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Cross-sex hormone therapy in transgender persons affects total body weight, body fat, and lean body mass: a meta-analysis

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SUMMARY

Weight gain and body fat increase the risk of cardiometabolic disease. Cross-sex hormone therapy in transgender persons leads to changes in body weight and body composition, but it is unclear to what extent. We performed a meta-analysis to investigate the changes in body weight, body fat and lean body mass during cross-sex hormone therapy in transgender persons. We searched the PubMed database for eligible studies until November 2015. Ten studies reporting changes in body weight, body fat or lean mass in hormone naive transgender persons were included, examining 171 male-to-female and 354 female-to-male transgender people. Pooled effect estimates in the male-to-female group were +1.8 kg (95% CI: 0.2;3.4) for body weight, +3.0 kg (95% CI 2.0;3.9) for body fat, and –2.4 kg (95% CI –2.8; –2.1) for lean body mass. In the female-to-male group, body weight changed with +1.7 kg (95% CI 0.7;2.7), body fat with –2.6 kg (95% CI –3.9; –1.4) and lean body mass with +3.9 kg (95% CI 3.2;4.5). Cross-sex hormone therapy increases body weight in both sexes. In the male-to-female group, a gain in body fat and a decline in lean body mass are observed, while the opposite effects are seen in the female-to-male group. Possibly, these changes increase the risk of cardiometabolic disease in the male-to-female group.

INTRODUCTION

Part of the gender affirming therapy of trans persons is treatment with cross-sex hormones which aims to induce the secondary sex characteristics of the desired sex. Male-to-female trans persons (MtFs) receive anti-androgens and estrogen therapy to induce feminization, and female-to-male trans persons (FtMs) receive androgen therapy to obtain masculinization. Most studies performed on the safety of this therapy found lower or similar cardiovascular morbidity in FtMs compared to control women, while multiple studies in MtFs observed more cardiovascular morbidity in comparison with biological men[1,2]. Possibly lifestyle factors or ethinyl oestradiol use resulting in thrombogenic haemostatic alterations may have contributed to the increased incidence of cardiovascular disease observed in MtFs in these studies.

Another possible explanation is that changes in body weight and body composition during cross-sex hormone therapy (CSHT) play a role in this increased cardiovascular risk in MtFs in comparison with biological men. Current studies suggest that CSHT increases body weight in both MtFs and FtMs[3-5]. Opposite effects for MtFs and FtMs are seen in body composition[4-7]. MtFs show an increase in body fat and a decrease in lean body mass, while a decrease in body fat and an increase in lean body mass are observed in FtMs[2,3,5,8,9]. It is well established that weight gain and body fat are associated with unfavorable cardiovascular risk factors such as dyslipidemia[6,10] and an increased risk of developing type 2 diabetes and hypertension[7,11,12]. Furthermore, obesity, weight gain and high body fat are associated with an increased overall risk of mortality[11-15]. An increase in lean body mass on the other hand has been associated with lower mortality[16].

Studies examining the effects of hormone therapy in hypogonadal men and women found similar effects of estrogen and testosterone therapy on body composition compared to CSHT. Additionally, those studies showed that type and duration of hormone treatment influence the magnitude of changes in body composition. In postmenopausal women, larger effects on body fat and lean body mass were seen in women using oral estrogens in comparison with transdermal estrogens[17]. In elderly men, lean body mass increased more in the group using testosterone injections in comparison with oral administration forms and a larger increase was seen in the first six months of treatment in comparison with a longer follow-up period[18]. Studies in trans persons examining the effects of CSHT on body weight and body composition used various treatment protocols. So far, the potential differential effects of these treatment protocols on body weight and body composition are unknown.

The aim of this study was to investigate the effects of CSHT on total body weight, body fat and lean body mass by performing a meta-analysis. Additionally, we evaluated the effects of different treatment types and varying duration of hormone treatment.

METHODS

Data sources and search method

A systematic search of the PubMed database was performed until 23rd of November 2015 using the following Mesh terms, entry terms, and related key words:

((“Transgendered Persons”[Mesh] OR “Transsexualism”[Mesh]) OR (transgend*[tiab] OR transsex*[tiab] OR transex*[tiab] OR trans-gend*[tiab] OR trans-sex*[tiab])) AND ((“Body Composition”[Mesh] OR “Body Mass Index”[Mesh] OR “Body Weight”[Mesh] OR “Adipose Tissue”[Mesh]) OR (body composition*[tiab] OR body weight*[tiab] OR adipose tissue*[tiab] OR fat tissue*[tiab] OR body fat[tiab] OR body mass[tiab] OR fat mass[tiab] OR lean mass[tiab] OR lean body mass[tiab] OR fat free mass[tiab] OR BMI[tiab])).

The search was performed in collaboration with a medical librarian.

Study selection

All titles and abstracts were screened by MK to select them for further analysis. We included published prospective and retrospective studies in all languages that studied CSHT in transgender individuals and reported data on body weight and/or body composition. Studies describing persons with a history of cross-sex hormone use were excluded to rule out influence of earlier hormone treatment on body weight and body composition. We checked for duplicate studies based on overlapping authorship, study description and number of patients.

Main outcome measures and data extraction

Main outcome measures were total body weight (kilograms [kg]), total body fat (kg) and total lean body mass (kg). Data extraction included numbers of MtFs and FtMs, study design, age, type of therapy and dosage, therapy duration and outcome measures. Means and standard deviations of pre- and post-measurements or absolute or relative change scores with associated *p*-values or confidence intervals were extracted. If studies published unclear results, authors were contacted to obtain the correct data. After examination of our

own data[19], which showed an equal change in both patients with low or high body weight, body fat and lean body mass, we chose to present the results expressed as absolute changes. Results on body fat are presented as relative changes as well.

Statistical analysis

Treatment effects for body weight, body fat and lean body mass were calculated for each study by extraction or calculation of change scores and standard errors. Change scores were calculated as the difference in means between pre- and post-measurements. Standard errors, important to calculate the effect size, were never reported and had to be computed from other reported data such as the standard deviation of the change score or the *p*-value. A detailed description of these methods can be found in Appendix A. The analyses of pooled data to calculate the effect sizes were performed with a random-effects model and only included studies performed after 12 months of therapy.

Publication bias and heterogeneity

To test for evidence of publication bias, we examined a Begg's funnel plot[20]. In addition, we performed a Begg's rank correlation test[21] and the Egger's test[20]. Heterogeneity was assessed for each outcome in MtFs and FtMs. The Cochran's Q statistic, associated *p*-value and I^2 were provided by RevMan 5.3, where I^2 represents the percentage of the variability in effect estimates that is due to heterogeneity rather than change.

Meta-regression

A random-effects meta-regression was performed in Stata version 13.1 (StataCorp LP) to assess the associations between type and duration of treatment and changes in body weight, body fat and lean body mass. Duration of treatment was classified as ≤6, 12 or 24 months of treatment. In MtFs, four types of treatment were examined: cyproterone acetate either in combination with 17ß-estradiol valerate (orally), a 17ß-estradiol patch or ethinyl oestradiol (orally) and goserelin acetate (gonadotropin-releasing hormone analogue (GnRH)) in combination with 17β-estradiol valerate (intramuscularly). In FtMs, the following types of treatment were analyzed: Nebido®, Sustanon®, Testoviron® and Androgel®. In the analyses on type of treatment, only studies with a 12-month follow-up were included. If studies described a group of patients using different types of medication, but did not provide any insight in possible differences between the therapy groups in the result section, they were excluded from meta-regression analysis on type of treatment. Data are expressed as changes in kilograms against the reference group.

Sensitivity analysis

We conducted sensitivity analyses to assess the impact of individual studies on the overall estimate of outcome measures. In these analyses, summary estimates were repeatedly computed, omitting a single study in each cycle, to evaluate its effect on the summary estimate. Another sensitivity analysis was performed to assess whether the use of imputed correlation coefficients, used to calculate the standard errors, influenced the overall result of the analysis.

This meta-analysis only contains published data, so no separate ethics committee approval was needed.

RESULTS

Selected studies

The initial PubMed search yielded 79 articles. All titles and abstracts were explored to determine whether the predefined data could be extracted, which resulted in 17 selected articles. Five studies were excluded because of the use of duplicate patients in articles with different topics[22-26]. One study was excluded[27] because they described patients which had a history of cross-sex hormone use, and another study was excluded because they provided insufficient information[28]. This resulted in ten studies of which seven studies examined the effects on main outcome measures after 12 months of therapy. In MtF, three studies were used in body weight and body fat analyses and two studies were included for lean body mass analyses. In FtMs, all analyses included five studies. The year of publication ranged from 1998 to 2015.

Participant and treatment characteristics

A total of 171 MtFs and 354 FtMs participated in the included studies. Table 1 shows information on each included study. The mean age of the included patients was 32.8 ± 3.6 years for MtFs and 30.1 ± 4.2 years for FtMs.

Types of CSHT used by MtFs were cyproterone acetate or spironolactone in combination with 17β-estradiol (valerate), a 17β-estradiol patch or ethinyl estradiol[3,8,29]. In one study, MtFs used goserelin acetate (GnRH analogue) in combination with 17β-estradiol valerate[4]. FtMs used testosterone undecanoate (Nebido®)[5,9,29-32], Sustanon®[8,32], testosterone cypionate[3], Testoviron®[33,34], testosterone gel[3,5] or a testosterone patch[3]. The dosages and administration routes used in each study are described in Table 1. Treatment duration varied from 3–4 to 24 months.

Changes in body weight, body fat, and lean body mass

Three studies in MtFs (*N*=155) and five studies in FtMs (*N*=211) were available for the analyses of effects of CSHT on total body weight. Most studies in MtFs showed an increase in total body weight, ranging from 0 to 3.7 kg. The pooled estimate of total body weight change was +1.8 kg (95% confidence interval [CI] 0.2;3.4). Studies in FtMs showed effects ranging from 0 to 3.5 kg, with a pooled estimate effect of +1.7 kg (95% CI 0.7;2.7) (Figures 1a and 2a).

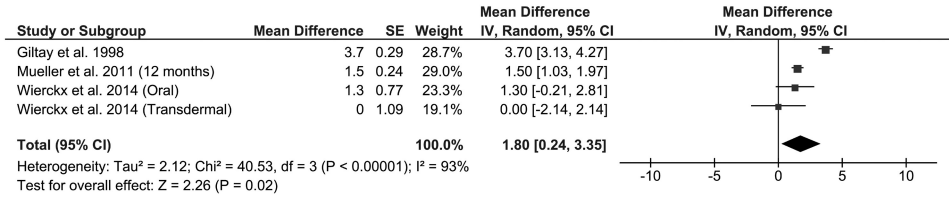
Table 1. Data description of all studies included in this meta-analysis

Study	Population	Age (years)	Study design	Medication	Duration of treatment	Body composition measurement
Deutsch et al. 2015 (3)	16 MtFs	29 ± 9.4	Prospective	Spironolactone 100mg/day[1] + N=14 E2 4mg/day (SL) N=1 E2 patch 100 mcg/day (TD) N=1 E2 valerate 20mg/ 2 weeks (IM)	6 months	-
	31 FtMs	29 ± 6.9		N=28 Testosterone cypionate 50 mg/week (SC)[2] N=2 Testosterone gel 1% 5 mg/day (TD) N=1 Testosterone patch 4mg/day (TD)		
van Caenegem et al. 2015 (8)	23 FtMs	27 ± 9	Prospective	TU 1000mg/12 weeks (IM)*	12 months	DEXA
Wierckx et al. 2014 (18)	53 MtFs	30.3 ± 4.0	Prospective	N=40 CPA 50mg/day + E2 valerate 4mg/day (PO) N=13 CPA 50mg/day + E2 patch 100 mcg/24h (TD)	12 months	DEXA
	53 FtMs	24.6 ± 2.8		TU 1000mg/12 weeks (IM)*		
Pelusi et al. 2014 (4)testosterone gel (50\u2009mg/die; n\u2009=\ u200915	45 FtMs	29.5 ± 1.1	Prospective	N=15 Testoviron 100mg/10 days (IM) N=15 Testosterone gel 50mg/day (TD) N=15 TU 1000mg/12 weeks (IM)*	54 weeks 30 weeks	DEXA
Mueller et al. 2011 (5)	84 MtFs	36.3 ± 11.3	Prospective	Goserelin acetate 3.8 mg/4 weeks (SC) + E2 valerate 10mg/10 days (IM)	12 months 24 months	DEXA
Mueller et al. 2010 (29)	45 FtMs	30.4 ± 9.1	Prospective	TU 1000mg/12 weeks (IM)	12 months 24 months	DEXA
Cupisti et al. 2010 (30)	45 FtMs	29.9 ± 1.1	Prospective	TU 1000mg/12 weeks (IM)	12 months	-
Berra et al. 2006 (32)	16 FtMs	30.4 ± 5.4	Prospective	Testoviron 100mg/10 days (IM)	6 months	BIA
Giltay et al. 2004 (31)	81 FtMs	36.7 (21-61)	Retrospective	N=61 Sustanon 250mg/2 weeks (IM) N=20 TU 240mg/day (PO)	3-4 months	-
Giltay et al. 1998 (9)	18 MtFs	27.0 (18-37)	Prospective	CPA 100mg/day+ Ethinyl estradiol 100 mcg/day (PO)	12 months	BIA
	15 FtMs	23.0 (16-33)		Sustanon 250mg/2 wkn (IM)		

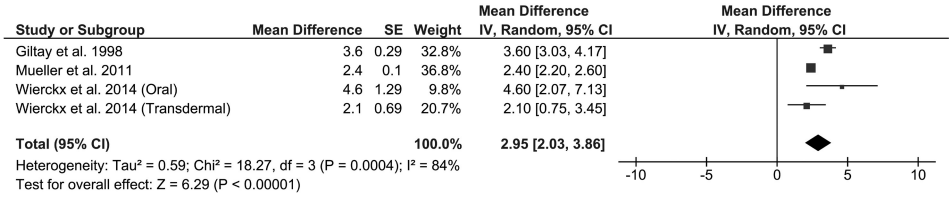
E2: 17-ß Estradiol; CPA: Cyproterone acetate; TU: Testosterone undecanoate, (some studies gave initially an extra dose at 6 weeks); Testoviron: Testosterone enanthate; Sustanon: Testosterone propionate 30 mg, -phenylpropionate 60 mg, -isocaproate 60 mg, –decanoate 100 mg; DEXA: Dual X-ray absorptiometry; SL: sublingual; TD: transdermal; IM: intramuscular; PO: per os; BIA: bioimpedance analyzer.*

[1] 66% of the patients increased to 200mg/day at 3 months.

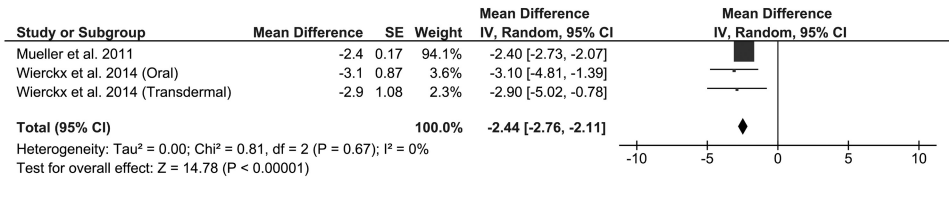
[2] 10 participants were increased to 70 mg/week after 3 months.



a) Body weight (kg) in MtFs

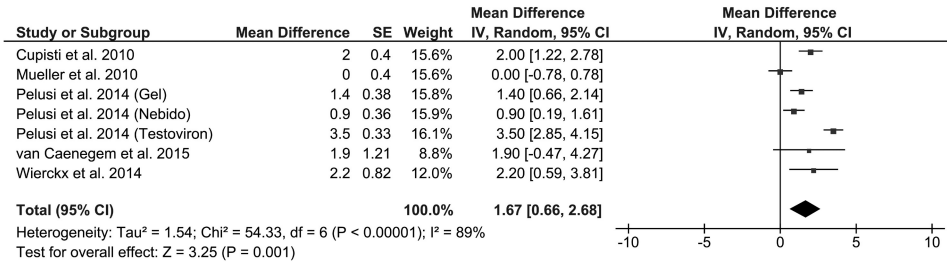


b) Body fat (kg) in MtFs

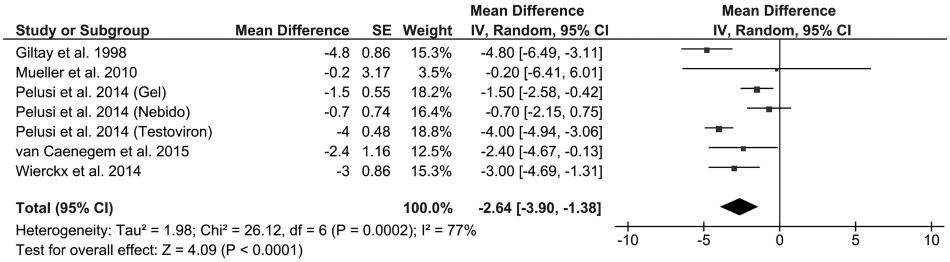


c) Lean body mass (kg) in MtFs

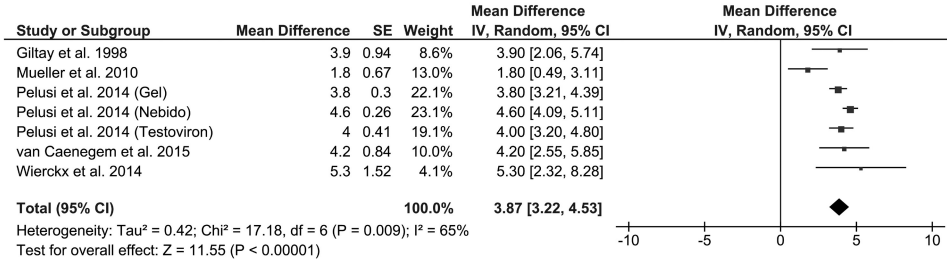
Figure 1. Changes in total body weight, body fat and lean body mass in MtFs.



a) Body weight (kg) in FtMs



b) Body fat (kg) in FtMs



c) Lean body mass (kg) in FtMs

Figure 2. Changes in total body weight, body fat and lean body mass in FtMs.

The same three studies in MtFs (*N*=155) and five studies in FtMs (*N*=181) were included for the analyses of the effects of CSHT on total body fat. All studies in MtFs showed an increase in body fat ranging from 2.1 to 4.6 kg, with a pooled estimate effect of +3.0 kg (95% CI 2.0;3.9). This equals an increase in body fat of 25% (95% CI 12.7;39.9). In FtMs, studies showed changes in body fat ranging from a decrease of –0.2 kg to a decrease in body fat of –4.8 kg. The pooled estimate effect was –2.6 kg (95% CI –3.9; –1.4). This corresponds to a decrease in body fat of –10.5% (95% CI –1.1; –24.2) (Figures 1b and 2b).

Two studies in MtFs (*N*=137) and five studies in FtMs (*N*=181) were used for the analyses of the effects of CSHT on lean body mass. In MtFs, the effects on lean body mass ranged from –2.4 to –3.1 kg. The pooled estimate effect was –2.4 kg (95% CI –2.8; –2.1). Studies in FtMs showed increases in lean body mass ranging from 1.8 to 5.3 kg, with a pooled estimate effect of +3.9 kg (95% CI 3.2;4.5) (Figures 1c and 2c).

Publication bias and heterogeneity

Examination of funnel plots showed considerable symmetry, suggesting there was no publication bias. Additional testing with a Begg's rank correlation and an Egger's test, respectively, showed no publication bias in MtFs for body weight ($p = .45$, $p = .44$), body fat ($p = .81$, $p = .93$) and lean body mass ($p = .50$, $p = .73$). Also in FtMs, no publication bias was found in body weight ($p = .83$, $p = .95$), body fat ($p = .47$, $p = .76$) and lean body mass ($p = .84$, $p = .60$), although this does not rule out any kind of bias.

Substantial heterogeneity was present in analyses in FtMs of body weight ($X^2 = 54.3$, $p < .00001$, $I^2 = 89\%$), body fat ($X^2 = 26.1$, $p = .0002$, $I^2 = 77\%$) and lean body mass ($X^2 = 17.2$, $p = .009$, $I^2 = 65\%$). In MtFs, heterogeneity was found in body weight analyses ($X^2 = 40.5$, $p < .00001$, $I^2 = 93\%$) and analyses of body fat ($X^2 = 18.3$, $p = .0004$, $I^2 = 84\%$) but not in lean body mass analyses ($X^2 = 0.8$, $p = .67$, $I^2 = 0\%$).

Meta-regression

Duration of treatment

In MtFs and FtMs, respectively, one and four studies evaluated the effects on outcome measures at ≤6 months and single studies investigated the effects after 24 months of CSHT. In MtFs, although based on a single study, a trend was seen towards an increase in body weight (+1.2 kg, 95% CI –2.0;4.4) and body fat (+0.6 kg, 95% CI –0.8;2.2) in the second year of therapy, resulting in total increases of +3.0 kg (95% CI 2.4;3.6) in body weight and +3.6 kg (95% CI 3.4;3.8) in body fat after two years of therapy. Furthermore, a decrease in lean body mass (–1.8 kg, 95% CI –2.2; –1.3) in the second year of treatment was observed, resulting in a total decrease of –4.2 kg (95% CI –4.5; –3.9) after two years of treatment. In FtMs, in the first six months, a trend towards a large increase in body weight (+2.5 kg, 95% CI 1.0;4.0) and lean body mass (+6.0 kg, 95% CI 4.4;7.6) was seen, after which these changes from baseline tended to be smaller at 12 and 24 months of therapy (Table 2). Changes in individual studies are illustrated in Figure 3.

Type of treatment

In FtMs, increases in body weight were 1.4 kg for the Androgel® group, 1.2 kg for the Nebido® group and 3.5 kg for persons using Testoviron® with a difference between the last two groups of 2.3 kg (95% CI 0.4;4.1) (Table 2). Body fat decreased more in FtMs using Nebido® (–3.6 kg) in comparison with persons using Testoviron® (–0.7 kg) (difference of 2.9 kg, 95% CI 1.2;4.5) or Androgel® (–1.5 kg) (difference of 2.1 kg, 95% CI 0.8;3.4) (Table 2). FtMs using Sustanon® lost the most body fat (–4.8 kg), logically resulting in even larger differences with the Testoviron® group (difference of 4.1 kg, 95% CI 1.9;6.3) and the Androgel® group (difference of 3.3 kg, 95% CI 1.3;5.3). MtFs using cyproterone acetate (CPA) and ethinyl estradiol tended to gain more body weight (+3.7 kg) than persons using CPA and estradiol valerate (orally) (+1.3 kg) (difference of 2.4 kg, 95% CI 0.0;4.8) (Table 2) and MtFs using CPA in combination with estradiol patches (+0 kg) (difference of 3.7 kg, 95% CI 1.7;5.7).

Table 2. Changes in body weight, body fat, and lean body mass, subdivided into categories of varying type and duration of treatment

	Body weight			Body fat			Lean body mass		
MtF	**Δ from baseline + confidence interval**	**Δ with reference + confidence interval**	**N=**	**Δ from baseline + confidence interval**	**Δ with reference + confidence interval**	**N=**	**Δ from baseline + confidence interval**	**Δ with reference + confidence interval**	**N=**
Duration (months)									
≤6	-0.6 kg (-2.8; 1.6, P=0.59)	-2.4 kg (-6.2;1.4, P=0.22)	N=1	-	-	-	-	-	-
12 (ref)	+ 1.8 kg (0.2;3.4, P=0.02)	-	N=3	+ 3.0 kg (2.0;3.9, P=0.00)	-	N=3	-2.4 kg (-2.8;-2.1, P=0.00)	-	N=3
24	+ 3.0 kg (2.4; 3.6, P=0.00)	+1.2 kg (-2.0;4.4, P=0.47)	N=1	+ 3.6 kg (3.4;3.8, P=0.00)	+ 0.6 kg (-0.8;2.2, P=0.37)	N=1	-4.2 kg (-4.5;-3.9, P=0.00)	-1.8 kg (-2.2;-1.3, P=0.00)	N=1
Type of treatment									
CPA+EV (ref)	+ 1.3 kg (-0.2;2.8, P=0.09)	-	N=1	+ 4.6 kg (2.1;7.1, P=0.00)	-	N=1	-3.1 kg (-4.8;-1.4, P=0.00)	-	N=1
CPA+EE	+ 3.7 kg (3.1;4.3, P=0.00)	+2.4 kg (0.0;4.8, P=0.05)	N=1	+3.6 kg (3.0;4.2, P=0.00)	-1.0 kg (-4.9;2.9, P=0.62)	N=1	-	-	-
CPA+ EP	0 kg (-2.1;2.1, P=1.0)	-1.3 kg (-4.3;1.7, P=0.40)	N=1	+2.1 kg (0.8;3.4, P=0.00)	-2.5 kg (-7.1;2.1, P=0.28)	N=1	-2.9 kg (-5.0;-0.8, P=0.00)	+0.2 kg (-3.1;3.5, P=0.90)	N=1
GnRH+EV	+ 1.5 kg (1.0;2.0, P=0.00)	+0.2 kg (-1.1;2.5, P=0.90)	N=1	+2.4 kg (2.2;2.6, P=0.00)	-2.2 kg (-0.4;-4.0, P=0.02)	N=1	-2.4 kg (-2.7;-2.1, P=0.00)	+0.7 kg (-0.6;2.0, P=0.29)	N=1
FtM									
Duration (months)									
≤6	+ 2.5 kg (1.0; 4.0, P=0.00)	+0.8 kg (-0.8;2.3, P=0.32)	N=4	-2.3 kg (-5.1;0.5, P=0.11)	+ 0.3 kg (-3.8;4.5, P=0.87	N=1	+ 6.0 kg (4.5;7.5, P=0.00)	+ 2.1 kg (-0.1;4.3, P=0.06)	N=1
12 (ref)	+ 1.7 kg (0.7;2.7, P=0.00)	-	N=6	-2.6 kg (-3.9;-1.4, P=0.00)	-	N=5	+ 3.9 kg (3.2;4.5, P=0.00)	-	N=5
24	+ 0.3 kg (-0.6;1.2, P=0.52)	-1.4 kg (-4.1;1.4, P=0.33)	N=1	-0.3 kg (-3.6;3.0, P=0.86)	+ 2.3 kg (-2.2;6.8, P=0.31)	N=1	+ 1.9 kg (0.5;3.3, P=0.00)	-2.0 kg (-4.1;0.2, P=0.07)	N=1
Type of treatment									
Nebido (ref)	+ 1.2 kg (0.4;2.1, P=0.00)	-	N=5	-3.6 kg (-4.3;-2.8, P=0.00)	-	N=4	+ 3.8 kg (2.4;5.3, P=0.00)	-	N=4
Sustanon	-	-	-	-4.8 kg (-6.5;-3.1, P=0.00)	-1.2 kg (-3.1;0.6, P=0.19)	N=1	+ 3.9 kg (2.0;5.8, P=0.00)	+0.1 kg (-3.3;3.4, P=0.97)	N=1
Testoviron	+ 3.5 kg (2.8;4.2, P=0.00)	+ 2.3 kg (0.4;4.1, P=0.02)	N=1	-0.7 kg (-2.1;0.7, P=0.34)	+2.9 kg (1.2;4.5, P=0.00)	N=1	+ 4.0 kg (3.2;4.8, P=0.00)	+0.2 kg (-2.7;3.1, P=0.91)	N=1
Androgel	+ 1.4 kg (0.6;2.2, P=0.00)	+ 0.2 kg (-1.7;2.0, P=0.87)	N=1	-1.5 kg (-2.5;-0.4, P=0.00)	+2.1 kg (0.8;3.4, P=0.00)	N=1	+ 3.8 kg (3.2;4.4, P=0.00)	0 kg (-2.9;2.8, P=0.98)	N=1

CPA: Cyproterone acetate; EV: 17ß-Estradiol valerate; EE: Ethinyl estradiol; EP: 17ß-Estradiol patch; GnRH: Goserelin acetate; Nebido: testosterone undecanoate; Testoviron: Testosterone enanthate; Sustanon: Testosterone propionate 30 mg, -phenylpropionate 60 mg, -isocaproate 60 mg, –decanoate 100 mg;

N: number of included studies.

Data are expressed as changes in kg with (95% confidence intervals and p-values).

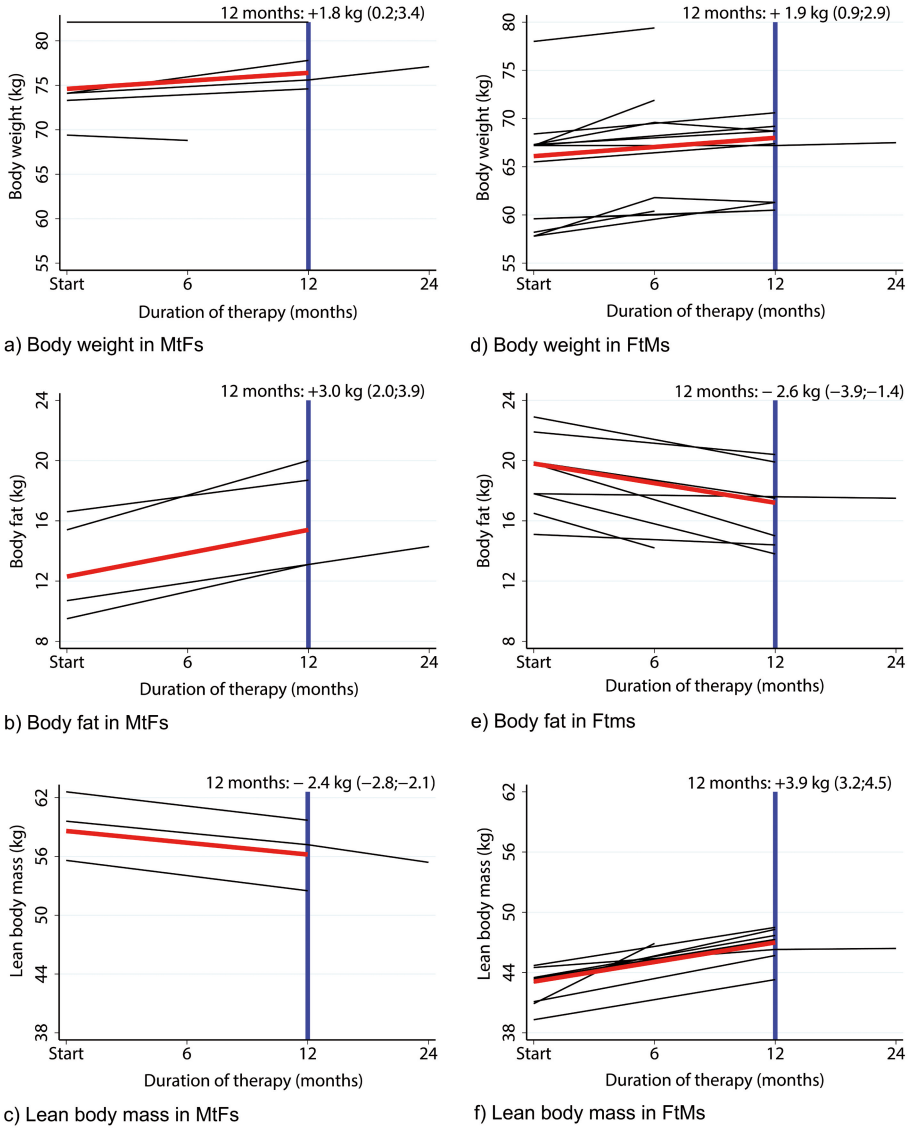


Figure 3. Changes in individual studies in body weight, body fat and lean body mass in MtFs and FtMs.

Sensitivity analyses

Multiple sensitivity analyses were performed including omitting studies one by one, which did not change our overall effect estimates of body weight, body fat and lean body mass remarkably. Another performed analysis showed that the use of varying imputed correlation coefficients seemed to have limited impact on the calculated standard errors.

DISCUSSION

Main findings

This meta-analysis confirms that CSHT increases total body weight in both MtFs and FtMs. In addition, we showed that MtFs experience a gain in body fat with a decrease in lean body mass, while the opposite was observed in FtMs. In MtFs, but not in FtMs, a trend of continuing effects regarding all outcomes was seen in the second year of therapy. Furthermore, we found a larger increase in body weight in FtMs using Testoviron® in comparison with patients using Nebido®. Probably, this is due to the observed smaller decrease in body fat in patients using Testoviron® in comparison with the Nebido® group as no differences in effects on lean body mass between both patient groups were seen. However, as only few studies were included for each type of treatment category, we should be cautious to draw firm conclusions.

Strengths and limitations

This meta-analysis is the first to systematically aggregate data of the effects of CSHT on body weight and body composition. It provides clinicians with an overview of the magnitude of these effects, so clinicians are better able to estimate the consequences of CSHT on body composition and better inform their patients. A limitation of our meta-analysis is that all included studies have an observational design and did not include control groups. Therefore, it is difficult to assess whether the observed effects are due to the CSHT or to other factors such as the normal ageing process. However, the increase in body weight in MtFs and FtMs in the first year of therapy is higher than the mean yearly change in body weight in the general Dutch population (0.67 kg for men and 0.61 kg for women of 20–29 years of age)[35], thereby suggesting a causal effect of the CSHT. Another limitation of our study is that we cannot fully explain the discrepancy between the estimated effects in body fat and lean body mass and the net increase in body weight in MtFs. In MtFs, we found an increase in body fat of 3.0 kg with simultaneously a 2.4 kg decrease in lean body mass, which should result in an increase in body weight of 0.6 kg. However, we

found an increase of 1.8 kg. If we only select the two studies reporting all three outcome measures[4,29], we find a lower weight change of 1.4 kg and a lower increase in body fat of 2.5 kg. This leaves a weight gain of 1.3 kg unexplained. These discrepancies are found in both original studies as well. In FtMs, we do not find this unexplained difference if we only select studies reporting all three outcome measures. Probably, the use of different measuring instruments as the weighing scale and the dual-energy X-ray absorptiometry (DEXA) or rounding to the nearest (half-) kilogram may explain these differences.

Mechanisms of action of sex steroid hormones

Sex steroids might have direct and indirect effects on body fat and lean body mass. Direct effects could be due to the binding of estrogens to estrogen receptors stimulating pre-adipocyte proliferation[36] and lipoprotein lipase (LPL) activity which promotes body fat storage[37]. In contrast, the binding of testosterone to androgen receptors inhibits LPL activity and increases adipose tissue lipolysis[38]. Furthermore, androgens stimulate an increase in muscle protein synthesis by inhibiting their differentiation into adipogenic cells and promoting their differentiating into cells of the myogenic lineage[39]. Indirect effects are explained by the binding of estradiol to estrogen receptors (ERα) in the hypothalamus, or elsewhere in the brain, which may represent a mechanism by which estradiol regulates energy expenditure, leptin sensitivity, body weight, body fat distribution and possibly physical activity[37,40]. Also, estrogen is believed to regulate food intake by decreasing appetite simulating neuropeptides, such as neuropeptide Y, ghrelin and melanin-concentrating hormone, and interacting with appetite suppressing neuropeptides such as insulin, serotonin, cholecystokinin and leptin[40].

Clinical implications

The increase in body weight and body fat in MtFs may have a negative impact on their cardiovascular risk profile and might partly explain the increased occurrence of cardiovascular disease. Although FtMs gain body weight, this is attributable to an increase in lean body mass which actually might have a positive influence on their cardiometabolic risk profile. Clinicians should inform their patients in an early stage about these potential negative effects of CSHT, so that patients can start with lifestyle interventions if necessary and optimize other risk factors such as smoking, blood pressure or cholesterol levels.

Our study may have implications for other patient groups as well. Comparing our results with previous studies, our study found that, as observed in post-menopausal women[17], therapy with oral estrogens tended to increase body fat more than transdermal estrogens.

Similar to a study performed in elderly men[18], in FtMs, lean body mass tended to increase most in the first six months of therapy with a decline in lean body mass after that. This may imply that estrogen or testosterone therapy acts similarly in biological men and women compared to MtFs and FtMs. Furthermore, our observations in MtFs resemble the changes in body composition as seen in ageing men (with low testosterone levels) or hypogonadal men with prostate cancer, in which lean body mass decreases and body weight and body fat increases with about the same amount as we observed in MtFs[39]. This may indicate that changes in body composition in biological men or MtFs are mainly due to changes in testosterone levels.

Future research

Large prospective studies with multiple treatment protocols and a longer follow-up are needed to examine the effects of CSHT on the long term and the differences between the several types of treatment. Because fat stored in the visceral area (in and around organs) may exert higher cardiometabolic risk than total fat mass, future studies should focus on visceral fat. Furthermore, there is a need for studies examining the underlying mechanisms influencing body weight and body composition during CSHT, such as the effects of CSHT on metabolic rate. Finally, prospective studies with a longer follow-up time are needed to investigate the consequences of these changes in body weight and body composition on the development of type 2 diabetes and cardiovascular disease in MtFs and FtMs.

CONCLUSIONS

CSHT increases body weight in both MtFs and FtMs. In MtFs, a gain in body fat and a decline in lean body mass are observed, while the opposite effects are seen in FtMs. Possibly, these changes in MtFs increase their risk of cardiometabolic disease. As a small number of studies were included, no firm conclusions can be drawn on the effects of different treatment types and varying duration of hormone treatment.

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APPENDIX A DESCRIPTION OF THE EXTRACTION OR CALCULATION OF THE CHANGE SCORES AND STANDARD ERRORS.

Change scores and standard errors for body weight, body fat and lean body mass were derived from the papers to obtain pooled effect estimates. In case when changes scores were presented as an effect estimate with an 95% confidence interval, the standard error could easily be calculated from the formula of the confidence interval (± 1.96*SE).

One study[31] presented the standard deviation of the change score, so the standard error could be easily determined. Some studies[8,29,31,32] presented an *p*-value derived from a test using a t-distribution, so the standard error could be calculated through the t-statistic. For upper boundary *p*-values, for example $p<0.05$, we used the upper bound to calculate the standard error.

However, most studies presented their results as pre- and post-measurements showing the mean and standard deviation of the pre- and post-measurement without mentioning a *p*-value or confidence interval. In those cases, the standard error (SE) could be determined using this formula:

$$SE = \sqrt{\left(\frac{S1^2}{n1} + \frac{S2^2}{n2}\right) - 2(r12)\left(\frac{S1}{\sqrt{n1}}\right)\left(\frac{S2}{\sqrt{n2}}\right)}$$

where
n1= number of persons in the pre-measurement
n2= number of persons in the post-measurement.
r12= correlation coefficient
S1= standard deviation in the pre-measurement
S2= standard deviation in the post-measurement

To use this formula, the assumption was made that the correlation coefficient (r12), between the pre- and post-measurement, was similar across studies, as recommended by Follmann et al.[41] and previously used in published meta-analysis[42]. A weighted mean correlation coefficient was derived for each outcome measure in MtFs and FtMs from studies performed after 12 months of therapy. As no correlations were described, these

were calculated for each study reporting (or providing enough data to exactly calculate) the standard deviations of the pre-measurement, the post-measurement and the change score of each outcome measure after a treatment duration of 12 months. In MtFs, a correlation coefficient was used of r=0.96 for body weight[29], r=0.89 for body fat[29], and r=0.91 for lean body mass[29]. In FtMs, a correlation was used of r=0.93 for body weight[29], r=0.77 for body fat[31], and r=0.81 for lean body mass[31]. Aforementioned formula was also used to calculate the standard error in studies presenting *p*-values derived from nonparametric tests.

Some studies presented data on body mass index (BMI), for which change scores and standard deviations for body weight were extracted. A weighted average of total body weight and its standard deviation at baseline were extracted from all studies reporting data on body weight, resulting in 74.1 ± 4.2 kg for MtFs[3,29] and 67.2 ± 7.1 kg for FtMs[3,5,29,33]. In each study reporting data on BMI, the ratio of BMI scores and standard deviations (BMI-post / BMI-pre) were multiplied by the above-mentioned weighted average and standard deviation, to calculate the change score with standard deviation for body weight.

If medians and interquartile ranges were presented[3], a normal distribution was assumed and a mean and standard deviation were derived. If no standard deviation of the post-measurement was reported[8], the given standard deviation of the pre-measurement was imputed.