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CLINICAL STUDY

Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis

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Abstract

Objective: Few randomized clinical studies have evaluated the impact of diet and physical activity on testosterone levels in obese men with conflicting results. Conversely, studies on bariatric surgery in men generally have shown an increase in testosterone levels. The aim of this study is to perform a systematic review and meta-analysis of available trials on the effect of body weight loss on sex hormones levels.

Design: Meta-analysis.

Methods: An extensive Medline search was performed including the following words: 'testosterone', 'diet', 'weight loss', 'bariatric surgery', and 'males'. The search was restricted to data from January 1, 1969 up to August 31, 2012.

Results: Out of 266 retrieved articles, 24 were included in the study. Of the latter, 22 evaluated the effect of diet or bariatric surgery, whereas two compared diet and bariatric surgery. Overall, both a low-calorie diet and bariatric surgery are associated with a significant ($P<0.0001$) increase in plasma sex hormone-binding globulin-bound and -unbound testosterone levels (total testosterone (TT)), with bariatric surgery being more effective in comparison with the low-calorie diet (TT increase: 8.73 (6.51–10.95) vs 2.87 (1.68–4.07) for bariatric surgery and the low-calorie diet, respectively; both $P<0.0001$ vs baseline). Androgen rise is greater in those patients who lose more weight as well as in younger, non-diabetic subjects with a greater degree of obesity. Body weight loss is also associated with a decrease in estradiol and an increase in gonadotropins levels. Multiple regression analysis shows that the degree of body weight loss is the best determinant of TT rise ($B=2.50\pm0.98$, $P=0.029$).

Conclusions: These data show that weight loss is associated with an increase in both bound and unbound testosterone levels. The normalization of sex hormones induced by body weight loss is a possible mechanism contributing to the beneficial effects of surgery in morbid obesity.

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Introduction

Obesity is a complex condition with serious social and psychological dimensions, which affects virtually all age and socioeconomic groups and threatens to overwhelm both developed and developing countries. Recently, Finucane *et al.* (1) estimated the trends of BMI for adults aged 20 years and older in 199 countries and territories. Between 1980 and 2008, age-standardized mean BMI for men increased in every region apart from Central Africa and South Asia, with USA and UK being highest. The global change worldwide was 0.4 kg/m^2 per decade for men. Accordingly, the worldwide, age-standardized prevalence of obesity was 9.8% in men in 2008, which was nearly twice the 1980 prevalence of 4.8% (1). Contrary to conventional wisdom, the obesity epidemic is not restricted to developed societies. Accordingly, a recent large population-based study involving more than 3400 subjects from eight European centers (EMAS study) showed that about half of subjects were overweight or obese with an even higher prevalence in Eastern transitional countries (2). Excess body weight is a crucial risk factor for mortality and morbidity not only for cardiovascular diseases (CVD) but also for type 2 diabetes mellitus (T2DM), cancer, and musculoskeletal disorders; these complications cause nearly 3 million deaths every year worldwide (3, 4, 5, 6, 7, 8). Despite this evidence, obesity is one of today's most blatantly visible – yet most neglected – public health problems.

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Several studies have demonstrated that, in individuals at risk, intensive lifestyle interventions, which include nutritional counseling and physical activity, are able to reduce body weight and insulin resistance, preventing the progression to overt T2DM and CVD (9, 10, 11, 12). However, many observational studies have shown that most of the weight lost with diet and exercise is regained in the long term, at least in the majority of patients (13). Bariatric surgery is another possibility to rapidly reduce body weight in individuals at risk, with beneficial effects in obesity-related metabolic disturbances. A meta-analysis of observational studies of bariatric surgery involving 3188 patients with T2DM has reported that 78% had normalization of blood glucose in the absence of medications (14). However, available randomized trials are still very few and of limited size and duration (15, 16). Furthermore, some recent observational studies have suggested caution about the benefits of bariatric surgery, showing no improvement in mortality when compared with standard care (17) and a high rate of long-term surgical complications especially for laparoscopic gastric banding procedures (18).

It is known that obesity in men is associated with low testosterone and reduced sex hormone-binding globulin (SHBG) levels (19, 20, 21, 22, 23). An obesity-associated decline in SHBG might partially explain the observed fall in testosterone levels (19, 20, 21, 22, 23). However, it is important to note that an increased BMI was associated with a low measured, or calculated, free and bioavailable testosterone (24). Specific pathogenetic mechanisms involved in this phenomenon are complex and not completely understood. Evidence indicates that testosterone deficiency induces increased adiposity while increased adiposity induces hypogonadism (22, 25). Few randomized clinical studies have specifically evaluated the impact of diet and physical activity on testosterone levels in obese men. The results of these studies are essentially conflicting: some of them showed an increase of testosterone (26, 27, 28, 29, 30, 31, 32, 33, 34), others showed no change (35, 36, 37, 38, 39), and one small study has shown even a decrease in testosterone levels (40). Similarly, in the last 10 years, several trials have evaluated the impact of bariatric surgery on testosterone levels in men generally, showing an increase in testosterone levels (41, 42, 43, 44, 45, 46, 47, 48).

The aim of this study was to perform a systematic review and meta-analysis of available trials on the effect of body weight loss on sex hormones levels.

Materials and methods

A meta-analysis was performed including all studies, comparing testosterone levels before and after the diet or bariatric surgery. An extensive Medline, Embase, and Cochrane search was performed including the following words: 'testosterone', 'diet', 'weight loss', and 'bariatric surgery'. The search, which accrued data from January 1, 1969 up to August 31, 2012, was restricted to English language articles and studies of human participants. Only studies with an observational period of at least 2 weeks were considered.

The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (G Corona and G Rastrelli), and conflicts resolved by the third investigator (M Monami). The quality of studies was assessed using the Cochrane criteria (49).

Completed but still unpublished trials were identified through a search of the www.clinicaltrials.gov website and the results, when not already available on the website, were obtained through a formal request to the authors.

Statistical analysis

Heterogeneity studies were assessed using the I^2 statistics for total testosterone (TT). Considering that heterogeneity could not be excluded ($I^2 = 51.236\%$), mean differences in TT, SHBG, estradiol (E_2), calculated free testosterone (cFT), LH, and FSH between subjects before and after the diet or bariatric surgery were calculated using both a random- and fixed-effect model. For a more conservative approach, results of random-effect models are presented; fixed-effect model is presented only when it differed from the random-effect model. In addition, in some trials, significance of between-group comparisons (P) was not reported; these studies could not be included in the analysis described above. As a consequence, a sensitivity analysis was performed, evaluating endpoint values of each parameter in different treatment groups, in a non-paired fashion (non-paired analysis). Given that most of the studies that did not describe P values reported a non-significant difference across groups, the mean (paired) analysis, which excludes these data, is likely to overestimate the effect of treatments. On the other hand, the non-paired analysis is a very conservative approach, which could underestimate the treatment effect. Meta-regression analysis was performed to test the effect of age, BMI, diabetes, and delta of weight before or after any body-weight-loss interventions on TT and E_2 levels. In addition, different linear age-adjusted regression analysis models, weighting each study for the number of subjects enrolled, were performed to verify the independent effect of baseline BMI and DM as well as percent reduction in BMI (Δ-BMI) and E_2 (Δ-E_2) on TT after weight loss. A further multivariate model was performed, considering Δ-TT as the dependent variable and baseline TT, baseline BMI, and Δ-BMI as covariates.

All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA).

Multivariate analyses were performed on Statistical Package for the Social Sciences (SPSS) for Windows 17.1.

Results

Out of 266 retrieved articles, 24 were included in the study. Of the included studies (see the trial flow summary in Fig. 1), 22 evaluated the effect of diet or bariatric surgery, whereas two compared diet and bariatric surgery. The characteristics of the trials included in the meta-analysis are summarized in Table 1.

Effect of Diet or bariatric surgery on hormonal modifications

Studies comparing the effect of diet or bariatric surgery on hormonal parameters enrolled 479 patients with a mean follow-up of 38 weeks. In particular, 13 studies evaluated the effect of low-calorie diet, whereas 11 investigated the role of bariatric surgery (two gastroplasty, six biliopancreatic diversion, and three mixed interventions respectively). Information on TT, SHBG, and cFT, according to Vermeulen's formula, was available in 23, 15, and nine studies respectively. In addition, data on E_2, FSH, and LH were available in 14, 10, and 10 studies respectively. The mean percent body weight loss at endpoint was $9.8 \pm 4.5\%$ in the low-calorie diet and $32.0 \pm 5.4\%$ in bariatric surgery.

The Begg adjusted rank correlation test (Kendall's $\tau = 0.02$, $P = 0.88$), calculated on the basis of TT, suggested no major publication bias.

The results of fixed-effect models were not different from those of random-effect models; therefore, only the latter will be reported. When considering data on TT, both low-calorie diet and bariatric surgery were associated with a significant ($P < 0.0001$) increase in plasma TT, with bariatric surgery being more significantly effective in comparison with the low-calorie diet (Fig. 2A). In particular, malabsorptive surgery (including studies which performed biliopancreatic diversion, see references (35, 43, 44, 46, 50)) determined a more consistent increase in TT when compared with non-malabsorptive surgery (including studies which performed gastroplasty approach, see references (41, 42)) (11.58 (7.12–16.03) vs 6.08 (2.38–9.78) nmol/l, respectively; both $P < 0.0001$). However, the latter was not confirmed after adjusting for percent weight loss of BMI (Δ-BMI).

Meta-regression analysis showed that differences in TT, after any approach for body weight loss, were significantly higher in patients with higher TT at baseline as well as in younger and more obese subjects (Fig. 3A, B and C). Furthermore, a higher Δ-BMI was associated with a higher testosterone increase (Fig. 3D). The prevalence of diabetes at baseline was, conversely, inversely related to the TT increase after body weight loss (Fig. 3E). However, meta-regression analysis did not show any association between the Δ-E_2 and TT modifications after weight loss (data not shown).

In order to evaluate the major determinants of the percent increase in TT after weight loss (Δ-TT), alternative, age-adjusted, stepwise, logistic regression analyses were explored using Δ-TT as the dependent variable and baseline TT, BMI, and DM as well as percent reduction in BMI (Δ-BMI) and E_2 (Δ-E_2) after body weight loss as putative predictors. Baseline TT, BMI, and Δ-BMI as well as the percent increase in SHBG (Δ-SHBG) were all significantly associated with Δ-TT ($B = 5.16 \pm 2.13$, $P = 0.022$; $B = 2.51 \pm 0.84$, $P = 0.007$; $B = 2.76 \pm 0.71$, $P = 0.001$; and $B = 0.70 \pm 0.24$, $P = 0.013$ respectively), whereas no association between Δ-TT and Δ-E_2 or DM at baseline was observed after adjusting for age (data not shown). When a further model was performed considering Δ-TT as the dependent variable and baseline TT, BMI, and Δ-BMI as covariates, only Δ-BMI retained a significant association with Δ-TT ($B = 2.50 \pm 0.98$, $P = 0.029$).

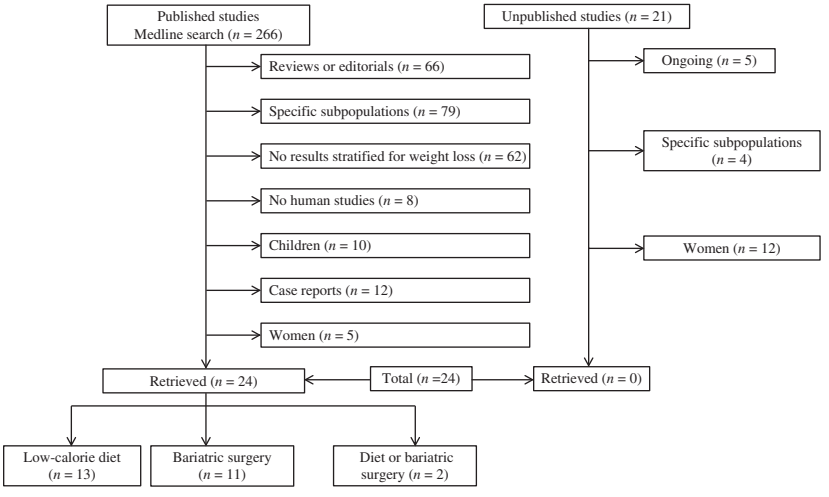


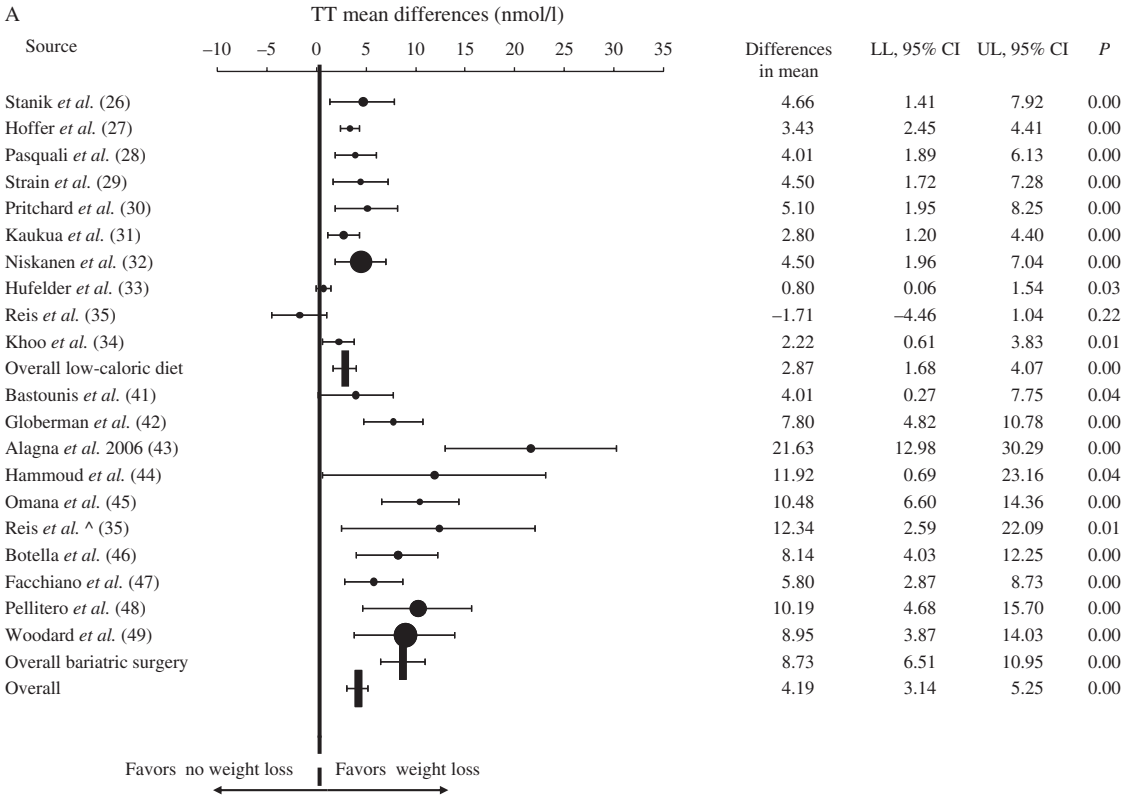
Figure 1 Trial flow diagram. Unpublished studies were identified through a search of the www.clinicaltrials.gov website.

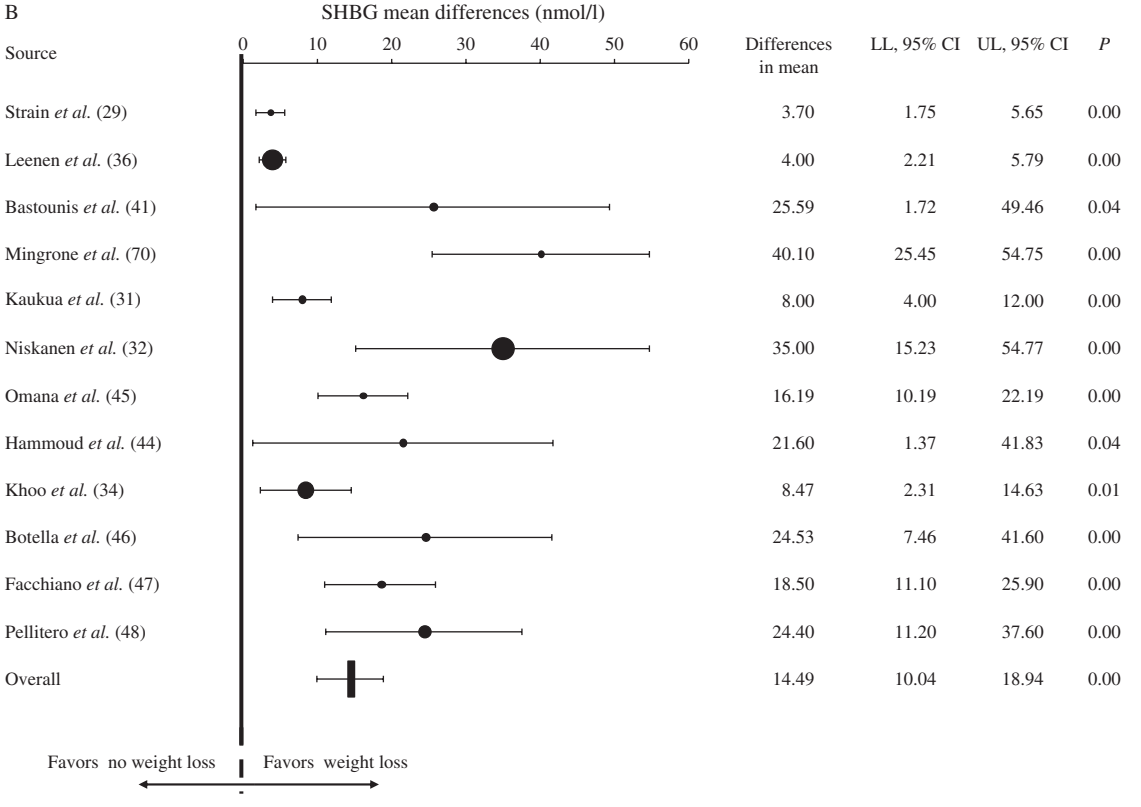
Table 1 Moderators and outcome variables in individual studies included in the meta-analysis. All data are reported as mean±S.D.

Study	Location	Int.	Type of study	FU (weeks)	Age (years)	BMI (kg/m^2)	DM (%)	TT (nmol/l)	LH (U/l)	FSH (U/l)	SHBG (nmol/l)	cFT (pmol/l)	E_2 (pg/ml)
Stanik *et al.* (26)	Sepulveda, CA, USA	LCD	BA	8	–	–	4.2	13.9±3.4	–	–	–	–	36.0±14.7
Hoffer *et al.* (27)	Boston, MA, USA	LCD	BA	4	34.0±7.0	33.1	0	13.0±1.0	–	–	–	–	–
Pasquali *et al.* (28)	Bologna, Italy	LCD	BA	10	35.2±5.6	43.4±6.3	22.2	11.9	8.4	8.8	9.0	–	45
Strain *et al.* (29)	New York, NY, USA	LCD	BA	68	34.0±11.0	–	0	8.3±4.0	10.3	6.5±4.7	9.2±3.2	–	54.0±26.0
Leenen *et al.* (36)	Utrecht, The Netherlands	LCD	BA	13	40.0±6.0	30.7±2.2	0	12.7±3.2	–	–	17.0±6.0	–	27.7±7.9
Pritchard *et al.* (30)	Laval, Canada	LCD	BA	13	21.0±0.8	26.2±5.5	0	12.3±4.1	–	–	–	–	–
Kraemer *et al.*[a] (37)	Pennsylvania, USA	LCD	RCT	12	39.7±6.6	33.1	0	15.9±7.7	–	–	–	–	–
Kraemer *et al.*[b] (37)	Pennsylvania, USA	LCD	RCT	12	38.0±8.2	31.3	0	17.4±4.2	–	–	–	–	–
Kraemer *et al.*[c] (37)	Pennsylvania, USA	LCD	RCT	12	39.6±6.6	29.2	0	18.1±5.2	–	–	–	–	–
Volek *et al.* (38)	Storrs, CT, USA	LCD	BA	6	36.0±11.9	–	0	21.5±7.6	–	–	42.8±32.0	–	–
Mingrone *et al.* (70)	Rome, Italy	LCD	RCT	54	–	47.8±8.8	0	–	–	–	19.7±11.0	–	–
Kaukua *et al.* (31)	Helsinki, Finland	LCD	RCT	10	45.9±9.0	39.3±3.3	5.3	11.1±3.4	3.6±2.2	4.9±2.8	29.0±14.0	201.3±58.9	–
Niskanen *et al.* (32)	Kuopio, Finland	LCD	BA	9	46.3±7.5	36.1±3.8	24.0	11.2±3.9	–	–	27.6±11.9	185.0±66.0	12.1±1.1
Hufelder *et al.* (33)	Berlin, Germany	LCD	RCT	52	55.9±6.0	32.5±2.4	100	10.4±0.8	–	–	39.7±8.0	–	–
Reis *et al.* (35)	São Paulo, Brazil	LCD	RCT	104	42.2±10.5	54.0±6.7	0	11.7±5.1	4.7±1.5	3.4±1.6	–	–	37.2±11.2
Khoo *et al.* (34)	Adelaide, Australia	LCD	CBA	8	49.6±11.0	34.4±4.0	38.8	20.2±6.9	–	–	22.2±8.7	507.0±300.6	–
Khoo *et al.* (39)	Adelaide, SA, Australia	LCD	RCT	52	62.3±5.9	35.6±4.8	100	13.9±3.3	–	–	30.4±13.9	296.0±47.0	–
Khoo *et al.*[d] (39)	Adelaide, SA, Australia	LCD	RCT	52	58.1±11.4	35.1±4.3	100	11.7±3.6	–	–	22.5±9.3	285.0±87.0	–
Bastounis *et al.* (41)	Athens, Greece	BS[e]	BA	52	34.7±7.7	57.1±7.4	0	12.3±6.2	2.4±1.6	2.9±2.0	20.3±16.8	–	64.4±24.9
Mingrone *et al.* (70)	Rome, Italy	BS[f]	RCT	54	–	48.0±5.4	0	–	–	–	13.2±6.5	–	–
Globerman *et al.* (42)	Tel-Aviv, Israel	BS[e]	BA	46.4	38.2±10.1	44.3±6.8	35.3	13.4±7.2	4.9±3.2	8.0±5.6	–	–	11.1±3.4
Alagna *et al.* (43)	Sassari, Italy	BS[f]	BA	52	–	47.3	75	9.6±3.7	2.4±1.6	2.9±1.9	–	–	44.0±29.0
Hammoud *et al.* (44)	Salt Lake City, UT, USA	BS[f]	CBA	104	48.9±9.6	46.2±7.2	–	11.8±5.9	–	–	–	244.3±9.9	39.0±26.7
Omana *et al.* (45)	St Louis, MO, USA	BS[g]	BA	52	48	48.3	43.2	10.6±	5.1	13.4	35.9	199.0	34.4
Reis *et al.* (35)	São Paulo, Brazil	BS[f]	RCT	104	36.7±11.5	55.7±7.8	0	11.7±4.5	4.8±1.7	4.0±3.4	–	–	47.8±15.5
Botella *et al.*[h] (46)	Madrid, Spain	BS[f]	BA	24	40.0±10.3	47.1±6.0	35	10.1±3.5	3.2±2.2	4.2±2.2	18.3±8.3	258.0±100.4	37.6±13.4
Facchiano *et al.* (47)	Florence, Italy	BS[g]	BA	24	39.2	45.7±6.3	25	8.6±3.1	2.8±1.9	3.7±2.5	19.6±7.6	219.0±62.6	43.8±13.4
Pellitero *et al.* (48)	Barcelona, Spain	BS[g]	BA	52	40.5±9.9	50.3±6.1	15.2	8.6±3.2	–	–	18.3±11.8	230.2±82.6	42.3±9.9
Woodard *et al.* (50)	Stanford, CA, USA	BS[f]	BA	52	48.1±10.4	48.2±12.0	42.0	9.0±4.0	–	–	–	–	–

Int., intervention; LCD, low-calorie diet; BS, bariatric surgery; FU, follow-up (weeks); DM, diabetes mellitus; TT, total testosterone; E_2, estradiol; SHBG, sex hormone-binding globulin; cFT, calculated free testosterone; BA, controlled cohort before-and-after comparisons in the same group of patients; RCT, randomized controlled trials; CBA, controlled before-and-after study between two or more groups of participants receiving different interventions.

[a]Low-calorie diet-only group.
[b]Low-calorie diet and aerobic exercise three-times-a-week group.
[c]Low-calorie diet and aerobic and strength training three-times-a-week group.
[d]Low-energy diet group.
[e]Gastroplasty approach.
[f]Biliopancreatic diversion.
[g]Mixed interventions.
[h]High-protein, low-fat diet group.





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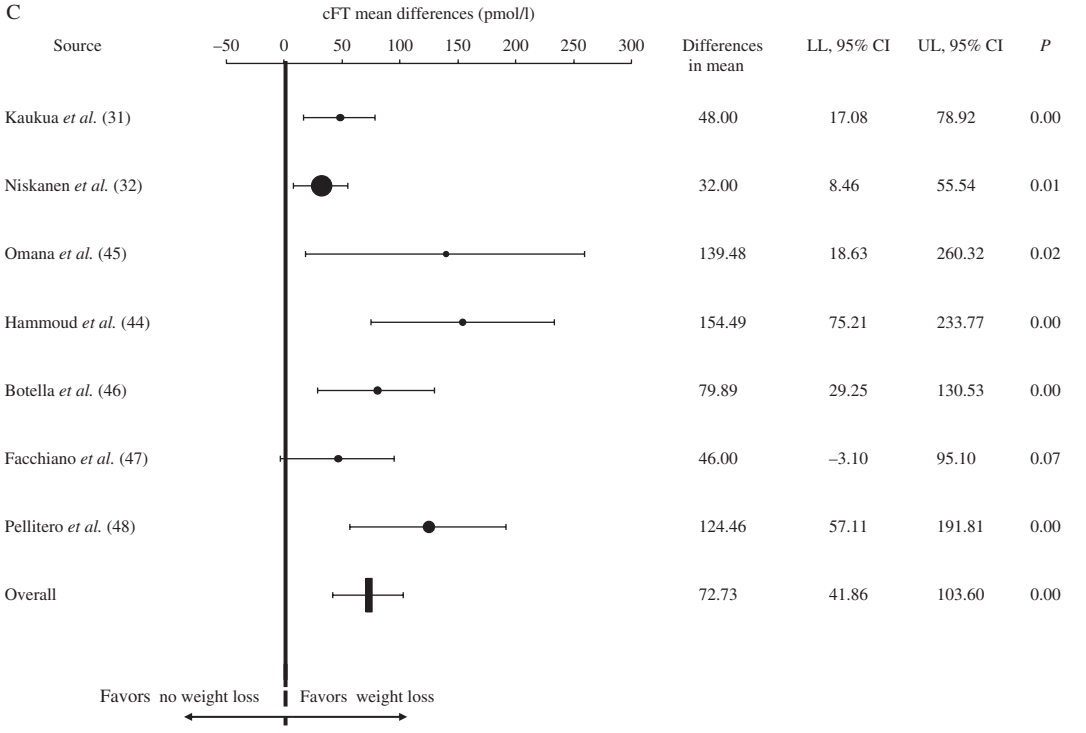

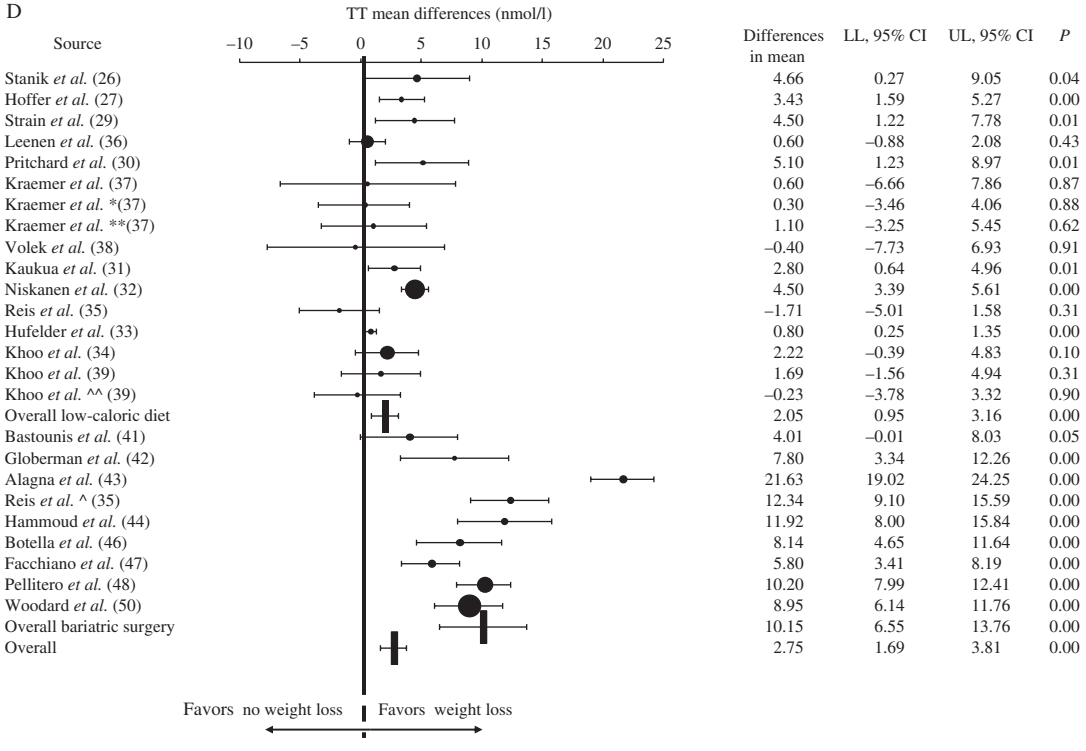

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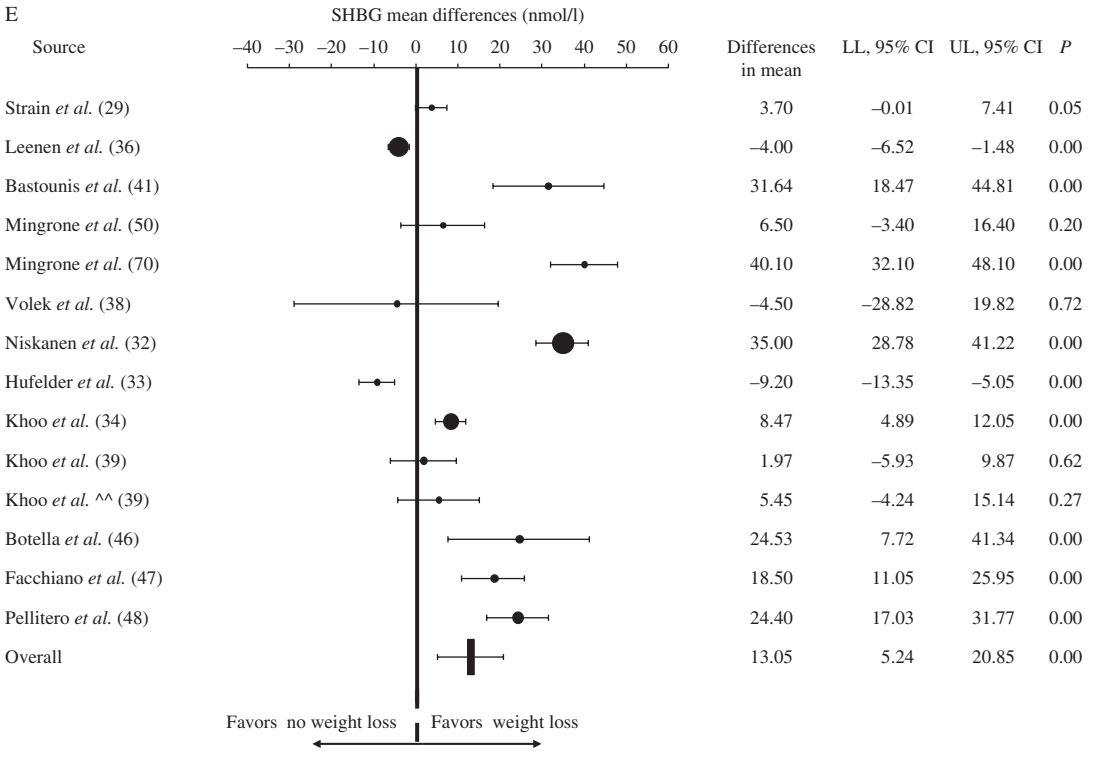


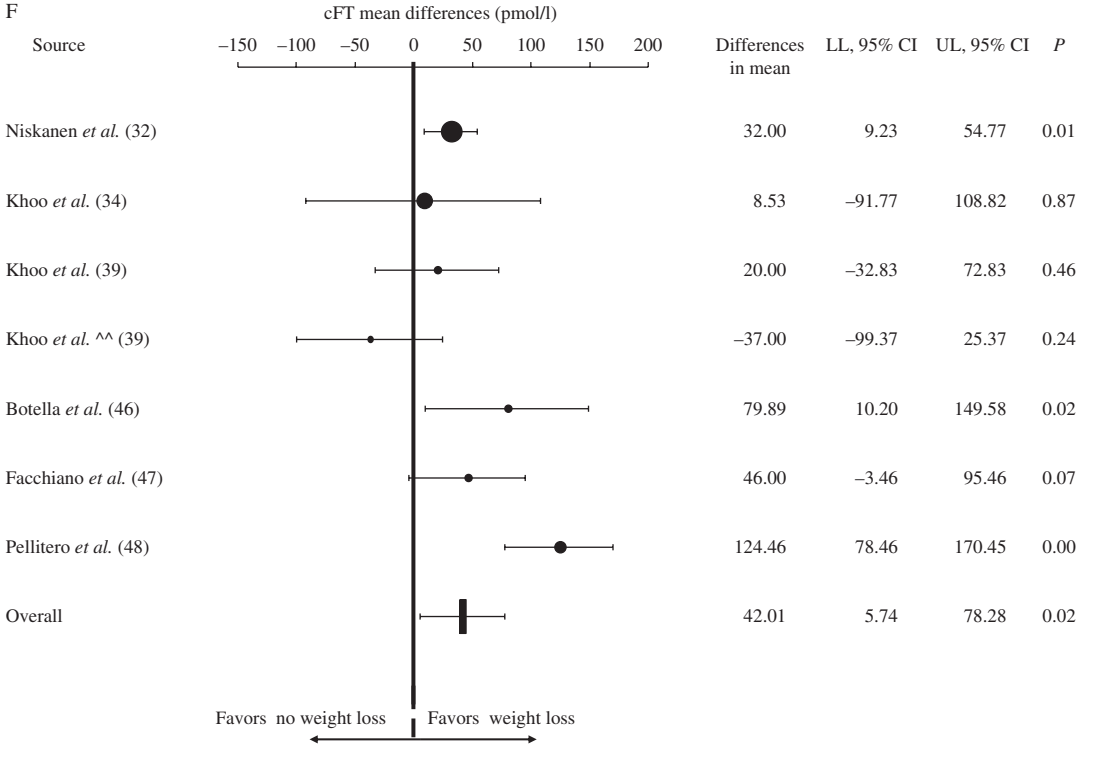


Figure 2 Weighted differences (with 95% CI) of mean total testosterone (TT), sex hormone-binding globulin (SHBG), and calculated free testosterone (cFT) before and after weight loss. Data are presented as derived from the paired *t*-test (A, B and C) and from non-paired analyses (D, E and F). ^Bariatric surgery group; ^^high-protein, low-fat diet group; *low-calorie diet and aerobic exercise three-times-a-week group; and **low-calorie diet and aerobic and strength training three-times-a-week group. LL, lower limit; UL, upper limit.

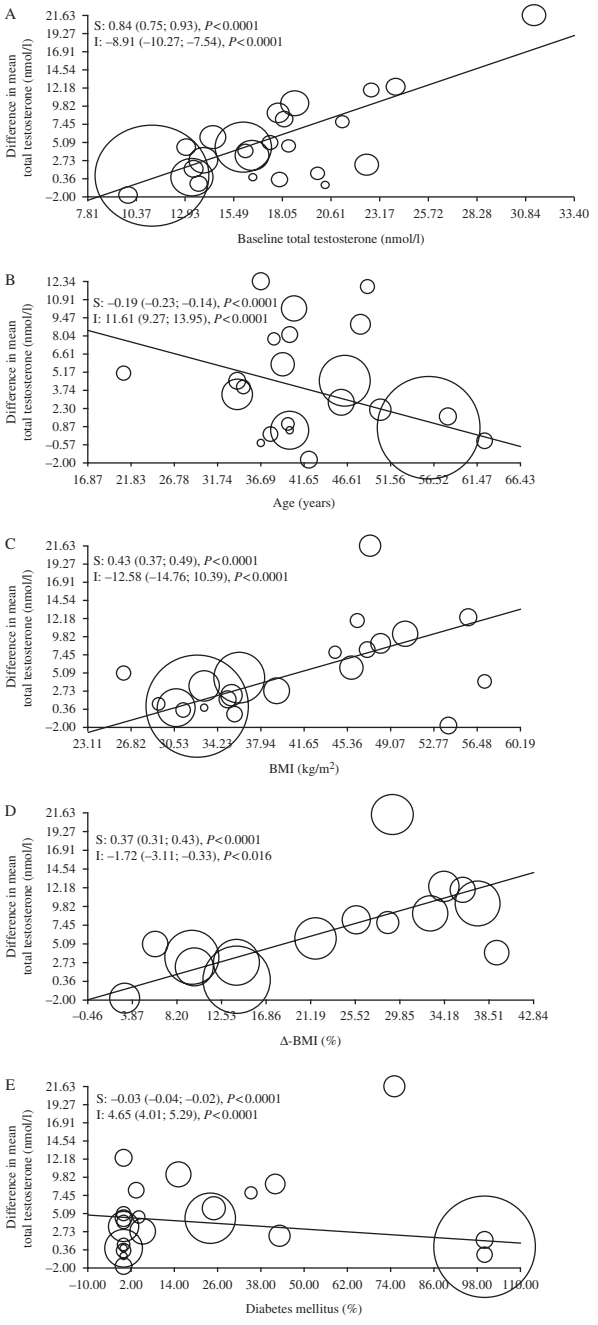


Figure 3 Influence of baseline total testosterone (TT; A), age (B), BMI (C), percent BMI loss (D), and diabetes mellitus (DM; E) on TT weighted mean differences before and after body weight loss. I, interception; S, slope.

Similar to what was observed for TT, SHBG ($P<0.0001$) and cFT levels significantly increased after body weight loss ($P<0.0001$; see also Fig. 2B and C). No subgroup analyses for the body-weight-loss reduction approach were performed for SHBG and cFT, due to insufficient available data. All these data were confirmed when non-paired analyses were applied (Fig. 2D, E and F).

When considering data on E_2, body weight loss was associated with a significant reduction in plasma E_2 (mean changes -8.87 (-15.22; -2.52) pmol/l, $P<0.0001$; Fig. 4A). The data were confirmed when non-paired analysis was applied (Fig. 4B). No subgroup analyses for the body-weight-loss reduction approach and no meta-regression analyses were performed for E_2, due to insufficient data.

Finally, body weight loss, whatever obtained, was significantly associated with a significant increase in both LH and FSH levels (1.31 (0.80–1.82) and 1.79 (1.28–2.30) U/l for LH and FSH, respectively; both $P<0.0001$, see also Fig. 5A and B). No subgroup analyses for the body-weight-loss reduction approach were performed for LH and FSH due to insufficient available data. All these data were confirmed when non-paired analyses were applied (Fig. 5C and D).

Discussion

This meta-analysis shows that body weight loss is associated with a relevant increase in gonadotropins and in bound and unbound testosterone, with a decline in the estrogen level. Androgen rise is greater in those patients who lose more weight. The beneficial effects of body weight loss are more apparent in younger, non-diabetic subjects with a greater degree of obesity; however, this could be due to a greater body weight loss.

It is well known that in morbidly obese men, LH levels and pulse amplitude were attenuated, when compared with normal-weight controls (51, 52). Conversely, no modification of LH pulse frequency has been reported in obese men (51, 52). Based on these and other studies (53, 54), obesity-related male hypogonadism is now considered as a form of hypogonadotropic hypogonadism (see for a review, references (55, 56)). Obesity is characterized by a relative abundance of estrogens since P450 aromatase is highly expressed by fat tissue. The increased amount of estrogen levels might, in turn, play a negative feedback on both the hypothalamus and the pituitary, leading to decreased LH secretion (22, 55). Accordingly, it has been reported that a weekly low dose (2.5 mg) of the aromatase inhibitor letrozole can restore testosterone levels and increase LH levels in severely obese hypogonadal men (57). In line with this view, we now show that body weight loss, obtained either by a lifestyle or bariatric intervention, is associated with a decline in estrogen levels and a rise in gonadotropins and testosterone. However, no effect of Δ-E_2 on TT after weight loss was observed in the meta-regression analysis. In addition, when Δ-E_2 was introduced in a multiple regression model along with other covariates, Δ-BMI, and not Δ-E_2, resulted as the most important determinant of the testosterone increase. Hence, other fat-associated factors, besides estrogens, should mediate a weight reduction-induced improvement in testosterone levels. It should be recognized, however, that local

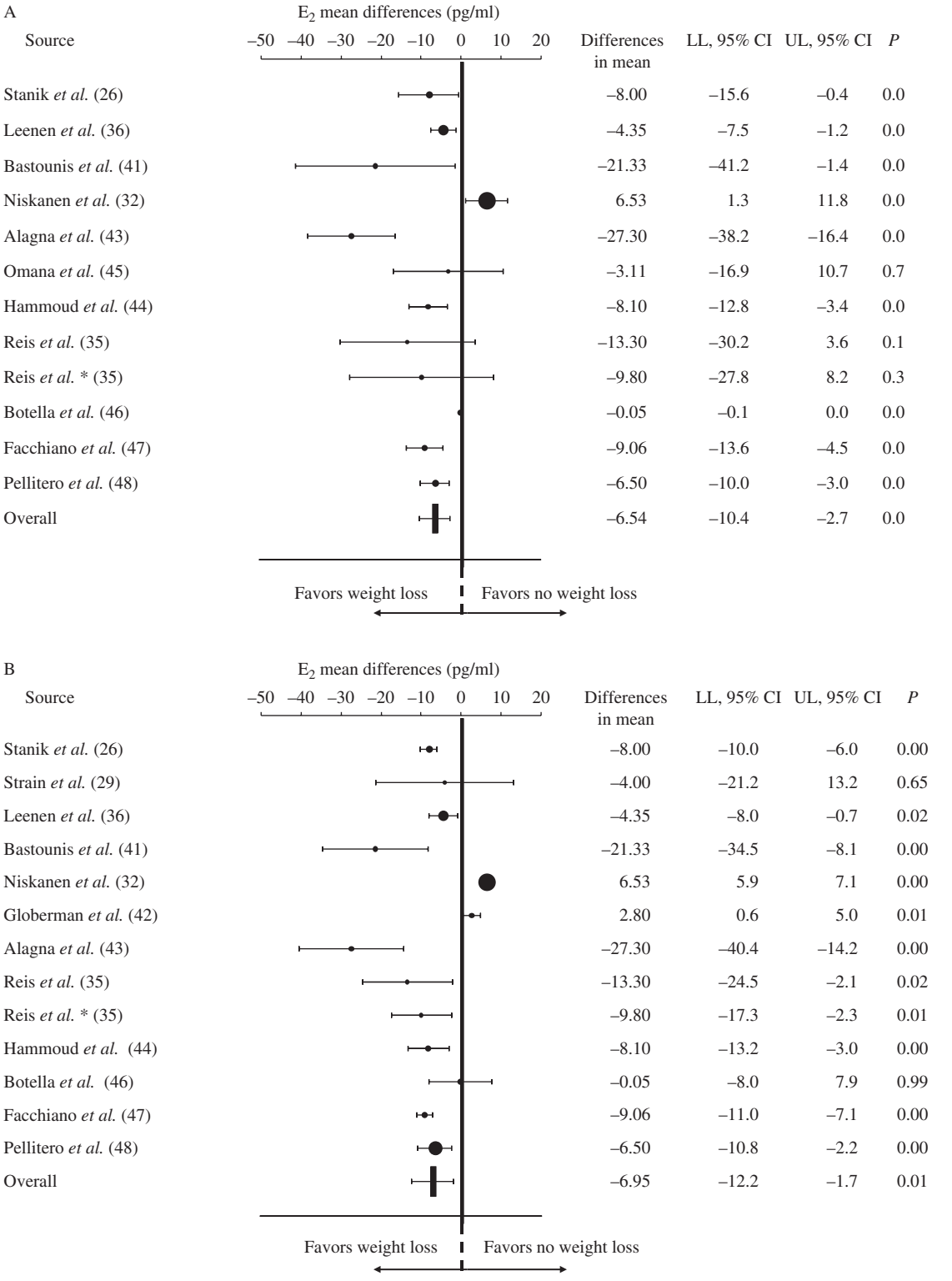
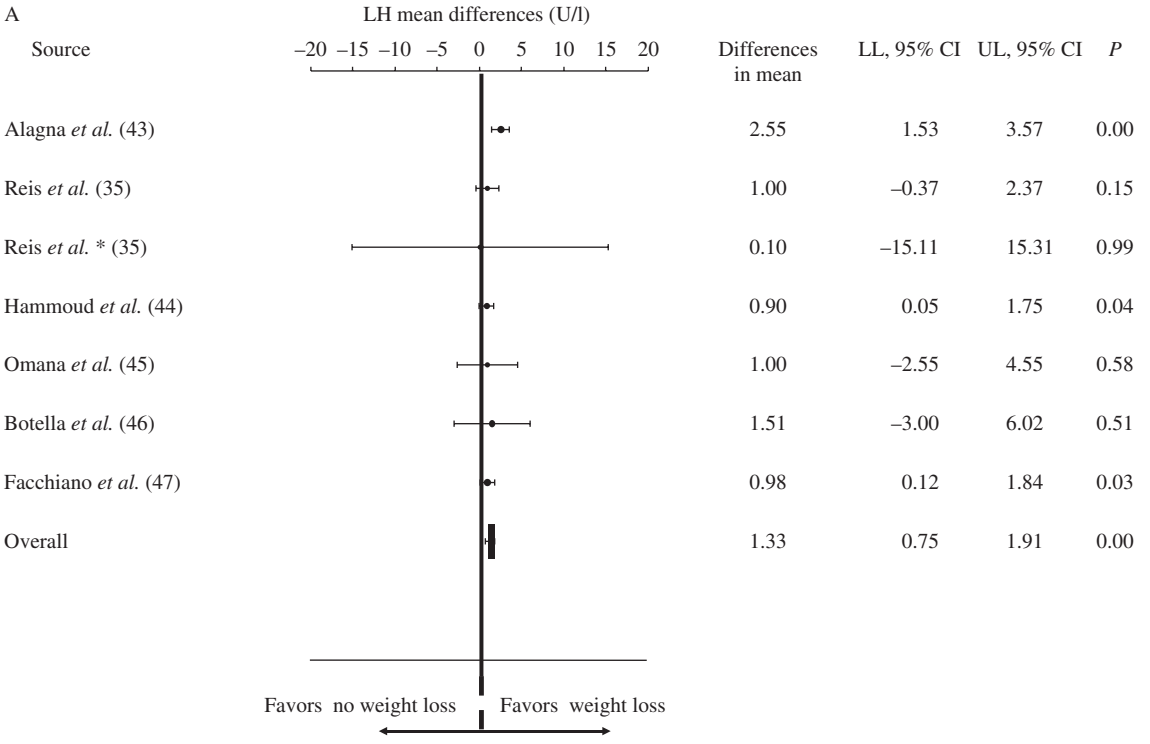


Figure 4 Weighted differences (with 95% CI) of mean estradiol (E_2) before and after weight loss. Data are presented as derived from the paired *t*-test (A) and from non-paired analysis (B). *Bariatric surgery group.



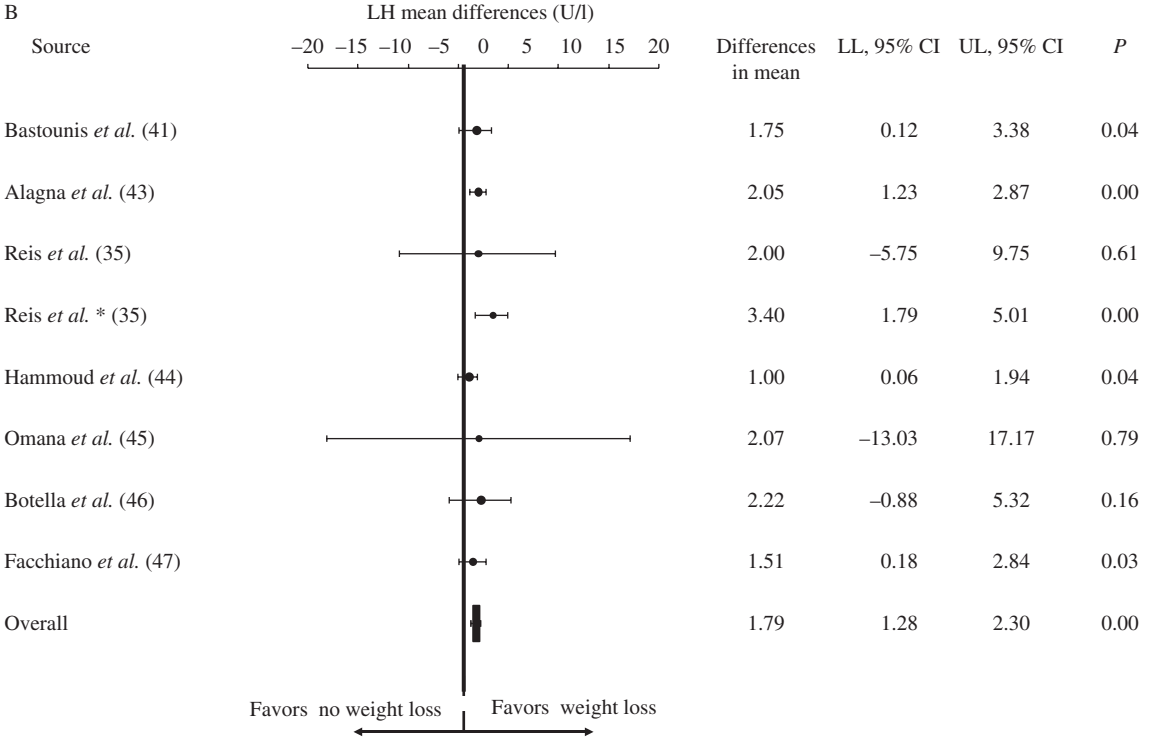
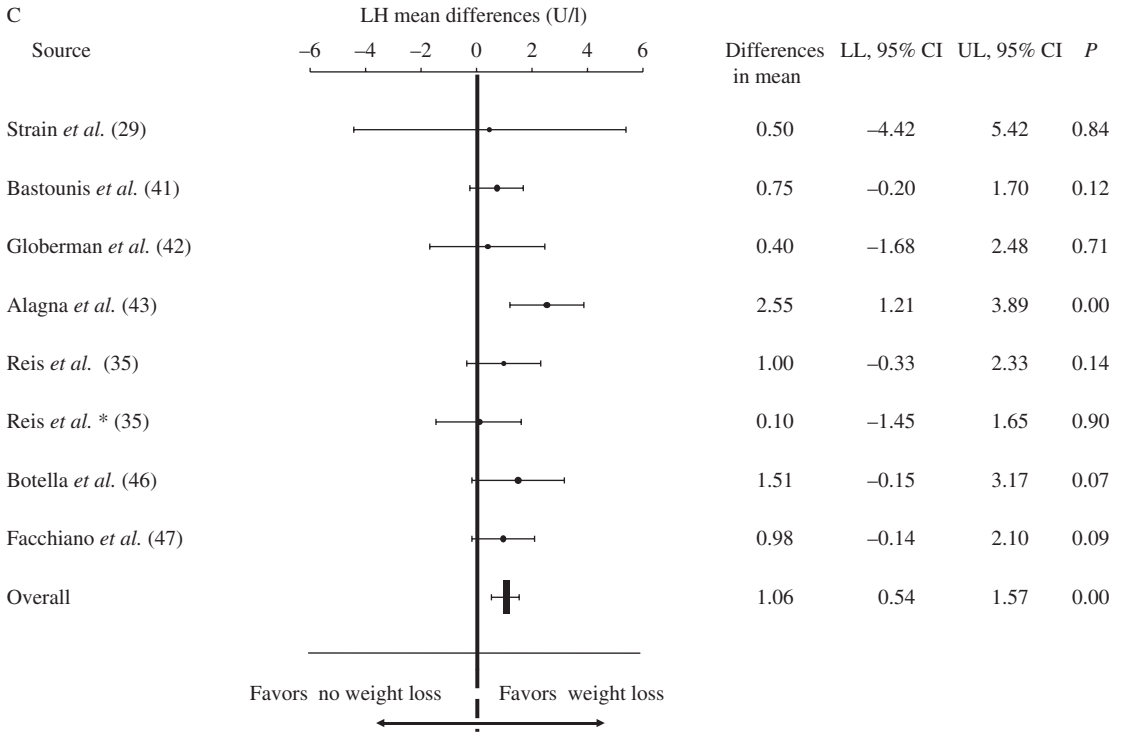


Figure 5 (*Legend continued.*)



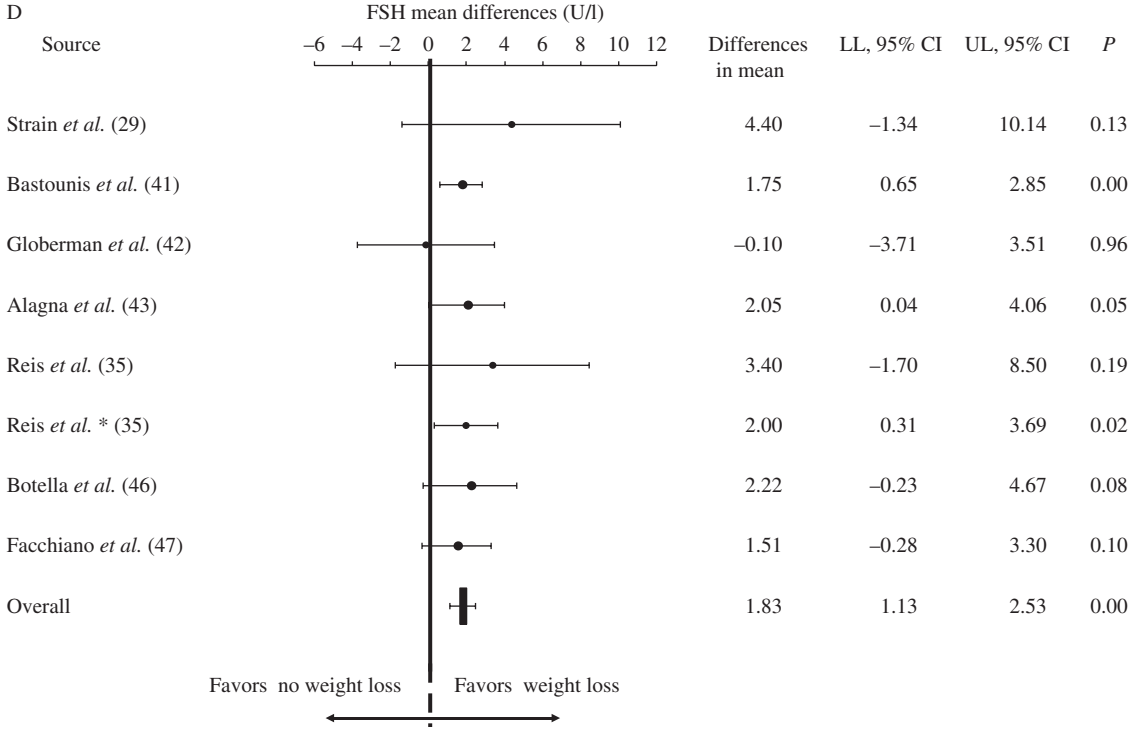


Figure 5 Weighted differences (with 95% CI) of mean LH and FSH before and after weight loss. Data are presented as derived from the paired *t*-test (A and B) and from non-paired analysis (C and D). *Bariatric surgery group.

aromatization at the hypothalamus–pituitary unit could explain the effect of aromatase inhibitors on LH and testosterone, rather than circulating E_2 itself and that, therefore, the best predictor of local E_2 concentrations is systemic testosterone concentrations.

A series of adipokines has been proposed as a link between obesity and reproductive axis disorders and among them, the most extensively studied are leptin, ghrelin, and adiponectin (58). However, information on adipokine variation levels after a lifestyle or bariatric intervention is not available.

An alternative possibility is that weight reduction is associated with increased insulin sensitivity, with insulin having a permissive role on GnRH neuron activity (59). Accordingly, patients with T2DM and insulin resistance show a higher prevalence of hypogonadotropic hypogonadism (54, 55, 60), and in a mouse model of central depletion of the insulin receptor, the phenotype recapitulates both the metabolic syndrome (MetS) and hypogonadotropic hypogonadism (61). Interestingly, we now report that the diabetic condition has a negative effect on testosterone rise after the intervention; however, this difference does not retain statistical significance after adjusting for Δ-BMI, suggesting that it could be due to a greater body weight loss in non-diabetic patients.

In line with this data, the Endocrine Society Guidelines (62) and the Third International Consultation on Sexual Medicine (63) emphasized that lifestyle modifications should be strongly encouraged in hypogonadal subjects with obesity, T2DM, and the MetS. This meta-analysis demonstrates that, in fact, body weight loss significantly increases testosterone levels. However, the testosterone rise induced by lifestyle interventions was only modest, probably reflecting the relatively modest results of the targeted diet and physical activity on body weight loss (9.8% with diet vs 32% with surgery in the studies included in this meta-analysis).

Our knowledge of the long-term effects of bariatric surgery is based only on observational, non-randomized studies, often of poor methodological quality. These studies showed a relevant beneficial effect of surgery on body weight loss, survival, and obesity-related comorbidities (64, 65). These effects are evident only in patients with severe forms of morbid obesity (64). This meta-analysis shows that bariatric surgery is associated with a greater increase in testosterone levels than lifestyle interventions, particularly in those with a higher baseline BMI and who also show a greater body weight loss. It is possible that the consistent testosterone rise in patients with higher degrees of obesity might mediate some of the aforementioned positive effects of surgical interventions on health status such as the lower incidence of diabetes, the MetS, CVD, and mortality (66, 67, 68).

Male hypogonadism can be considered as one of the many adverse consequences of overweight and obesity. Body weight loss and lifestyle interventions should be the first approach offered to obese hypogonadal men. However, their effect on testosterone levels is modest. An interesting alternative is the combination of lifestyle interventions and testosterone supplementation. In a small randomized controlled trial (RCT) involving 16 subjects with newly diagnosed T2DM and the MetS, Heufelder *et al.* (33) demonstrated that the combination of testosterone-replacement therapy (TRT) and lifestyle interventions leads to greater therapeutic improvements in glycemic control and reverses the MetS condition after 52 weeks of treatment in comparison with lifestyle interventions only. Similarly, an 18-week, placebo-controlled RCT in obese patients with obstructive sleep apnea demonstrated that the combination of TRT and lifestyle modifications improved insulin sensitivity, reduced liver fat, and increased muscle mass in comparison with placebo and lifestyle modifications alone (69). Hence, although the combination of TRT and the diet would be expected to further improve weight loss-associated testosterone rise, larger studies are advisable to confirm this hypothesis.

Some limitations should be recognized. First, hormonal assays and reference values were not often comparable. In addition, local aromatization at the hypothalamus–pituitary unit could explain the effect of aromatase inhibitors on LH and testosterone, rather than circulating E_2 itself and, therefore, the best predictor of local E_2 concentrations should be systemic testosterone concentrations. Accordingly, our data suggest that circulating E_2 does not represent the major determinant of testosterone increase after weight loss.

In conclusion, body weight loss induces a consistent increase in TT levels, which is greater in those who lose more body weight. Furthermore, a reduction in body weight is associated with an increase in SHBG, cFT, LH, and FSH and a reduction in E_2. The normalization of sex hormones induced by body weight loss is a possible mechanism contributing to the beneficial effects of surgery in morbid obesity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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