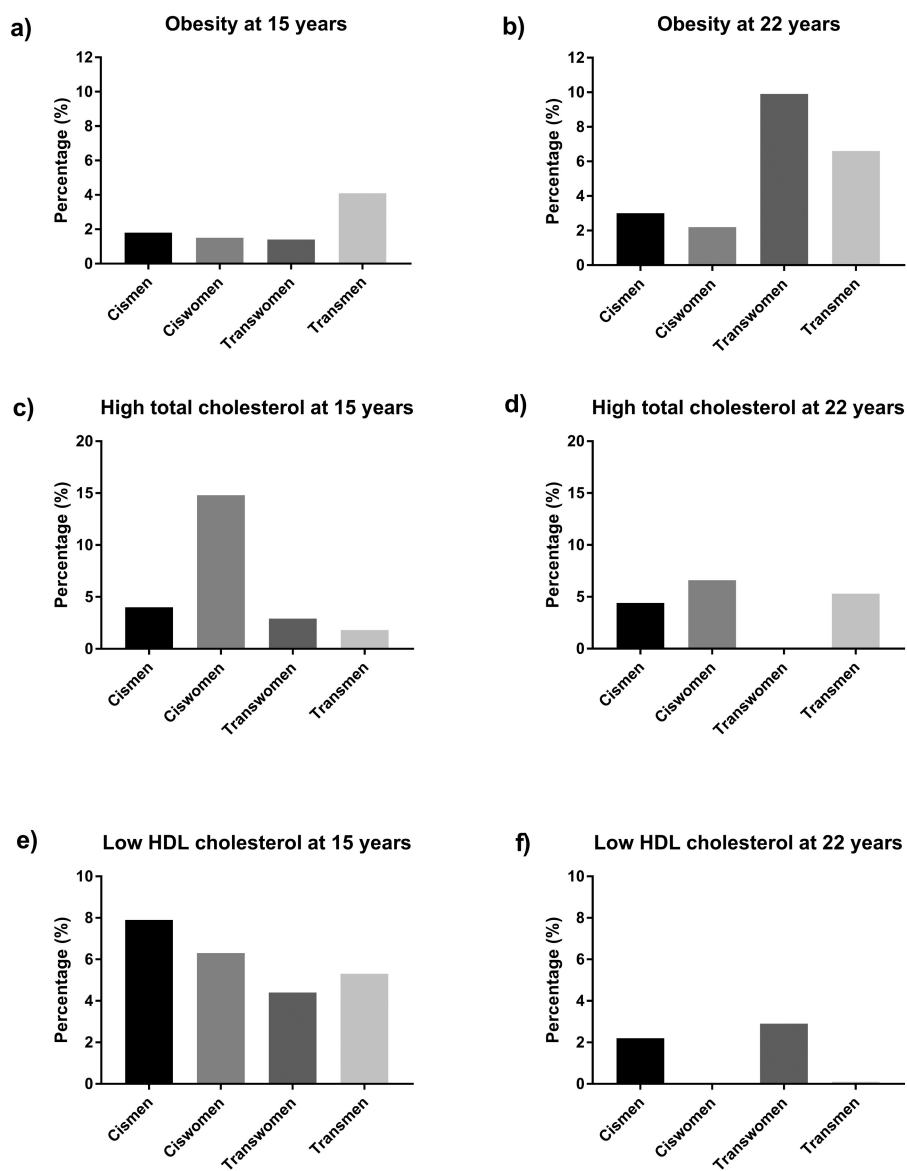
TRANSWOMEN						TRANSMEN					
	Start GnRHa	22 years	Δ during GnRHa alone	Δ between start GAH and 22 years	Difference between transwomen at 22 and ciswomen at 22		Start GnRHa	22 years	Δ during GnRHa alone	Δ after addition of GAH	Difference between transmen at 22 and cismen at 22
BMI (kg/m <sup>2</sup> )	20.2 (19.4;20.9)	23.2 (21.6;24.8)	+1.1 (0.7;1.5)	+1.9 (0.6;3.2)	+1.2 (0.1;2.2)	BMI (kg/m <sup>2</sup> )	21.6 (20.9;22.3)	23.9 (23.0;24.7)	+0.9 (0.5;1.3)	+1.4 (0.8;2.0)	+1.5 (0.6;2.3)
Sys blood pressure (mmHg)	120 (116;123)	117 (113;122)	+1 (-3;5)	-3 (-8;2)	-7 (-11;-3)	Sys blood pressure (mmHg)	120 (118;122)	126 (122;130)	+2 (-1;4)	+5 (1;9)	-9 (-13;-5)
Dias blood pressure (mmHg)	65 (63;67)	75 (72;78)	+4 (1;7)	+6 (3;10)	-3 (-6;0)	Dias blood pressure (mmHg)	67 (66;69)	74 (72;77)	+1 (-1;3)	+6 (4;9)	-6 (-8;-3)
Glucose (mmol/l)	5.0 (4.8;5.2)	5.0 (4.8;5.1)	-0.1 (-0.3;0.1)	+0.1 (-0.1;0.2)	+0.5 (-9.2;10.2)	Glucose (mmol/l)	4.8 (4.7;4.9)	4.8 (4.7;5.0)	+0.1 (-0.1;0.2)	0.0 (-0.2;0.2)	+0.1 (-4.8;5.0)
Insulin (mU/L)	9.5 (6.7;12.2)	13.0 (8.4;17.6)	+0.8 (-2.5;4.1)	+2.7 (-1.7;7.1)	+5.0 (3.0;7.0)	Insulin (mU/L)	9.5 (8.0;11.0)	8.6 (6.9;10.2)	+1.2 (-0.6;3.0)	-2.1 (-3.9;-0.3)	+0.6 (-0.9;2.1)
HOMA-IR	2.3 (1.2;3.4)	2.9 (1.9;3.9)	0.0 (-1.2;1.2)	+0.7 (-0.2;1.5)	+1.1 (0.7;1.6)	HOMA-IR	2.1 (1.6;2.5)	1.8 (1.4;2.2)	+0.3 (-0.2;0.8)	-0.5 (-1.0;-0.1)	+0.2 (-0.2;0.5)
Total cholesterol (mmol/l)	3.7 (3.5;3.9)	4.1 (3.8;4.4)	0.3 (0.2;0.5)	0.1 (-0.2;0.4)	-0.8 (-1.1;-0.4)	Total cholesterol (mmol/l)	3.9 (3.7;4.0)	4.6 (4.3;4.8)	+0.3 (0.2;0.4)	+0.4 (0.2;0.6)	+0.0 (-0.3;0.3)
HDL cholesterol (mmol/l)	1.4 (1.3;1.5)	1.6 (1.4;1.7)	+0.2 (0.1;0.3)	0.0 (-0.1;0.2)	+0.8 (0.6;0.9)	HDL cholesterol (mmol/l)	1.5 (1.4;1.5)	1.3 (1.2;1.3)	+0.1 (0.1;0.2)	-0.3 (-0.4;-0.2)	+0.4 (0.3;0.5)
LDL cholesterol (mmol/l)	1.9 (1.7;2.1)	2.0 (1.8;2.3)	+0.2 (0.0;0.3)	0.0 (-0.3;0.2)	-0.7 (-1.0;-0.4)	LDL cholesterol (mmol/l)	2.1 (1.9;2.2)	2.6 (2.4;2.8)	+0.2 (0.1;0.3)	+0.4 (0.2;0.6)	-0.1 (-0.3;0.1)
Triglycerides (mmol/l)	0.8 (0.7;0.9)	1.1 (0.9;1.4)	+0.1 (-0.1;0.2)	+0.2 (0.0;0.5)	+0.1 (-0.1;0.3)	Triglycerides (mmol/l)	0.8 (0.7;0.8)	1.3 (1.1;1.5)	0.0 (0.0;0.1)	+0.5 (0.3;0.7)	+0.1 (-0.1;0.4)

Data are shown as means (+95% confidence intervals). BMI: body mass index, HOMA-IR: homeostatic model assessment insulin resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, GnRHa: gonadotropin releasing hormone agonists, GAH: gender affirming hormones. Number of participants at baseline: Transwomen: BMI n=69; Total body fat=62; systolic/diastolic blood pressure n=63; glucose n=40; insulin n=40; HOMA-IR n=36; total cholesterol/HDL cholesterol/triglycerides n=43. Transmen: BMI=118; Total body fat n=108; systolic/diastolic blood pressure n=115; glucose n=78; insulin n=81, HOMA-IR n=75; total cholesterol/HDL cholesterol/LDL cholesterol/triglycerides n=85. Number of participants at 22 years: Transwomen: BMI n=37; Total body fat n=26; systolic/diastolic blood pressure n=36; glucose n=18; insulin n=12; total cholesterol n=21; HDL cholesterol/LDL cholesterol/triglycerides n=20. Transmen: BMI n=55; Total body fat n=42; systolic/diastolic blood pressure n=66; glucose n=43; insulin n=18; HOMA-IR n=18; total cholesterol n=44; HDL cholesterol/LDL cholesterol/triglycerides n=43.



**Figure 1.** Changes in BMI (a), systolic blood pressure (b), diastolic blood pressure (c), glucose (d), HOMA-IR (e), total cholesterol (f), HDL cholesterol (g), LDL cholesterol (h), triglycerides (i) during adolescence in trans people treated with GnRH<sub>a</sub> and gender affirming hormones and in ciswomen and cismen.

BMI: body mass index; GAH: gender affirming hormones; GnRH<sub>a</sub>: gonadotropin-releasing hormone agonists; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment insulin resistance; LDL: low-density lipoprotein.



**Figure 2.** Age-adjusted prevalences of obesity (a, b), high total cholesterol (c, d), and low HDL cholesterol (e, f) in trans people treated with GnRHa and gender affirming hormones and in ciswomen and cismen.

*GnRHa: gonadotropin-releasing hormone agonists; HDL: high-density lipoprotein;*

## DISCUSSION

This retrospective study in 71 adolescent transwomen and 121 adolescent transmen using hormonal treatment followed from the start of GnRHa at 15 years to the age of 22 years shows 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 trans people at 22 years is just slightly higher than in ciswomen and cismen, a higher prevalence of obesity in both young adult transwomen and transmen was found. In transmen, the pre-treatment obesity prevalence was already higher compared to the general population, but the increase in prevalence (+1.6%) is comparable to cismen (+1.2%). In contrast, the increase of obesity prevalence in transwomen (+8.5%) was remarkable compared to the increase in ciswomen (+0.7%). Thus, a subset of transwomen proved to be more prone for excessive weight gain, which may be due to numerous factors such as a more indoor sedentary lifestyle compared to the general population<sup>16,41</sup> or dietary habits.

Also, transwomen tended to increase more in HOMA-IR after the addition of estradiol than ciswomen, resulting in a higher, but still within the normal range, HOMA-IR value at 22 years. Possibly, this increase is due to the large increase in body fat in transwomen<sup>6</sup>. This large change in HOMA-IR, compared to the relatively stable values of the cis population, might be due to the fast and large changes in body composition after the addition of gender affirming hormones, while body composition changes in the cis population occur more gradual during several years<sup>42</sup>. Also, direct effects of gender affirming hormones on glucose metabolism in the liver or muscle might contribute to these divergent changes in HOMA-IR<sup>43-45</sup>.

Further, transwomen at 22 years have a more favorable lipid profile than ciswomen, except for a higher prevalence of low HDL cholesterol. In addition to lower total cholesterol and LDL cholesterol levels before treatment, the start of estradiol treatment 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 showed these partial beneficial effects of estradiol on lipids in men<sup>46</sup> and in adult transwomen<sup>14</sup>. In transmen at 22 years, lipid levels are comparable to lipid levels in cis men, except for their 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<sup>47</sup>.

Only two previous studies investigated the effects of GnRHa and gender affirming hormones on cardiovascular risk factors in transgender adolescents<sup>2,48</sup>. One of these studies reported no change in lipids after a minimum treatment duration of 2 years in 10 transwomen and 11 transmen<sup>2</sup>. The other study examining 16 transwomen after three years of GnRHa and estradiol treatment, found an increase in BMI of 0.7 kg/m<sup>2</sup>, and no changes in systolic blood pressure<sup>48</sup>. 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 triglycerides in both sexes with a decrease in HDL cholesterol 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 GnRHa and estradiol showed increases in BMI, body fat, and HDL cholesterol. No changes were seen in total cholesterol, LDL cholesterol, and triglycerides after 12 or 24 months of treatment<sup>49,50</sup>. 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 GnRHa or gender affirming hormones, 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 such a large number of participants. Further, we present data with a long follow-up period from the start of GnRHa 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 showed similar results. Also, we could not include control groups of transmen and transwomen without hormonal treatment, since it would be unethical to withhold them from treatment. It is conceivable that trans people have a different lifestyle than their peers in the general population. Therefore, it is unclear to what extent changes as shown in Figure 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 GnRHa and gender affirming hormones 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 teens.

In conclusion, treatment with GnRHa and gender affirming hormones 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 to the young adult general population. Therefore, body weight management should be an important part of the endocrinological treatment in transgender adolescents and young adults.

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