The use of testosterone replacement therapy for the treatment of adult males with type 2 diabetes and hypogonadism: a meta-analysis of randomised controlled trials

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February 28, 2023

Abstract:

Despite varying findings, TST has been used for a long time to treat hypogonadal males with type 2 diabetes mellitus (T2DM). The function of TST was evaluated in this meta-analysis in hypogonadal males with type 2 diabetes. Relevant randomised controlled trials and observational studies were identified by searching PubMed, Embase, and Google Scholar. The effects of TST were evaluated using pooled mean differences (MDs) and relative risks with 95% confidence intervals (CIs).

Our meta-analysis includes 3,002 hypogonadal, type 2 diabetics from 13 randomised controlled trials and 2 observational studies. Total testosterone levels increase significantly with testosterone replacement, and TST significantly improves glycemic management compared to placebo by lowering homeostatic model assessment of insulin resistance (WMD = -1.47 [-3.14, 0.19]; p=0.08; I2=56.3%), fasting glucose (WMD = -0.30 [-0.75, 0.15]; p=0.19; I2= 84.4%), fasting insulin (WMD = -2.95 [-8. Overall, TST resulted in a greater increase in free testosterone levels compared to placebo (WMD = 81.21 [23.87, 138.54] p=0.07; I2= 70%) when comparing patients' individual measurements.

We conclude that TST can help hypogonadal Type 2 Diabetes patients with better glycemic control and hormone levels, as well as lower total cholesterol, triglyceride, and LDL cholesterol while raising HDL cholesterol. Therefore, in addition to the usual care for diabetes, we advise TST for these individuals.

Introduction:

An abnormality in one or more of the testicular hormone concentrations along the hypothalamic-pituitary-testicular axis is the cause of the clinical syndrome known as hypogonadism. In men, hypogonadism is diagnosed when low levels of testosterone (both total and free) are found in the blood. [1] The annual incidence rate of hypogonadism is 12.3 per 1000 people, affecting between 5.1% and 12.3% of men between the ages of 30 and 79. When free testosterone levels fall below 225 pmol/l (65 pg/ml), a pathology is present and treatment is necessary. [2] Due to the devastating effects it can have on a patient's ability to perform basic bodily functions and their overall quality of life, hypogonadism is a global health problem. Recent studies have found strong evidence connecting hypogonadism and type 2 diabetes mellitus (T2DM). This is because low T levels cause an increase in fat storage, insulin resistance, and poor glycemic control, and a higher risk of obesity increases the likelihood of TD. [3] The use of testosterone in routine clinical care for type 2 diabetes is being questioned by a growing (and sometimes conflicting) body of research. Numerous

studies have shown that testosterone treatment lowers the risk factors for cardiovascular disease and diabetes in men with type 2 diabetes, including systolic and diastolic blood pressure, lipid profiles, insulin sensitivity, inflammation, and levels of fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c). It has also been suggested that men with hypogonadism who undergo long-term testosterone therapy have a lower chance of developing type 2 diabetes and a higher quality of life, as measured by the Aging Male Symptoms (AMS) questionnaire. [5] There were, however, studies that found the opposite. Hypogonadal patients with type 2 diabetes have been shown in multiple studies to benefit greatly from testosterone replacement therapy (TRT), as measured by decreases in fasting serum glucose (FSG), fasting serum insulin (FSI), and haemoglobin A1C (HBA1C). [6] These indicators did not significantly decrease in TRT groups, according to other data. Total cholesterol, triglyceride, and serum low-density lipoprotein (LDL) levels have all been shown to be reduced in studies where TRT was used, while high-density lipoprotein (HDL) levels were found to be increased. [7,8] But no other studies found evidence of a statistically significant improvement in lipid metabolism.Only a small number of randomised control trials and observational studies have looked at the role of TRT in male hypogonadism caused by TDM, and the results have been inconsistent. To better understand the role of TRT in hypogonadal males with type 2 diabetes, we conducted a systematic review and meta-analysis. As far as we can tell, this meta-analysis provides the most recent look at how testosterone therapy stacks up against no treatment or placebo.

Methods and Materials

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). [9]

Search strategy

Methods From the study's inception on September 5, 2022, to the present day, PubMed (Medline) and Cochrane were combed extensively. Searches on ClinicalTrials.gov, Google Scholar, and Medrxiv uncovered the grey literature and preprints. An indexing strategy was developed using both keywords and Medical Subject Headings (MESH terms). ['Testosterone' OR 'TST' OR Testosterone undecanoate] were among these. AND [[Diabetes Mellitus OR [Hypogonadism]]. Table S1 provides details on the search parameters and parameters. In conducting this search, we did not apply any filters or limitations. In the case of non-English text, Google Translate was used to produce an English version. The studies were located through manual searches of review articles. Two reviewers independently and anonymously evaluated the titles, abstracts, and full texts (MK and SK). The relevant studies were imported into Endnote X9 to avoid repetition (Clarivate Analytics, US).

Criteria for Eligibility

Criteria for inclusion

The studies were chosen based on their language, study design, patient population, intervention, comparison, outcomes of interest, and definition.

Publications were limited to those written in English, and studies had to be either randomised clinical trials or observational studies that met certain criteria for inclusion before the meta-analysis could be performed.

Hypogonadism patients are those who have type 2 diabetes and have been diagnosed with the condition.

Patients who participated in the study's exposure group included those who had received testosterone therapy.

The non-TST group served as a control and received either the gold standard of care or a placebo in this analysis.

Implications on glucose homeostasis and hormonal levels after treatment constitute the Primary Outcomes.

Measurements of cholesterol, body mass index, waist size, fat percentage, and systolic and diastolic blood pressure were recorded as secondary outcomes.

Criteria for exclusion

The following significant exclusion criteria were established to ensure the quality of this meta-analysis:

* There are no agreed-upon criteria for making a diagnosis of late-onset hypogonadism or type 2 diabetes, determining the appropriate population to study, dosage, or administration method for testosterone, or evaluating outcomes.

There are no control or placebo groups

* Duplicate publications * Inadequate data for estimating a mean difference (MD) with a 95% confidence interval

In addition, the 25-item CONSORT checklists, which stress describing how trials were conceived, analysed, and interpreted, were used to assess all included RCTs (Table S2). The 25 reported items were used to evaluate the quality of the included RCTs. The strength of a randomised controlled trial (RCT) correlates with the number of outcomes that were reported. All 25 criteria should be present in high-quality research.

Data ExtractionData Extraction

Two researchers (HN and RI) independently read and evaluated each article to determine whether or not it should be included in the review. Questions were answered and doubts dispelled. We collected the following data from each trial: first author's name, publication year, country, ethnicity, testosterone cut-off point, diabetes duration, testosterone regimen, medications on comparators, mean age, Hba1c percentage, and total serum testosterone level. Table 1 summarises these facts. Parameters such as HOMA-IR, fasting plasma glucose, fasting serum insulin, haemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, body fat percentage, body mass index, systolic blood pressure, diastolic blood pressure, erectile function, and the ageing male score are listed in Table 2.

Study quality assessment

Published RCT quality was evaluated using a modified version of the Cochrane Collaboration risk of bias tool [10], while observational study quality was measured using the New Castle Ottawa scale. [11]

Statistical analysis

The aforementioned meta-analysis was conducted using the statistics software Review Manager 5.4 (Cochrane Collaboration). For a simple yes/no outcome, we found the relative risk (RR) and 95% CI. The average and standard deviation were used to illustrate continuous results. In this meta-analysis, we show the combined effect of relative risks (RRs) and weighted mean differences (WMDs) calculated with the generic-inverse variance and continuous outcome functions using a random-effects model. Results were considered to be statistically significant when the p-value was less than 0.05. In order to assess the possibility of publication bias, funnel plots were constructed for primary outcomes.Using I2 statistics, we were able to quantify the degree of disagreement between studies. Low heterogeneity was represented by an I2 value of 25%, moderate heterogeneity by a value between 25% and 50%, and high heterogeneity by a value of 50% or more. A

sensitivity analysis on outcomes with a high degree of heterogeneity was performed to investigate the impact of individual studies on the overall pooled estimate.

Results

Study selection

The initial literature search yielded a total of 659 articles. Out of the initial 30 publications, only 15 met the inclusion criteria for this meta-analysis; 2 were observational [12,24] and 13 were randomised trials [5,8,13-23]. The distinguishing characteristics of the selected studies are outlined in (Supplementary table S2 and S3)

Baseline characteristics

Three thousand and two people met the criteria for hypogonadism across the 15 studies; 1484 received testosterone and 1518 received a placebo. Six studies [8,12,14,18,20,24] required the presence of at least three sexual symptoms and a total testosterone level of 12 nmol/L to diagnose hypogonadism, while the remaining studies [5,13,15,16,17,19,21,22] required the presence of a total testosterone level of 15 nmol/L or a free testosterone level of 225 pmol/L to make the diagnosis. The cutoff for hypogonadism in another study [13] was set at TT13 nmol/L. The primary testosterone regimens used in the included studies varied widely. Only one study () used oral testosterone, three (15,17,21) injected testosterone gel subcutaneously, and eleven (5,8,12-14,16,18-20,22,23,24) injected testosterone intramuscularly. Testosterone was administered in a wide variety of doses and at different intervals in these studies. Only two of the RCTs [17,19] lacked a control group entirely, while the other eleven [5,8,13-16,18,20-23] were double-blind placebo-controlled studies. Table 1 and Table 2 provide information about the participants' demographics, medical histories, hormone levels, and glycemic indices as appropriate for the study.

Quality assessment and publication bias

According to the New Castle-Ottawa scale, an instrument for assessing the quality of studies, there is a low risk of bias in observational studies (Supplementary Table 4). The Cochrane method for evaluating randomised controlled trials yielded results of moderate to high quality (Supplementary Table 5). Publication bias did not affect the findings, as demonstrated by the funnel plots (Supplementary Figure S1).

Primary outcomes:

The effects of testosterone on glucometabolism were assessed by measuring HOMA-IR, haemoglobin A1c, fasting serum glucose (FSG), and fasting serum insulin (FSI). Data from 9 of the 15 studies reporting on HOMA-IR ([5,8,13,14,16,17,21,22,24]) showed that testosterone therapy was superior to placebo at lowering HOMA-IR levels (WMD = -1.47 [-3.14, 0.19]; p = 0.08; I2 = 56.3%). Patients in the testosterone group showed a greater decrease in FSG after treatment compared to those in the placebo group (WMD = -0.30 [-0.75, 0.15]; p=0.19; I2= 84.4%). FSG was measured in 14 [5,8,12-19,21-24] of the 15 studies. WMD = -2.95 [-8.64,2.74]; p = 0.31; I2 = 49.3%]; 8 [8,13,15-18,22,24] of 15 studies found that patients treated with testosterone had greater reductions in FSI levels. Among the 15 studies, 13 reported HbA1c values, and pooled analysis showed that testosterone treatment was associated with a greater improvement in post-treatment HbA1c levels (WMD = -0.29 [-0.57, -0.02] p=0.04; I2= 89.8%). (Figure 3)

Total testosterone, free testosterone, serum hormone binding protein (SHBG), and prostate specific antigen (PSA) were taken into account to determine testosterone's impact on hormone levels. The pooled analysis

of 9 studies that measured total testosterone levels [5,12,13,18,19,21-24] found that testosterone therapy is associated with a significant increase in total testosterone levels (WMD = 4.51 [2.40, 6.61] p0.0001; I2= 96.3%). The in-study heterogeneity was unaffected by excluding individual studies from the pooled analysis.

Combining data from three studies [13,14,21] found that patients on testosterone therapy experienced a greater increase in free testosterone levels compared to those on placebo (WMD = 81.21 [23.87, 138.54] p=0.07; I2= 70%). After pooling data from 5 studies [13,17,21,22,23], researchers found that SHBG level decreased more with testosterone therapy (WMD = -1.28 [-5.51, 2.96] p=0.55; I2 = 0%). There was no statistically significant difference in PSA levels between the two groups after therapy (WMD = -0.02 [-0.13, 0.08] p=0.65; I2 = 0%) across seven studies [8,13,14,15,17,21,23].

Secondary outcomes: (Table 3)

Treatment with testosterone has been shown in a pooled analysis of secondary outcomes to improve HDL cholesterol and IIEF, as well as reduce total cholesterol, LDL cholesterol, triglyceride, body fat, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, arterial mean stiffness, and mortality.

Discussion:

Recent studies have found that hypogonadism occurs in a high percentage of men with Type-2 diabetes. Despite growing knowledge of the correlation between T2D and hypogonadism, no universally accepted guidelines exist for dealing with the condition. The purpose of this meta-analysis was to develop clear, evidence-based recommendations for the treatment of hypogonadism in men with Type 2 diabetes mellitus who are taking testosterone replacement therapy. Evidence linking type 2 diabetes and low blood testosterone due to an amplified insulin signalling pathway has been established by multiple studies showing a significant incidence (30-80%) of hypogonadism in males with diabetes mellitus. [25] Hypogonadism is more common in males with diabetes than in non-diabetic men across the globe, including in the West, Asia, and Africa. The effects of testosterone replacement therapy in hypogonadal males with type 2 diabetes were compared to those in a control group in a systematic review and meta-analysis involving 15 studies and 3002 patients (T2DM). All men with Type 2 diabetes and all men with a body mass index (BMI) greater than 30 or a waist circumference greater than 104 cm were recommended for screening for hypogonadism by the American Academy of Clinical Endocrinologists in 2016. The 2018 Endocrine Society guidelines continue to discourage testosterone monitoring despite the high prevalence of hypogonadism in conditions like type 2 diabetes. [26] Screening for hypogonadism was advocated for in 2016 by the American Academy of Clinical Endocrinologists in all men with Type 2 diabetes and in all men with a body mass index (BMI) of 30 or higher, or a waist circumference of 104 centimetres or more. In spite of the high prevalence of hypogonadism in conditions such as type 2 diabetes, the Endocrine Society's 2018 guidelines still discourage testing for the hormone. [26] In men with hypogonadism, testosterone replacement therapy (TRT) has been shown to have a positive effect on a wide range of outcomes, including sexual desire and function, bone mineral density, muscle mass, body composition, mood, erythropoiesis, cognition, quality of life, and cardiovascular disease, but the indications for testosterone supplementation are still up for debate. Potential side effects of testosterone replacement therapy have been categorised by the guidelines into two groups: those with a strong association to testosterone therapy, such as acne and oily skin, an increase in hematocrit, decreased fertility, locally active prostatic carcinoma, and the development of metastatic prostatic carcinoma, and those with a weak association, such as gynecomastia, worsening sleep apnea, and the progression of breast cancer. [27] Our results confirm the findings of previous studies [5,8,12-19,21-24] showing that TRT can significantly enhance glucose control by decreasing Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), fasting serum glucose (FSG), fasting insulin (FSI), and glycated haemoglobin (HBA1C). Recent research has established a correlation between baseline HOMA-IR and body mass index, waist circumference,

and C-peptide. Insulin sensitivity, as measured by changes in HOMA-IR, HOMA-%, and blood C-peptide and proinsulin levels, was also enhanced by testosterone supplementation, demonstrating the presence of metabolic syndrome. [28] Testosterone replacement therapy for hypogonadal males with diabetes has been linked to improvements in both body mass index and glucose control. The testosterone treatment group showed statistically significant improvements in body mass index, fasting glucose, A1C, blood pressure, lipid profiles, and liver enzymes, according to a study. [29] Twelve months of testosterone treatment (adjusted to mid-normal concentrations for healthy men) decreased insulin resistance modestly, HOMA-IR 0.6, $p = 0.03$, but had no effect on body weight or waist circumference in a large testosterone trial involving 788 men over the age of 65 (72% were obese and 37% had diabetes at baseline). [29] Testosterone therapy has been linked to long-term weight loss, a marked decrease in cardiometabolic risk factors, and in some cases, the complete reversal of diabetes, according to a number of case studies. Treatment with testosterone undecanoate depot injections was initiated for a 57-year-old man with benign prostatic hyperplasia, erectile dysfunction, apathy, and subpar physical fitness (intramuscular injections at 3-month intervals following a 6-week gap). Patients on testosterone therapy saw improvements in fasting blood glucose (to 6.0 mmol/L after 3 months, to below 5.7 mmol/L after 12 months, and then permanently below this value), insulin resistance (HOMA-IR: 3.9 at month 24), and serum lipid levels (LDL/HDL ratio: 3 and triglycerides: 2.5 mmol/L). [30] To fully understand the connection between circulating sex hormones and glucose metabolism, more interventional studies are required.

In our meta-analysis, we looked at a lipid panel consisting of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels. Thirteen studies found that testosterone recipients had lower total cholesterol levels compared to placebo recipients. On the other hand, 14 studies showed that while HDL cholesterol increased, triglyceride levels decreased. However, there was less of a difference in LDL cholesterol levels between the two groups. Similarly, Si Hyun Kim et al2021 .'s meta-analysis found that TRT significantly lowered total cholesterol compared to placebo. There was also a reduction in triglycerides, though it was not statistically significant. HDL levels unexpectedly dropped after TRT compared to the placebo group. TRT's role in HDL was unclear due to a lack of evidence and conflicting results. It has been shown that high doses of TRT lower levels of HDL and lipoprotein A. TRT's effect on blood lipid and lipoprotein levels is controversial, however. [31] The 14 studies that made up our meta-analysis all showed a reduction in diastolic blood pressure (DBP) and a modest rise in systolic blood pressure (SBP). The effects of testosterone on lipid profiles in the blood are ambiguous. In men with and without type 2 diabetes, low testosterone has been linked to elevated levels of LDL and triglycerides and decreased HDL. In patients with high endogenous testosterone profiles, several cross-sectional studies found no association between elevated serum lipid levels or even elevated LDL. TRT has been shown to significantly reduce LDL-C and total cholesterol in men with eugonadism and hypogonadism in numerous systematic reviews and meta-analyses. [32] Measurements of the patient's waist and body mass index (BMI) can be used for screening for cardiometabolic risk. Testosterone supplementation is gaining popularity as an anti-obesity medication due to its ability to decrease visceral adipose tissue and increase muscle mass in males with hypogonadism. Thirteen additional studies, which contradict the aforementioned randomised controlled trials, have found that testosterone therapy results in a greater reduction in body mass index. [32]

A significant correlation between total serum testosterone and AMS and IIEF scores was found in three studies. Treatment with testosterone significantly reduced AMS scores while increasing IIEF. Slight enhancements in sexual functioning, as measured by the AMS scale, the IIEF erectile dysfunction domain, and the IIEF-5 scale, have been associated with low testosterone in older men (testosterone threshold, 10.4 nmol/L [300 ng/dL]). Physical function, depressive symptoms, energy, vitality, and cognitive abilities do not significantly improve, however, according to the literature. Since the AMS scale was the only source of data on life satisfaction, we can assume that the slight improvement in quality of life was attributable to a rise in sexual satisfaction. [33] Different levels of testosterone were analysed including total, free, SHBG, and PSA. Both total and free testosterone levels increased significantly, while SHBG dropped significantly. However, PSA levels were not related to this therapy. The impact of TRT on PSA has been the subject of multiple meta-analyses. Despite this, the primary focus of the papers reviewed was not on PSA and testosterone but

on TRT and the risk of prostate cancer. Risk factors for cardiovascular disease (CVD) such as obesity, hypertension, dyslipidemia, and diabetes are often co-occurring with androgen insufficiency. Androgens have a direct effect on PSA, and the protein's level has been suggested as a possible indicator of androgen deficiency in a number of studies. According to the research conducted by Do Kyung Kim et al., TRT significantly increased PSA levels compared to placebo. [34]

Numerous benefits can be gained from our meta-analysis. If we add two more studies to our meta-analysis, we'll have about twice as large of a sample to work with. (2) A sensitivity analysis was run to determine the impact of various studies on the final tally. (3) Multiple plots and tests, such as the funnel plot, Egger's test, and Begg's test, were used to evaluate estimates of publication biases, and all of them concluded that the estimates were not statistically significant. Our meta-analysis also included an additional observational study, and we checked it for publication bias using the New Castle-Ottawa Scale. (4) We integrated mortality, total testosterone, free testosterone, SHBG, and PSA to account for new information in the literature that is rarely mentioned in individual studies.

While we did collect a substantial amount of statistical data, it is important to note the caveats of our study. 1) Most studies had different follow-up times, with some indicating longer times. Because of the significance of homeostasis in the body, longitudinal follow-up studies are preferred when evaluating hormonal diseases like hypogonadism. Testosterone was used in a wide variety of doses and administration routes across a large number of studies spanning many weeks. This clinical heterogeneity may be attributable to (2) differences in study designs, interventions, and patient factors (including body mass index, age, sample size, ethnicity, and trial characteristics). (3) There have been few randomised controlled trials investigating the association between body fat, AMS and IIEF scores, free testosterone, and mortality rates. (4) All included RCTs displayed signs of selective reporting bias, except for Groti 2020. More research was needed to ascertain how testosterone therapy affected libido. (5) Also, most studies did not include information on doses for control groups, which may have added uncertainty.

Conclusion

Our results demonstrate that hypogonadal T2DM patients who underwent long-term testosterone replacement therapy experienced a sustained remission of their diabetes. This therapy improved glycemic control, decreased total cholesterol, HDL levels, and triglycerides, and reduced body mass index and waist circumference. We propose that this treatment be taken in conjunction with anti-diabetes medications for these patients. The intervention's long-term durability, safety, and cardiovascular effects need to be studied further.

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Legends to figures

Figure 1: Prisma flow chart

Figure 2: Effects on Glucometabolism; A= HOMA-IR (Homeostatic model assessment for insulin resistance), B= FSG (Fasting serum glucose), C= FSI (Fasting serum insulin), D= HbA1C (Glycated hemoglobin), WMD= weighted mean difference, CI= confidence interval

Figure 3: Effects on Hormonal levels; A= TT (Total testosterone), B= FT (Free testosterone), C = SBHG (sex hormone binding globulin), D= PSA (Prostate specific antigen).

Table 1: Baseline characteristics of included studies

Study	**Study design**	**Total no of patients**	**Hypogonadism cut off point**
TRT	**Placebo**	**TRT**	**Placebo**
Dhindsa (2015)[13]	RCT	34	FT<225 pmmol/L
Gianatti (2014)[8]	RCT	67	TT<12 nmmol/L
Hackett (2014)[14]	RCT	186	TT<12 nmmol/L
Jones (2011)[15]	RCT	137	TT<11 nmmol/L
Gopal (2010)[16]	RCT crossover	22	FT<225 pmmol/L
Heufelder (2009)[17]	RCT	32	TT<11 nmmol/L
Kapoor (2006)[18]	RCT crossover	27	TT<12 nmmol/L
Boyanov (2003)[19]	RCT	48	TT<15 nmmol/
Hackett (2018)[20]	RCT	537	TT<12 nmmol/L
Yassin (2019)[12]	Observational study	316	TT< 12.1nmol/L
Khirpun (2018)[21]	RCT	80	serum levels of total testosterone two times belo
Groti (2020)[5]	RCT	55	(total testosterone [TT] below 11 nmol/L and fr
Groti (2018)[22]	RCT	55	total testosterone (TT) level <11 nmol/l and/or
Wittert (2021) [23]	RCT	1007	13·0 nmol/L
Haider (2020) [24]	Prospective observational	356	total testosterone levels [?]12.1 nmol/L (350 ng/

SD: Standard deviation, Ft: free testosterone, TT: total testosterone

Table 2: Baseline glucometabolic, lipid and blood pressure parameters

Study	**Fasting plasma glucose (mmol/L) (Mean ±SD)**	**Fasting serum insulin (Mean ±SD)**	**H**
	TRT	**Placebo**	**T**
Dhindsa (2015)[13]	6.99 ± 0.44	6.60 ± 0.55	1
Gianatti (2014)[8]	9.57 ± 3.78	9.11 ± 3.65	N
Hackett (2014)[14]	9.05 ± 3.18	8.49 ± 2.84	2
Jones (2011)[15]	7.9 ± 4.3	9.2 ± 3.4	1
Gopal (2010)[16]	7.9 ± 0.2	8.3 ± 0.2	1
Heufelder (2009)[17]	7.83 ± 0.49	7.6 ± 0.43	1

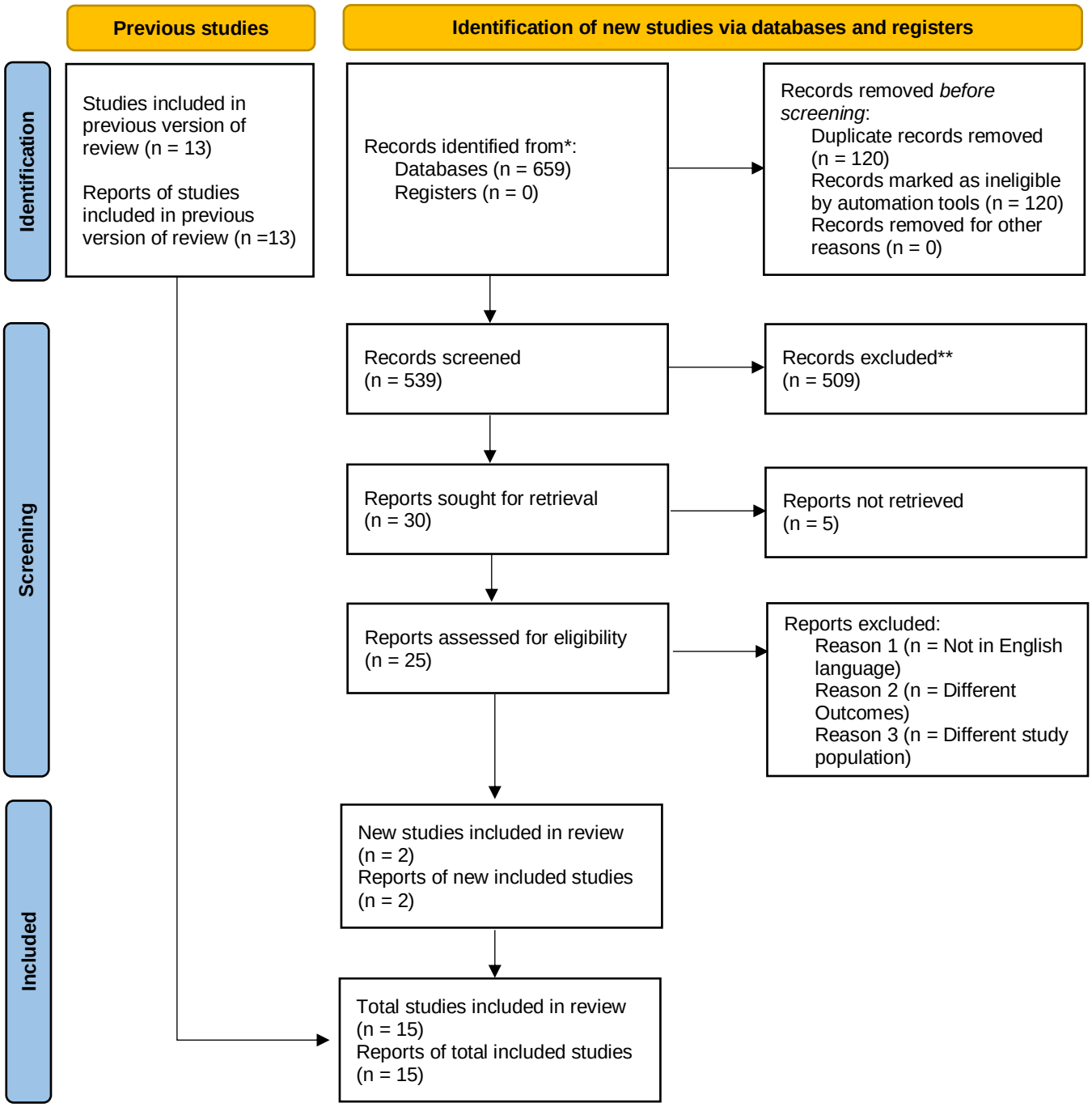
Kapoor (2006)[18]	8.0 ± 2.6	8.4 ± 2.8	N
Boyanov (2003)[19]	N/A	N/A	N
Hackett (2018)[20]	5.3 ± 0.8	4.9 ± 1.3	N
Yassin (2019)[12]	8.1 ± 3.7	8.7 ± 5.0	N
Khirpun (2018)[21]	10.06 ± 1.44	9.77 ± 1.40	N
Groti (2020)[5]	10.06 ± 1.44	9.60 ± 1.44	2
Groti (2018)[22]	10.06 ± 1.44	9.60 ± 1.44	2
Wittert (2021) [23]	6·1 ± 0·9	6·1 ± 0·9	N
Haider (2020) [24]	7.8 ± 1.2	6.3 ± 0.7	2

SD: Standard deviation, HOMA-IR: Homeostasis model of insulin resistance, HbA1c: glycated hemoglobin

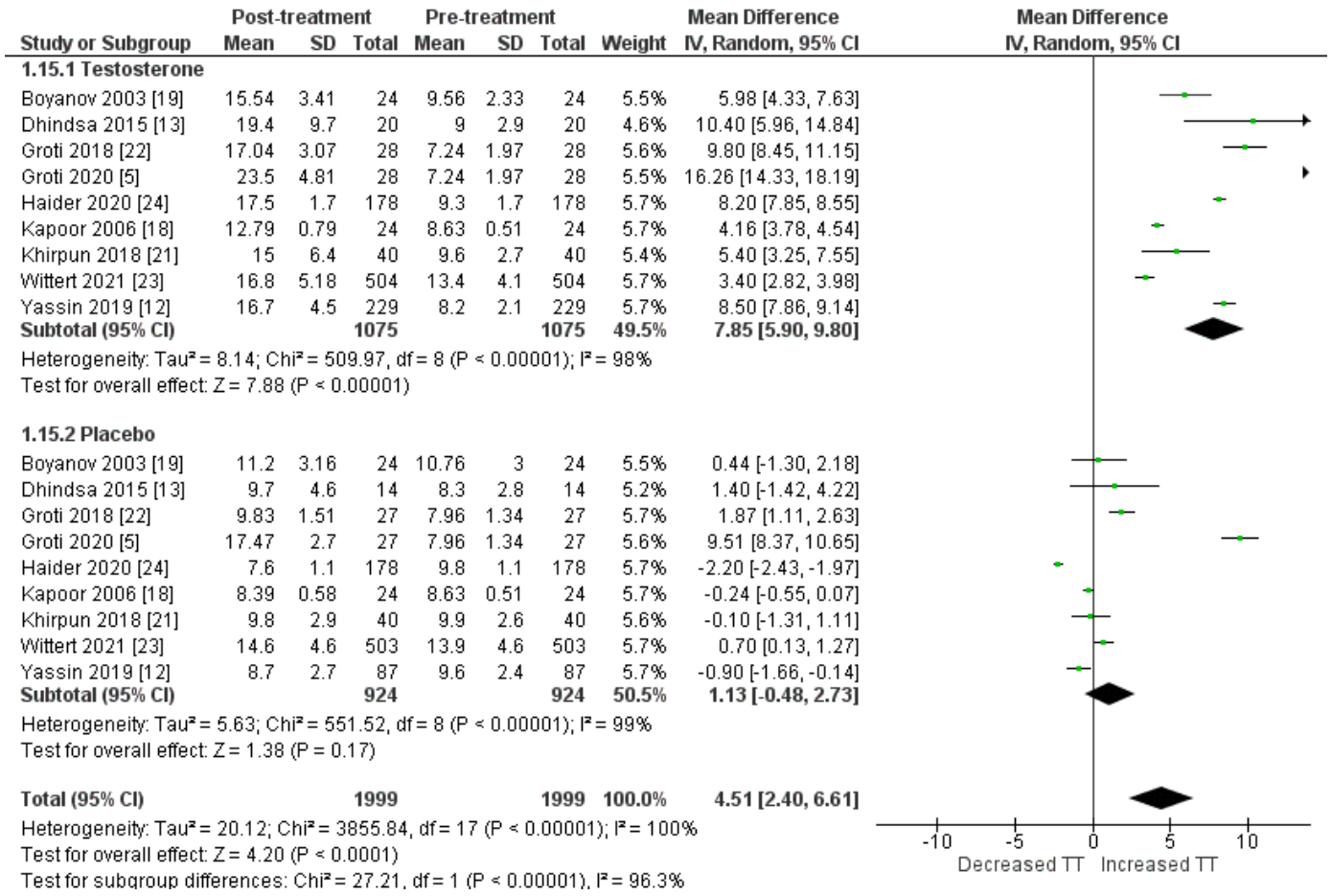
Table 3: Secondary outcomes

Outcome	**Testosterone**	**placebo**	**Effect size [CI]**	**Overall P value**	**heterogen**
Total cholesterol	-0.71 [-1.22, -0.21]	0.10 [-016, 0.35]	-0.32 [-0.64, 0.00]	0.05	87.2
Triglyceride	-0.47 [-0.75, - 0.20]	0.03 [-021, 0.27]	-0.23 [-0.47, 0.00]	0.05	86.6
LDL cholesterol	-0.20 [-1.12, 0.73]	0.17 [-0.13, 0.46]	-0.02 [-0.52, 0.48]	0.94	0
HDL cholesterol	0.10 [0.01, 0.20]	0.03 [-0.07, 0.13]	0.07 [0.00, 0.13]	0.04	8.7
Body fat	-0.98 [-1.59, -0.38]	-0.54 [-1.12, 0.03]	-0.75 [-1.17, -0.34]	0.0004	6.4
Waist circumference	-3.98 [-6.48, -1.48]	0.73 [-1.44, 2.89]	-1.68 [3.43, 0.07]	0.06	87.1
BMI	-1.12 [-2.98, 0.74]	0.05 [-0.51, 0.61]	-0.56 [-1.48, 0.36]	0.23	27.5
SBP	-0.90 [-12.07, 10.26]	-0.19 [-3.19, 2.81]	-0.51 [-6.24, 5.11]	0.85	0
DBP	-3.09 [-5.52, -0.65]	-0.23 [-1.98, 1.52]	-1.68 [-3.16, -0.21]	0.03	71.3
IIEF	6.98 [3.62, 10.33]	-3.94 [-10.97, 3.10]	1.66 [-6.75, 10.06]	0.70	86.7
AMS	-16.80 [-26.96, -6.64]	4.90 [-9.05, 18.85]	-5.94 [-21.87, 9.98]	0.46	83.5
Mortality	-		0.24 [0.15, 0.37]	<0.00001	0

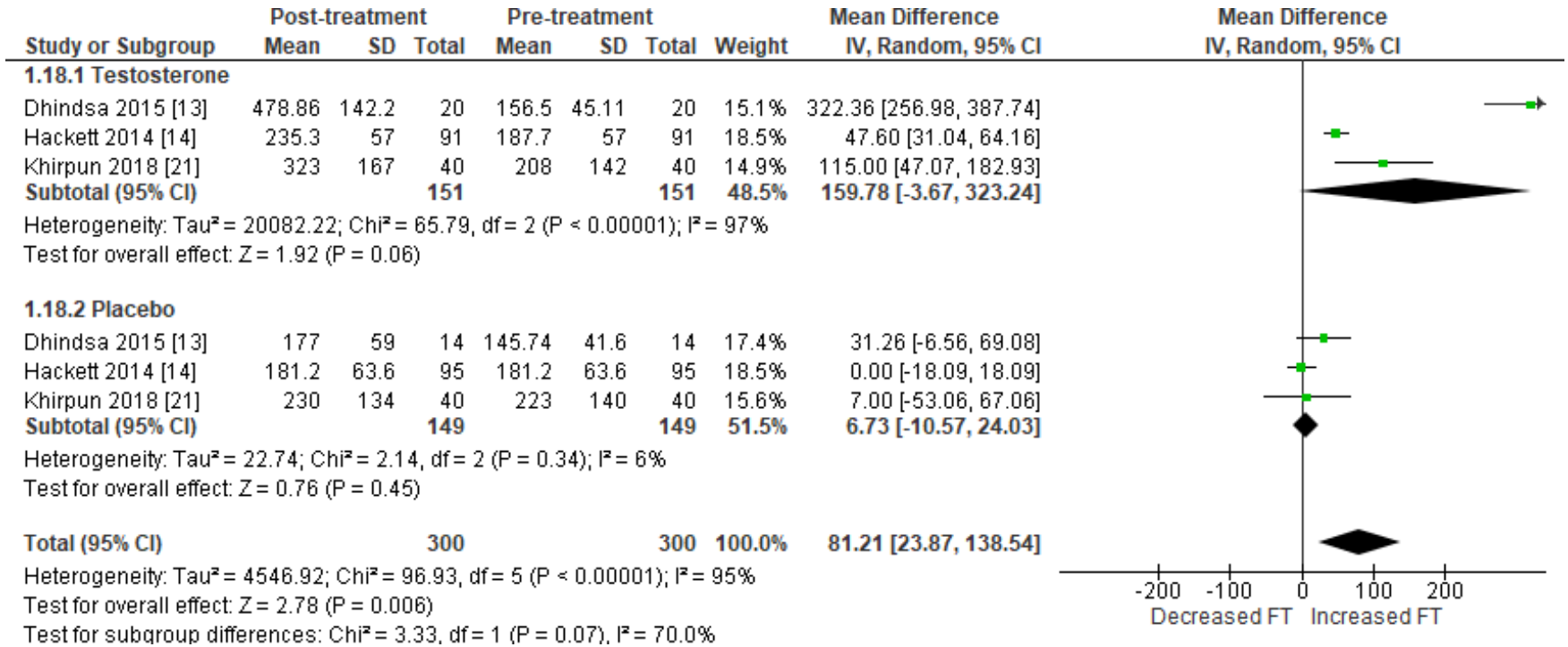
CI: Confidence interval, LDL: low density lipoprotein, HDL: High density lipoprotein, BMI: Body mass index; SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IIEF: international index of erectile function, AMS: Aging male score.


Previous studies
Identification of new studies via databases and registers
Identification
Screening
Included
Studies included in previous version of review (n = 13)
Reports of studies included in previous version of review (n =13)
Records identified from*:
Databases (n = 659)
Registers (n = 0)
Records removed *before screening*:
Duplicate records removed (n = 120)
Records marked as ineligible by automation tools (n = 120)
Records removed for other reasons (n = 0)
Records screened (n = 539)
Records excluded** (n = 509)
Reports sought for retrieval (n = 30)
Reports not retrieved (n = 5)
Reports assessed for eligibility (n = 25)
Reports excluded:
Reason 1 (n = Not in English language)
Reason 2 (n = Different Outcomes)
Reason 3 (n = Different study population)
New studies included in review (n = 2)
Reports of new included studies (n = 2)
Total studies included in review (n = 15)
Reports of total included studies (n = 15)

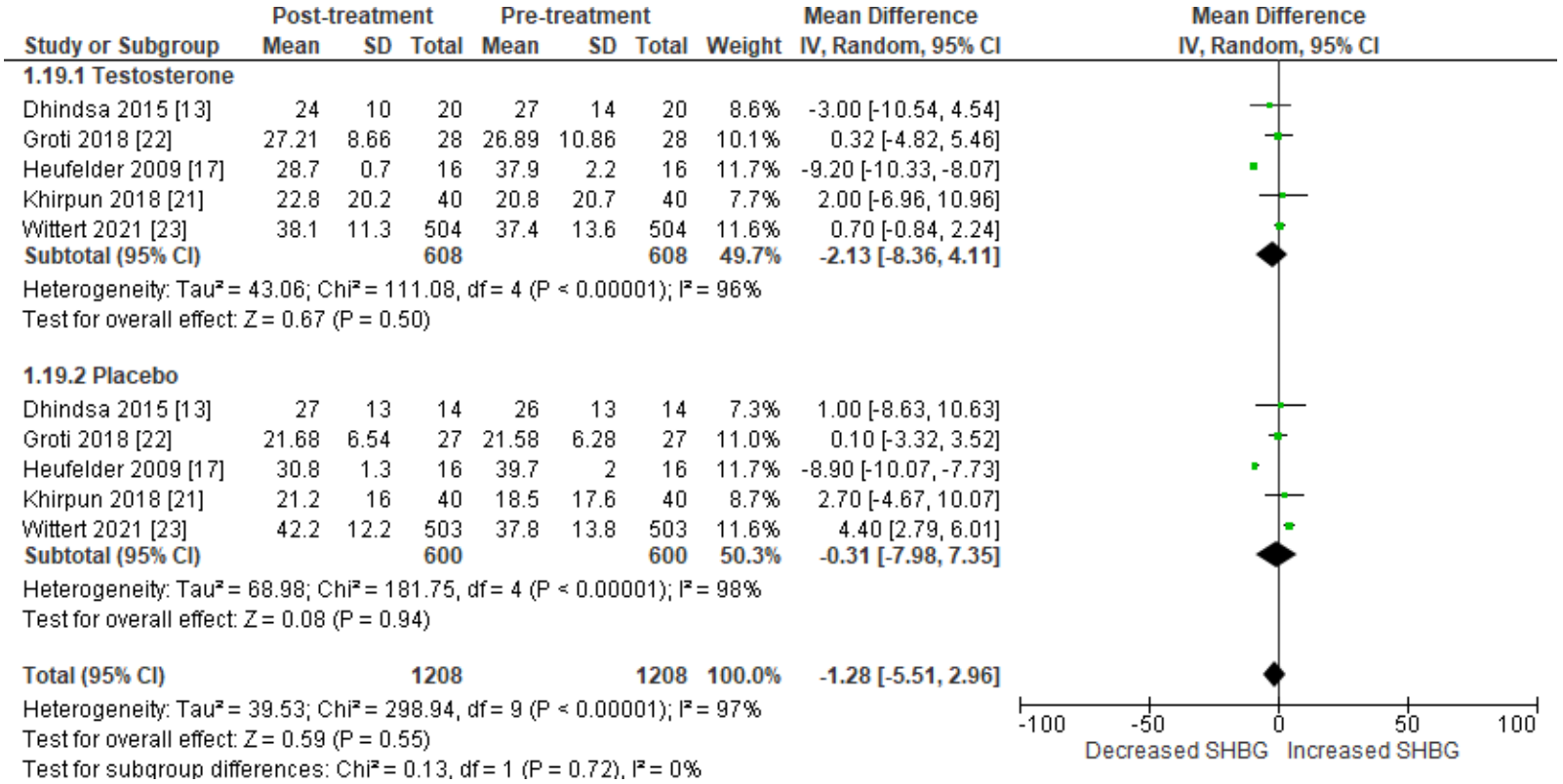
A


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.15.1 Testosterone
Boyanov 2003 [19] 15.54 3.41 24 9.56 2.33 24 5.5% 5.98 [4.33, 7.63]
Dhindsa 2015 [13] 19.4 9.7 20 9 2.9 20 4.6% 10.40 [5.96, 14.84]
Groti 2018 [22] 17.04 3.07 28 7.24 1.97 28 5.6% 9.80 [8.45, 11.15]
Groti 2020 [5] 23.5 4.81 28 7.24 1.97 28 5.5% 16.26 [14.33, 18.19]
Haider 2020 [24] 17.5 1.7 178 9.3 1.7 178 5.7% 8.20 [7.85, 8.55]
Kapoor 2006 [18] 12.79 0.79 24 8.63 0.51 24 5.7% 4.16 [3.78, 4.54]
Khirpun 2018 [21] 15 6.4 40 9.6 2.7 40 5.4% 5.40 [3.25, 7.55]
Wittert 2021 [23] 16.8 5.18 504 13.4 4.1 504 5.7% 3.40 [2.82, 3.98]
Yassin 2019 [12] 16.7 4.5 229 8.2 2.1 229 5.7% 8.50 [7.86, 9.14]
Subtotal (95% CI) 1075 1075 49.5% 7.85 [5.90, 9.80]
Heterogeneity: Tau² = 8.14; Chi² = 509.97, df = 8 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.88 (P < 0.00001)
1.15.2 Placebo
Boyanov 2003 [19] 11.2 3.16 24 10.76 3 24 5.5% 0.44 [-1.30, 2.18]
Dhindsa 2015 [13] 9.7 4.6 14 8.3 2.8 14 5.2% 1.40 [-1.42, 4.22]
Groti 2018 [22] 9.83 1.51 27 7.96 1.34 27 5.7% 1.87 [1.11, 2.63]
Groti 2020 [5] 17.47 2.7 27 7.96 1.34 27 5.6% 9.51 [8.37, 10.65]
Haider 2020 [24] 7.6 1.1 178 9.8 1.1 178 5.7% -2.20 [-2.43, -1.97]
Kapoor 2006 [18] 8.39 0.58 24 8.63 0.51 24 5.7% -0.24 [-0.55, 0.07]
Khirpun 2018 [21] 9.8 2.9 40 9.9 2.6 40 5.6% -0.10 [-1.31, 1.11]
Wittert 2021 [23] 14.6 4.6 503 13.9 4.6 503 5.7% 0.70 [0.13, 1.27]
Yassin 2019 [12] 8.7 2.7 87 9.6 2.4 87 5.7% -0.90 [-1.66, -0.14]
Subtotal (95% CI) 924 924 50.5% 1.13 [-0.48, 2.73]
Heterogeneity: Tau² = 5.63; Chi² = 551.52, df = 8 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.38 (P = 0.17)
Total (95% CI) 1999 1999 100.0% 4.51 [2.40, 6.61]
Heterogeneity: Tau² = 20.12; Chi² = 3855.84, df = 17 (P < 0.00001); I² = 100%
Test for overall effect: Z = 4.20 (P < 0.0001)
Test for subgroup differences: Chi² = 27.21, df = 1 (P < 0.00001), I² = 96.3%
-10
-5
0
5
10
Decreased TT
Increased TT

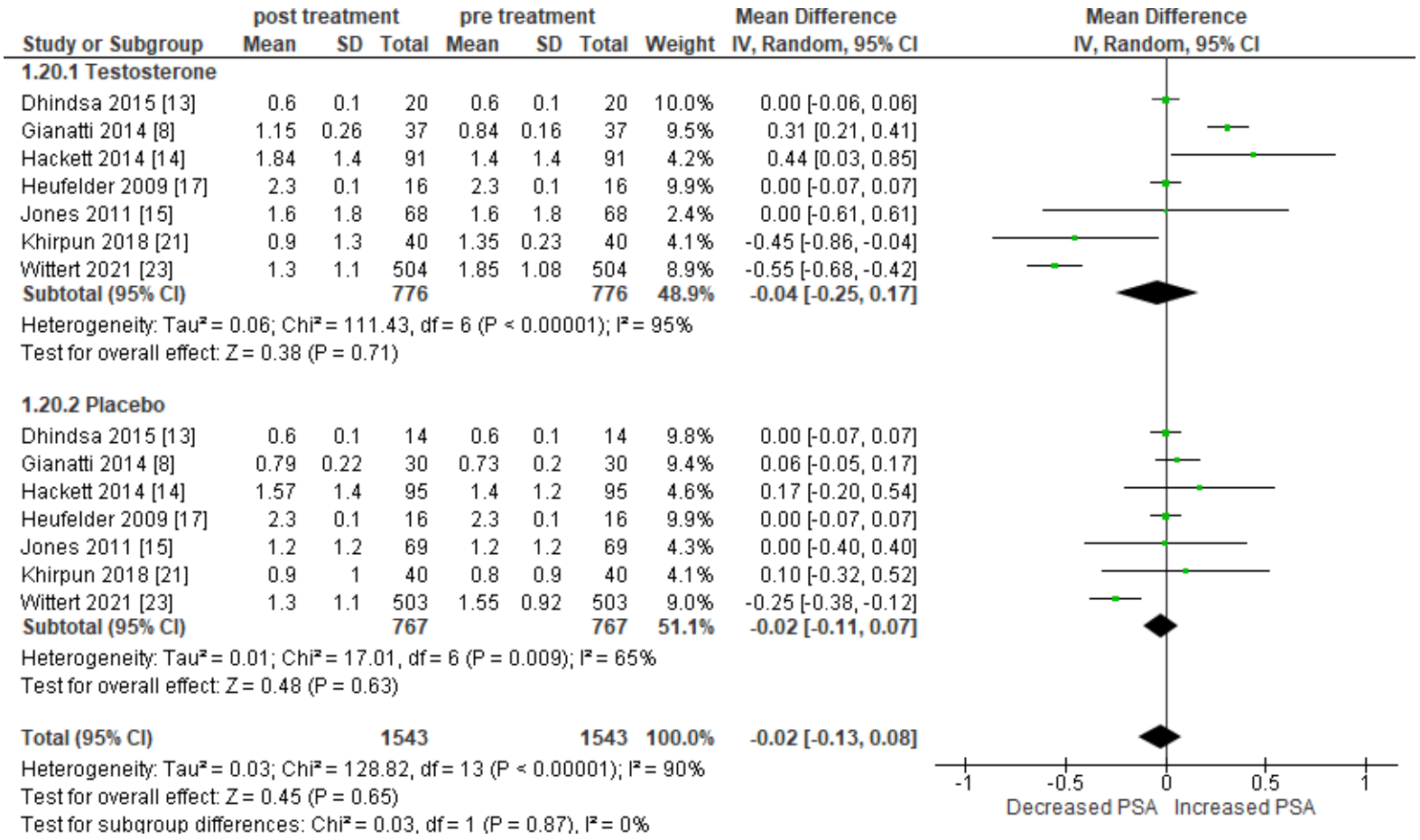
B


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.18.1 Testosterone
Dhindsa 2015 [13] 478.86 142.2 20 156.5 45.11 20 15.1% 322.36 [256.98, 387.74]
Hackett 2014 [14] 235.3 57 91 187.7 57 91 18.5% 47.60 [31.04, 64.16]
Khirpun 2018 [21] 323 167 40 208 142 40 14.9% 115.00 [47.07, 182.93]
Subtotal (95% CI) 151 151 48.5% 159.78 [-3.67, 323.24]
Heterogeneity: Tau² = 20082.22; Chi² = 65.79, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.92 (P = 0.06)
1.18.2 Placebo
Dhindsa 2015 [13] 177 59 14 145.74 41.6 14 17.4% 31.26 [-6.56, 69.08]
Hackett 2014 [14] 181.2 63.6 95 181.2 63.6 95 18.5% 0.00 [-18.09, 18.09]
Khirpun 2018 [21] 230 134 40 223 140 40 15.6% 7.00 [-53.06, 67.06]
Subtotal (95% CI) 149 149 51.5% 6.73 [-10.57, 24.03]
Heterogeneity: Tau² = 22.74; Chi² = 2.14, df = 2 (P = 0.34); I² = 6%
Test for overall effect: Z = 0.76 (P = 0.45)
Total (95% CI) 300 300 100.0% 81.21 [23.87, 138.54]
Heterogeneity: Tau² = 4546.92; Chi² = 96.93, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.78 (P = 0.006)
Test for subgroup differences: Chi² = 3.33, df = 1 (P = 0.07), I² = 70.0%
-200 -100 0 100 200
Decreased FT Increased FT

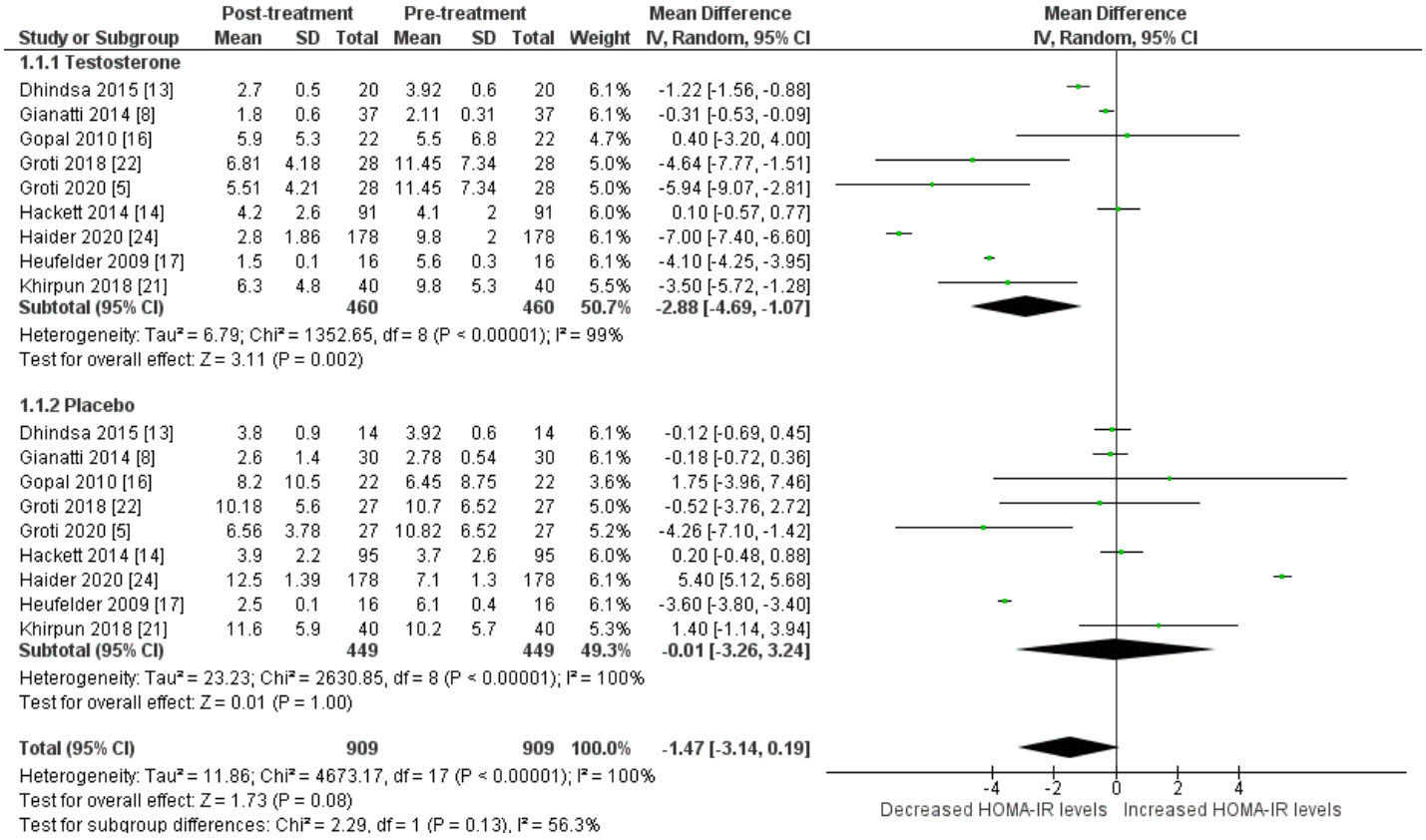
C


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.19.1 Testosterone
Dhindsa 2015 [13] 24 10 20 27 14 20 8.6% -3.00 [-10.54, 4.54]
Groti 2018 [22] 27.21 8.66 28 26.89 10.86 28 10.1% 0.32 [-4.82, 5.46]
Heufelder 2009 [17] 28.7 0.7 16 37.9 2.2 16 11.7% -9.20 [-10.33, -8.07]
Khirpun 2018 [21] 22.8 20.2 40 20.8 20.7 40 7.7% 2.00 [-6.96, 10.96]
Wittert 2021 [23] 38.1 11.3 504 37.4 13.6 504 11.6% 0.70 [-0.84, 2.24]
Subtotal (95% CI) 608 608 49.7% -2.13 [-8.36, 4.11]
Heterogeneity: Tau² = 43.06; Chi² = 111.08, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.67 (P = 0.50)
1.19.2 Placebo
Dhindsa 2015 [13] 27 13 14 26 13 14 7.3% 1.00 [-8.63, 10.63]
Groti 2018 [22] 21.68 6.54 27 21.58 6.28 27 11.0% 0.10 [-3.32, 3.52]
Heufelder 2009 [17] 30.8 1.3 16 39.7 2 16 11.7% -8.90 [-10.07, -7.73]
Khirpun 2018 [21] 21.2 16 40 18.5 17.6 40 8.7% 2.70 [-4.67, 10.07]
Wittert 2021 [23] 42.2 12.2 503 37.8 13.8 503 11.6% 4.40 [2.79, 6.01]
Subtotal (95% CI) 600 600 50.3% -0.31 [-7.98, 7.35]
Heterogeneity: Tau² = 68.98; Chi² = 181.75, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.08 (P = 0.94)
Total (95% CI) 1208 1208 100.0% -1.28 [-5.51, 2.96]
Heterogeneity: Tau² = 39.53; Chi² = 298.94, df = 9 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
-100
-50
0
50
100
Decreased SHBG
Increased SHBG

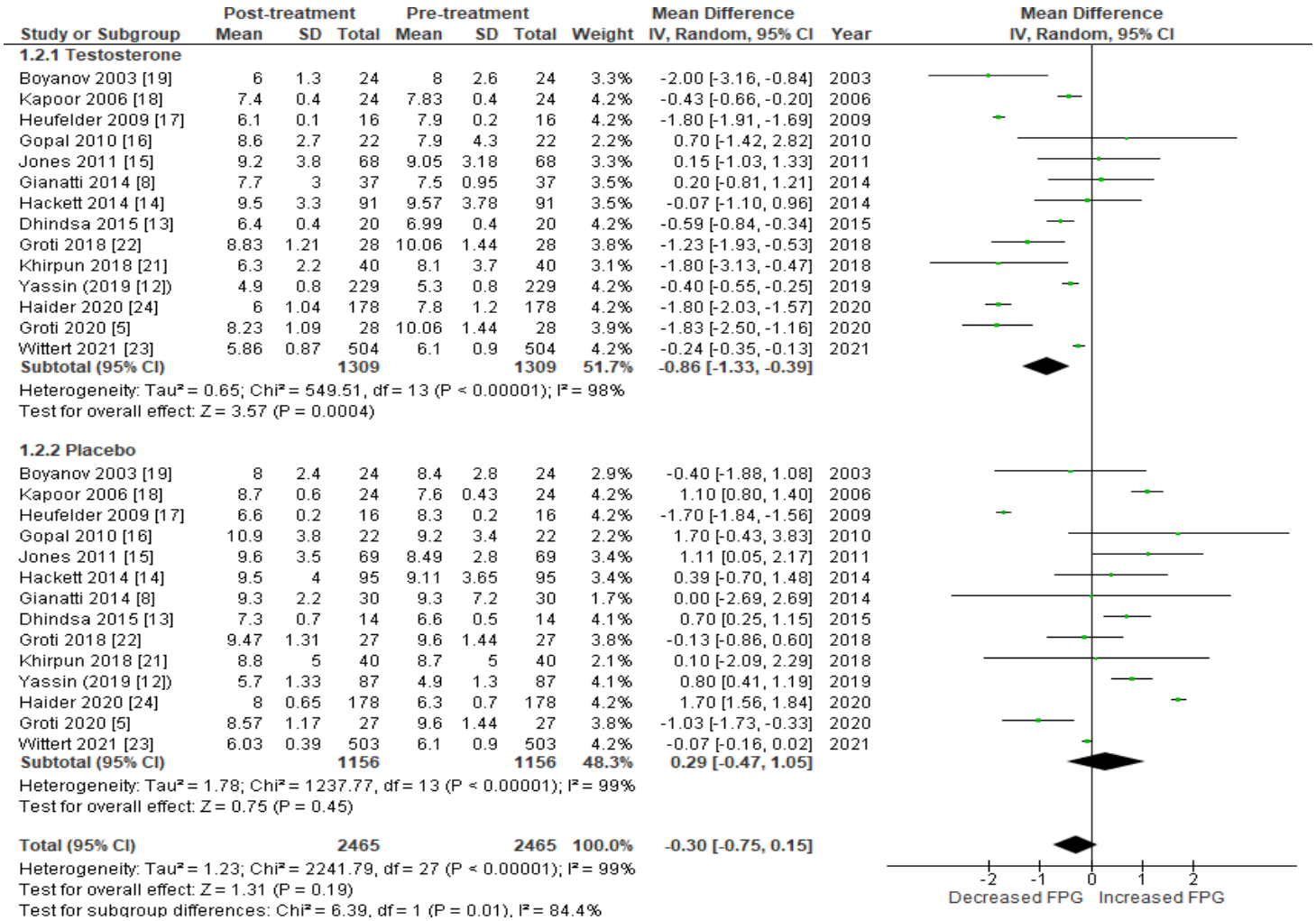
D


post treatment
pre treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.20.1 Testosterone
Dhindsa 2015 [13] 0.6 0.1 20 0.6 0.1 20 10.0% 0.00 [-0.06, 0.06]
Gianatti 2014 [8] 1.15 0.26 37 0.84 0.16 37 9.5% 0.31 [0.21, 0.41]
Hackett 2014 [14] 1.84 1.4 91 1.4 1.4 91 4.2% 0.44 [0.03, 0.85]
Heufelder 2009 [17] 2.3 0.1 16 2.3 0.1 16 9.9% 0.00 [-0.07, 0.07]
Jones 2011 [15] 1.6 1.8 68 1.6 1.8 68 2.4% 0.00 [-0.61, 0.61]
Khirpun 2018 [21] 0.9 1.3 40 1.35 0.23 40 4.1% -0.45 [-0.86, -0.04]
Wittert 2021 [23] 1.3 1.1 504 1.85 1.08 504 8.9% -0.55 [-0.68, -0.42]
Subtotal (95% CI) 776 776 48.9% -0.04 [-0.25, 0.17]
Heterogeneity: Tau² = 0.06; Chi² = 111.43, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.38 (P = 0.71)
1.20.2 Placebo
Dhindsa 2015 [13] 0.6 0.1 14 0.6 0.1 14 9.8% 0.00 [-0.07, 0.07]
Gianatti 2014 [8] 0.79 0.22 30 0.73 0.2 30 9.4% 0.06 [-0.05, 0.17]
Hackett 2014 [14] 1.57 1.4 95 1.4 1.2 95 4.6% 0.17 [-0.20, 0.54]
Heufelder 2009 [17] 2.3 0.1 16 2.3 0.1 16 9.9% 0.00 [-0.07, 0.07]
Jones 2011 [15] 1.2 1.2 69 1.2 1.2 69 4.3% 0.00 [-0.40, 0.40]
Khirpun 2018 [21] 0.9 1 40 0.8 0.9 40 4.1% 0.10 [-0.32, 0.52]
Wittert 2021 [23] 1.3 1.1 503 1.55 0.92 503 9.0% -0.25 [-0.38, -0.12]
Subtotal (95% CI) 767 767 51.1% -0.02 [-0.11, 0.07]
Heterogeneity: Tau² = 0.01; Chi² = 17.01, df = 6 (P = 0.009); I² = 65%
Test for overall effect: Z = 0.48 (P = 0.63)
Total (95% CI) 1543 1543 100.0% -0.02 [-0.13, 0.08]
Heterogeneity: Tau² = 0.03; Chi² = 128.82, df = 13 (P < 0.00001); I² = 90%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%
-1
-0.5
0
0.5
1
Decreased PSA
Increased PSA

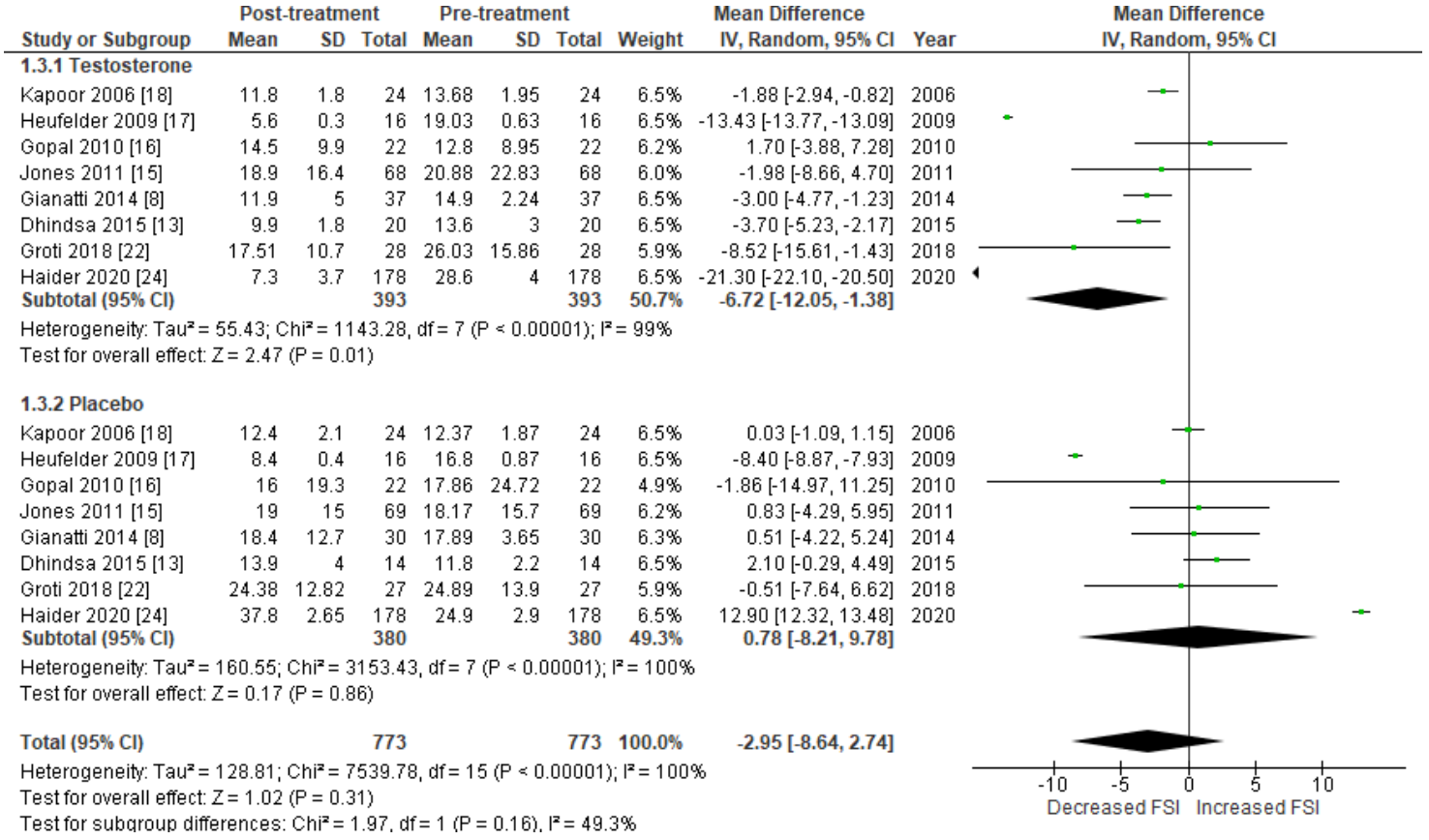
A


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Testosterone
Dhindsa 2015 [13] 2.7 0.5 20 3.92 0.6 20 6.1% -1.22 [-1.56, -0.88]
Gianatti 2014 [8] 1.8 0.6 37 2.11 0.31 37 6.1% -0.31 [-0.53, -0.09]
Gopal 2010 [16] 5.9 5.3 22 5.5 6.8 22 4.7% 0.40 [-3.20, 4.00]
Groti 2018 [22] 6.81 4.18 28 11.45 7.34 28 5.0% -4.64 [-7.77, -1.51]
Groti 2020 [5] 5.51 4.21 28 11.45 7.34 28 5.0% -5.94 [-9.07, -2.81]
Hackett 2014 [14] 4.2 2.6 91 4.1 2 91 6.0% 0.10 [-0.57, 0.77]
Haider 2020 [24] 2.8 1.86 178 9.8 2 178 6.1% -7.00 [-7.40, -6.60]
Heufelder 2009 [17] 1.5 0.1 16 5.6 0.3 16 6.1% -4.10 [-4.25, -3.95]
Khirpun 2018 [21] 6.3 4.8 40 9.8 5.3 40 5.5% -3.50 [-5.72, -1.28]
Subtotal (95% CI) 460 460 50.7% -2.88 [-4.69, -1.07]
Heterogeneity: Tau² = 6.79; Chi² = 1352.65, df = 8 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.11 (P = 0.002)
1.1.2 Placebo
Dhindsa 2015 [13] 3.8 0.9 14 3.92 0.6 14 6.1% -0.12 [-0.69, 0.45]
Gianatti 2014 [8] 2.6 1.4 30 2.78 0.54 30 6.1% -0.18 [-0.72, 0.36]
Gopal 2010 [16] 8.2 10.5 22 6.45 8.75 22 3.6% 1.75 [-3.96, 7.46]
Groti 2018 [22] 10.18 5.6 27 10.7 6.52 27 5.0% -0.52 [-3.76, 2.72]
Groti 2020 [5] 6.56 3.78 27 10.82 6.52 27 5.2% -4.26 [-7.10, -1.42]
Hackett 2014 [14] 3.9 2.2 95 3.7 2.6 95 6.0% 0.20 [-0.48, 0.88]
Haider 2020 [24] 12.5 1.39 178 7.1 1.3 178 6.1% 5.40 [5.12, 5.68]
Heufelder 2009 [17] 2.5 0.1 16 6.1 0.4 16 6.1% -3.60 [-3.80, -3.40]
Khirpun 2018 [21] 11.6 5.9 40 10.2 5.7 40 5.3% 1.40 [-1.14, 3.94]
Subtotal (95% CI) 449 449 49.3% -0.01 [-3.26, 3.24]
Heterogeneity: Tau² = 23.23; Chi² = 2630.85, df = 8 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.01 (P = 1.00)
Total (95% CI) 909 909 100.0% -1.47 [-3.14, 0.19]
Heterogeneity: Tau² = 11.86; Chi² = 4673.17, df = 17 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Chi² = 2.29, df = 1 (P = 0.13), I² = 56.3%
-4
-2
0
2
4
Decreased HOMA-IR levels
Increased HOMA-IR levels

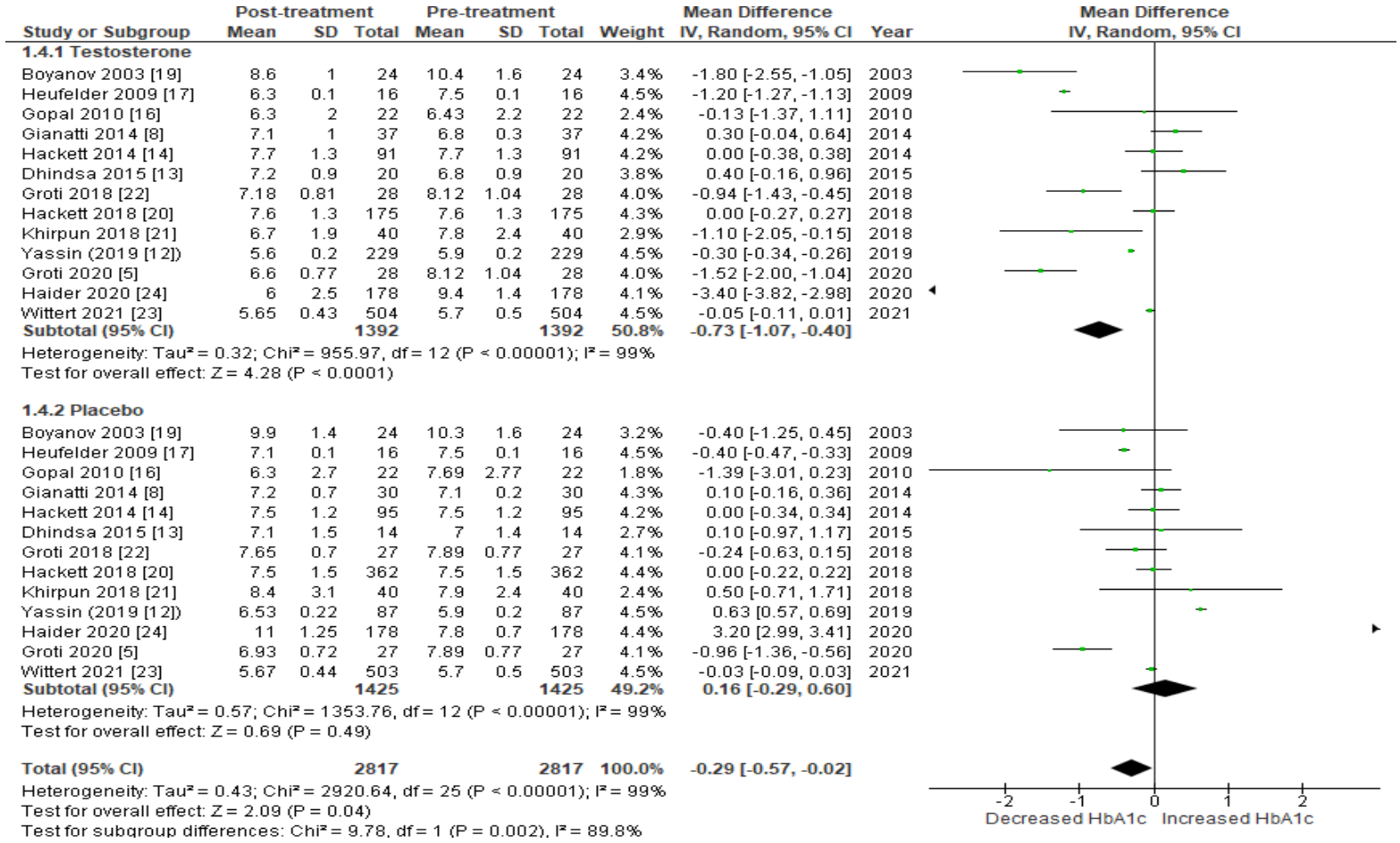
B


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
1.2.1 Testosterone
Boyanov 2003 [19] 6 1.3 24 8 2.6 24 3.3% -2.00 [-3.16, -0.84] 2003
Kapoor 2006 [18] 7.4 0.4 24 7.83 0.4 24 4.2% -0.43 [-0.66, -0.20] 2006
Heufelder 2009 [17] 6.1 0.1 16 7.9 0.2 16 4.2% -1.80 [-1.91, -1.69] 2009
Gopal 2010 [16] 8.6 2.7 22 7.9 4.3 22 2.2% 0.70 [-1.42, 2.82] 2010
Jones 2011 [15] 9.2 3.8 68 9.05 3.18 68 3.3% 0.15 [-1.03, 1.33] 2011
Gianatti 2014 [8] 7.7 3 37 7.5 0.95 37 3.5% 0.20 [-0.81, 1.21] 2014
Hackett 2014 [14] 9.5 3.3 91 9.57 3.78 91 3.5% -0.07 [-1.10, 0.96] 2014
Dhindsa 2015 [13] 6.4 0.4 20 6.99 0.4 20 4.2% -0.59 [-0.84, -0.34] 2015
Groti 2018 [22] 8.83 1.21 28 10.06 1.44 28 3.8% -1.23 [-1.93, -0.53] 2018
Khirpun 2018 [21] 6.3 2.2 40 8.1 3.7 40 3.1% -1.80 [-3.13, -0.47] 2018
Yassin (2019 [12]) 4.9 0.8 229 5.3 0.8 229 4.2% -0.40 [-0.55, -0.25] 2019
Haider 2020 [24] 6 1.04 178 7.8 1.2 178 4.2% -1.80 [-2.03, -1.57] 2020
Groti 2020 [5] 8.23 1.09 28 10.06 1.44 28 3.9% -1.83 [-2.50, -1.16] 2020
Wittert 2021 [23] 5.86 0.87 504 6.1 0.9 504 4.2% -0.24 [-0.35, -0.13] 2021
Subtotal (95% CI) 1309 1309 51.7% -0.86 [-1.33, -0.39]
Heterogeneity: Tau² = 0.65; Chi² = 549.51, df = 13 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.57 (P = 0.0004)
1.2.2 Placebo
Boyanov 2003 [19] 8 2.4 24 8.4 2.8 24 2.9% -0.40 [-1.88, 1.08] 2003
Kapoor 2006 [18] 8.7 0.6 24 7.6 0.43 24 4.2% 1.10 [0.80, 1.40] 2006
Heufelder 2009 [17] 6.6 0.2 16 8.3 0.2 16 4.2% -1.70 [-1.84, -1.56] 2009
Gopal 2010 [16] 10.9 3.8 22 9.2 3.4 22 2.2% 1.70 [-0.43, 3.83] 2010
Jones 2011 [15] 9.6 3.5 69 8.49 2.8 69 3.4% 1.11 [0.05, 2.17] 2011
Hackett 2014 [14] 9.5 4 95 9.11 3.65 95 3.4% 0.39 [-0.70, 1.48] 2014
Gianatti 2014 [8] 9.3 2.2 30 9.3 7.2 30 1.7% 0.00 [-2.69, 2.69] 2014
Dhindsa 2015 [13] 7.3 0.7 14 6.6 0.5 14 4.1% 0.70 [0.25, 1.15] 2015
Groti 2018 [22] 9.47 1.31 27 9.6 1.44 27 3.8% -0.13 [-0.86, 0.60] 2018
Khirpun 2018 [21] 8.8 5 40 8.7 5 40 2.1% 0.10 [-2.09, 2.29] 2018
Yassin (2019 [12]) 5.7 1.33 87 4.9 1.3 87 4.1% 0.80 [0.41, 1.19] 2019
Haider 2020 [24] 8 0.65 178 6.3 0.7 178 4.2% 1.70 [1.56, 1.84] 2020
Groti 2020 [5] 8.57 1.17 27 9.6 1.44 27 3.8% -1.03 [-1.73, -0.33] 2020
Wittert 2021 [23] 6.03 0.39 503 6.1 0.9 503 4.2% -0.07 [-0.16, 0.02] 2021
Subtotal (95% CI) 1156 1156 48.3% 0.29 [-0.47, 1.05]
Heterogeneity: Tau² = 1.78; Chi² = 1237.77, df = 13 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.75 (P = 0.45)
Total (95% CI) 2465 2465 100.0% -0.30 [-0.75, 0.15]
Heterogeneity: Tau² = 1.23; Chi² = 2241.79, df = 27 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Chi² = 6.39, df = 1 (P = 0.01), I² = 84.4%
-2 -1 0 1 2
Decreased FPG Increased FPG

C


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
1.3.1 Testosterone
Kapoor 2006 [18] 11.8 1.8 24 13.68 1.95 24 6.5% -1.88 [-2.94, -0.82] 2006
Heufelder 2009 [17] 5.6 0.3 16 19.03 0.63 16 6.5% -13.43 [-13.77, -13.09] 2009
Gopal 2010 [16] 14.5 9.9 22 12.8 8.95 22 6.2% 1.70 [-3.88, 7.28] 2010
Jones 2011 [15] 18.9 16.4 68 20.88 22.83 68 6.0% -1.98 [-8.66, 4.70] 2011
Gianatti 2014 [8] 11.9 5 37 14.9 2.24 37 6.5% -3.00 [-4.77, -1.23] 2014
Dhindsa 2015 [13] 9.9 1.8 20 13.6 3 20 6.5% -3.70 [-5.23, -2.17] 2015
Groti 2018 [22] 17.51 10.7 28 26.03 15.86 28 5.9% -8.52 [-15.61, -1.43] 2018
Haider 2020 [24] 7.3 3.7 178 28.6 4 178 6.5% -21.30 [-22.10, -20.50] 2020
Subtotal (95% CI) 393 393 50.7% -6.72 [-12.05, -1.38]
Heterogeneity: Tau² = 55.43; Chi² = 1143.28, df = 7 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.47 (P = 0.01)
1.3.2 Placebo
Kapoor 2006 [18] 12.4 2.1 24 12.37 1.87 24 6.5% 0.03 [-1.09, 1.15] 2006
Heufelder 2009 [17] 8.4 0.4 16 16.8 0.87 16 6.5% -8.40 [-8.87, -7.93] 2009
Gopal 2010 [16] 16 19.3 22 17.86 24.72 22 4.9% -1.86 [-14.97, 11.25] 2010
Jones 2011 [15] 19 15 69 18.17 15.7 69 6.2% 0.83 [-4.29, 5.95] 2011
Gianatti 2014 [8] 18.4 12.7 30 17.89 3.65 30 6.3% 0.51 [-4.22, 5.24] 2014
Dhindsa 2015 [13] 13.9 4 14 11.8 2.2 14 6.5% 2.10 [-0.29, 4.49] 2015
Groti 2018 [22] 24.38 12.82 27 24.89 13.9 27 5.9% -0.51 [-7.64, 6.62] 2018
Haider 2020 [24] 37.8 2.65 178 24.9 2.9 178 6.5% 12.90 [12.32, 13.48] 2020
Subtotal (95% CI) 380 380 49.3% 0.78 [-8.21, 9.78]
Heterogeneity: Tau² = 160.55; Chi² = 3153.43, df = 7 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.17 (P = 0.86)
Total (95% CI) 773 773 100.0% -2.95 [-8.64, 2.74]
Heterogeneity: Tau² = 128.81; Chi² = 7539.78, df = 15 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Chi² = 1.97, df = 1 (P = 0.16), I² = 49.3%
-10 -5 0 5 10
Decreased FSI Increased FSI

D


Post-treatment
Pre-treatment
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
1.4.1 Testosterone
Boyanov 2003 [19] 8.6 1 24 10.4 1.6 24 3.4% -1.80 [-2.55, -1.05] 2003
Heufelder 2009 [17] 6.3 0.1 16 7.5 0.1 16 4.5% -1.20 [-1.27, -1.13] 2009
Gopal 2010 [16] 6.3 2 22 6.43 2.2 22 2.4% -0.13 [-1.37, 1.11] 2010
Gianatti 2014 [8] 7.1 1 37 6.8 0.3 37 4.2% 0.30 [-0.04, 0.64] 2014
Hackett 2014 [14] 7.7 1.3 91 7.7 1.3 91 4.2% 0.00 [-0.38, 0.38] 2014
Dhindsa 2015 [13] 7.2 0.9 20 6.8 0.9 20 3.8% 0.40 [-0.16, 0.96] 2015
Groti 2018 [22] 7.18 0.81 28 8.12 1.04 28 4.0% -0.94 [-1.43, -0.45] 2018
Hackett 2018 [20] 7.6 1.3 175 7.6 1.3 175 4.3% 0.00 [-0.27, 0.27] 2018
Khirpun 2018 [21] 6.7 1.9 40 7.8 2.4 40 2.9% -1.10 [-2.05, -0.15] 2018
Yassin (2019 [12]) 5.6 0.2 229 5.9 0.2 229 4.5% -0.30 [-0.34, -0.26] 2019
Groti 2020 [5] 6.6 0.77 28 8.12 1.04 28 4.0% -1.52 [-2.00, -1.04] 2020
Haider 2020 [24] 6 2.5 178 9.4 1.4 178 4.1% -3.40 [-3.82, -2.98] 2020
Wittert 2021 [23] 5.65 0.43 504 5.7 0.5 504 4.5% -0.05 [-0.11, 0.01] 2021
Subtotal (95% CI) 1392 1392 50.8% -0.73 [-1.07, -0.40]
Heterogeneity: Tau² = 0.32; Chi² = 955.97, df = 12 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.28 (P < 0.0001)
1.4.2 Placebo
Boyanov 2003 [19] 9.9 1.4 24 10.3 1.6 24 3.2% -0.40 [-1.25, 0.45] 2003
Heufelder 2009 [17] 7.1 0.1 16 7.5 0.1 16 4.5% -0.40 [-0.47, -0.33] 2009
Gopal 2010 [16] 6.3 2.7 22 7.69 2.77 22 1.8% -1.39 [-3.01, 0.23] 2010
Gianatti 2014 [8] 7.2 0.7 30 7.1 0.2 30 4.3% 0.10 [-0.16, 0.36] 2014
Hackett 2014 [14] 7.5 1.2 95 7.5 1.2 95 4.2% 0.00 [-0.34, 0.34] 2014
Dhindsa 2015 [13] 7.1 1.5 14 7 1.4 14 2.7% 0.10 [-0.97, 1.17] 2015
Groti 2018 [22] 7.65 0.7 27 7.89 0.77 27 4.1% -0.24 [-0.63, 0.15] 2018
Hackett 2018 [20] 7.5 1.5 362 7.5 1.5 362 4.4% 0.00 [-0.22, 0.22] 2018
Khirpun 2018 [21] 8.4 3.1 40 7.9 2.4 40 2.4% 0.50 [-0.71, 1.71] 2018
Yassin (2019 [12]) 6.53 0.22 87 5.9 0.2 87 4.5% 0.63 [0.57, 0.69] 2019
Haider 2020 [24] 11 1.25 178 7.8 0.7 178 4.4% 3.20 [2.99, 3.41] 2020
Groti 2020 [5] 6.93 0.72 27 7.89 0.77 27 4.1% -0.96 [-1.36, -0.56] 2020
Wittert 2021 [23] 5.67 0.44 503 5.7 0.5 503 4.5% -0.03 [-0.09, 0.03] 2021
Subtotal (95% CI) 1425 1425 49.2% 0.16 [-0.29, 0.60]
Heterogeneity: Tau² = 0.57; Chi² = 1353.76, df = 12 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.69 (P = 0.49)
Total (95% CI) 2817 2817 100.0% -0.29 [-0.57, -0.02]
Heterogeneity: Tau² = 0.43; Chi² = 2920.64, df = 25 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Chi² = 9.78, df = 1 (P = 0.002), I² = 89.8%
-2
-1
0
1
2
Decreased HbA1c
Increased HbA1c

Supplementary Table S1: Detailed search strategy

Database	Search strategy	Results
PubMed	((((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	300
Google Scholar	((((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	284
Embase	((((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	75

Supplementary Table 2: Characteristics of RCTs

Characteristic	Dhindsa (2015) [13]	Gianatti (2014) [8]	Hackett (2014) [14]	Jones (2011) [15]	Gopal (2010) [16]	Heulfelder (2009) [17]	Kapoor (2006) [18]	Boyonav (2003) [19]	Hackett (2018) [20]	Khirpun (2018) [21]	Groti (2018) [22]	Groti (2020) [5]	Wittert (2021) [23]
Study name	Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men with Type 2 Diabetes	Effect of Testosterone Treatment on Glucose Metabolism in Men with Type 2 Diabetes: A Randomized Controlled Trial	Testosterone Replacement Therapy Improves Metabolic Parameters in Hypogonadal Men with Type 2 Diabetes but Not in Men with Coexisting Depression: The BLAST Study	Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or Metabolic Syndrome (the TIMES2 Study)	Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus	Fifty- two—Week Treatment with Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycaemic Control in Men with Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone	Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes	Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors	Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors	Influence of testosterone substitution on glycaemic control and endothelial markers in men with newly diagnosed functional hypogonadism and type 2 diabetes mellitus: a randomized controlled trial	The impact of testosterone replacement therapy on glycaemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes	Testosterone treatment longer than 1 year shows more effects on functional hypogonadism and related metabolic, vascular, diabetic and obesity parameters (results of the 2-year clinical trial)	Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial
Patients, n	94	88	211	220	22	32	27	48	857	80	55	55	1007
Enrolment	2010	2009	2008	2006	2006	2005	2002	1998	2007	2012	2014	2014	2013

Initiation													
Enrolment completion	2014	2013	2012	2007	2009	2008	2006	2002	2009	2017	2018	2018	2017
Year of completion	2014	2014	2014	2011	2010	2009	2006	2003	2018	2018	2018	2020	2021
Population	Male subjects with type 2 diabetes between the ages of 30 and 65 years, HbA1c #8% (64 mmol/mol), and stable diabetes regimen for 3 months	Study subjects were recruited from specialist diabetes clinics, primary care, and the general community	Patients were recruited from routine diabetes assessment	Male subjects with diabetes and hypogonadism.	Patients with T2DM in the 25- to 50-year age-group who were diagnosed with hypogonadism were included in the study.	Male patients with type 2 diabetes and hypogonadism	men aged over 30 years with type 2 diabetes and with hypogonadism.	middle-aged men with both type 2 diabetes mellitus and mild androgen deficiency.	Male subjects with diabetes and hypogonadism.	men newly diagnosed with T2DM according to the criteria of the American Diabetes Association and referring to HbA1c levels as leading parameter (HbA1c levels had to be measured two times within 4 weeks above 6.5%	Obese males with hypogonadism and diabetes	Obese males with hypogonadism and diabetes	men newly diagnosed with T2DM according to the criteria of the American Diabetes Association and referring to HbA1c levels as leading parameter (HbA1c levels had to be measured two times within 4 weeks above 6.5%
Trial type	randomized, parallel, placebo controlled, double-blind, prospective, single-centre trial	randomized, double-blind, placebo-controlled trial	double-blind, placebo-controlled intervention study	prospective, randomized, double-blind, placebo-controlled, multicentre study	double-blind, placebo-controlled, crossover study	randomized, double-blind, placebo-controlled trial	double-blind placebo-controlled crossover study	open-label, randomized, no-treatment controlled study	double -blind randomised placebo -controlled study	double -blind randomised placebo -controlled study	double -blind randomised placebo -controlled study	double -blind randomised placebo -controlled study	randomised, double-blind, placebo-controlled

Inclusion Criteria	Male subjects with type 2 diabetes between the ages of 30 and 65 years, HbA1c #8% (64 mmol/mol), and stable diabetes regimen for 3 months were recruited between December 2010 and January 2014	Men aged 35–70 years of age were eligible to participate in this trial if they had a history of T2D, and the total testosterone (TT) level (averaged from two fasting morning specimens) was #12.0 nmol/L (346 ng/dL).	Inclusion criteria for the BLAST intervention study were men aged 18–80 with type 2 diabetes and willing to give written informed consent. Eligibility included an initial finding of either a total testosterone between 8.1 and 12 nmol/L or FT 0.181–0.25 nmol/L (mild group), or total testosterone of 8.0 nmol/L or less or 0.18 nmol/L FT or less (severe group) according to the current 2006 ISSAM EAU guidelines, and with symptoms of	Men aged $40 years were eligible to enter the study if they had confirmed hypogonadism (early morning [08002 1000 h] total testosterone [TT] #11 nmol/L or free testosterone #255 pmol/L on two occasions $1 week apart), with at least two symptoms of hypogonadism (14) and fulfilled criteria for type 2 diabetes (15) and/or MetS	Patients with T2DM in the 25- to 50-year age-group who were diagnosed with hypogonadism were included in the study. Hypogonadism was defined as a calculated free testosterone (cFT) level less than 64.8 pg/mL (0.225 nmol/L) on at least 2 occasions in the presence of symptoms of hypogonadism.	males with the MetS and newly diagnosed T2D (fasting plasma glucose .7.0 at baseline and/or .11.1 after a 2-hour, 75-g oral glucose tolerance test, and an elevated level of HbA1c)	Type 2 diabetic men with HbA1c up to 9.5% showing no significant symptoms of hyperglycaemia. Hypogonadism was defined as total testosterone level!12 nmol/l (on two separate occasions) and symptoms of hypogonadism (positive ADAM score)	subjects had to be aged between 45 and 65 years, be married or living in a stable relationship with a female sexual partner for at least 6 months, have a waist–hip ratio (WHR) of at least 0.9, have symptoms of andropause or erectile dysfunction, and have serum testosterone	Men aged 18 to 80 years with an initial finding of either a TT (on 2 separate occasions) ≤12 nmol/L or FT≤0.18 nmol/L with symptoms of HG defined by the Ageing Male Symptom score.	Men with newly diagnosed diabetes potential functional hypogonadism according to the diagnostic criteria of the EAU guideline on male hypogonadism as of 2015 (serum levels of total testosterone two times below 12.1 nmol/L or serum levels of free testosterone two times below 243 pmol/L in combination of at least two symptoms or complaints of sexual or psychological nature)	men aged > 35 years body mass index > 30 kg/m2 confirmed hypogonadism type 2 diabetes mellitus treated with non-insulin therapy	men aged > 35 years body mass index > 30 kg/m2 confirmed hypogonadism type 2 diabetes mellitus treated with non-insulin therapy	. Men aged 50–74 years, with a waist circumference of 95 cm or higher, a serum testosterone concentration of 14·0 nmol/L or lower but without pathological hypogonadism, and impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose 7·8–11·0 mmol/L) or newly diagnosed type 2 diabetes (provided OGTT 2-h glucose ≤15·0 mmol/L)

			hypogonadism defined by the ageing male symptom (AMS)											
Exclusion criteria	Subjects on androgens, glucocorticoids, or opiates in the last 6 months or with panhypopituitarism, congenital HH, prolactinoma, head trauma, severe hepatic or kidney disease (glomerular filtration rate ,30 mL/min/m2), HIV, prostate specific antigen .4 ng/mL, or contraindications to testosterone replacement therapy were excluded from the study.	Exclusion criteria included testosterone treatment within 5 years prior to randomization, established pituitary or testicular disorder, screening TT level of ,5.0 nmol/L (144 ng/dL), luteinizing hormone (LH) level .1.53 upper limit of normal, or screening prostate-specific antigen (PSA) level. 4 mg/L, a history of urinary obstruction, prostate cancer, or breast cancer, hematocrit .0.50, uncontrolled hypertension (.160/90 mmHg despite treatment), untreated obstructive	Exclusion criteria included any past history of testosterone replacement, history of prostate, breast or hepatic cancer, abnormal digital rectal examination, severe symptoms of prostate hypertrophy or elevated prostate-specific antigen (PSA) (>4 mm// L), or hematocrit of 55% or greater. If, in the opinion of the principal investigator, the cause of elevated PSA was well-controlled	Exclusion criteria included TRT within 6 months of randomization, hormone modulating therapies or topical/systemic glucocorticoids within 3 months of randomization, or insulin therapy; a history of/ current prostate or breast cancer; abnormal digital rectal examination suggestive of prostate carcinoma; severe symptomatic benign prostatic hyperplasia or	Those with a history of pre-existing hypogonadism, panhypopituitarism, chronic renal failure, chronic liver disease, chronic alcoholism, radiation therapy, inflammatory disease or active infection, hormone therapy, or any contraindication to testosterone therapy such as elevation of the prostate-specific antigen (PSA) value beyond the age-adjusted reference	-	Patients were excluded if they had any inflammatory disease or infection with elevation of C-reactive protein O10 mg/l, were already on hormone therapy or had any contraindication to testosterone therapy such as elevation of prostate-specific antigen (PSA) beyond the age-adjusted normal range.	Subjects were excluded from the trial if they had concurrent illnesses other than diabetes or surgical interventions likely to impair sexual function, severe diabetic complications such as amputations or chronic renal failure, drug use other than antidiabetic medication or antihyper-tensives (angiotensin-converting enzyme (ACE inhibitors), history of alcoholism or major psycho-pathology; or any sign or	Exclusion criteria included any past history of testosterone therapy, history of prostate, breast or hepatic cancer, abnormal digital rectal examination, severe symptoms of prostate hypertrophy or elevated prostate-specific antigen>4 ng/mL or haematocrit≥55%.	Exclusion criteria were primary or secondary hypogonadism of any origin (testicular damage, diagnosis of pituitary/hypothalamic malfunction), as well as hyperprolactinemia and hypothyroidism. Also, any history of a malignant disease as well as elevated levels of PSA (>4 mg/dL) and the wish for paternity led to exclusion.	previously treated hypogonadism the 2-diabetes mellitus treated with insulin therapy a history of curren t prostate or breast cancer severe benign prostatic hyper plasia elevated prostate-specific antigen (PSA	previously treated hypogonadism the 2-diabetes mellitus treated with insulin therapy a history of current prostate or breast cancer severe benign prostatic hyperplasia elevated prostate-specific antigen (PSA > 4.0 lg/l) severe heart failure acute coronary event or procedure during the six months leading up to the study	p rimary or secondary hypogonadism of any origin (testicular damage, diagnosis of pituitary /hypothalamic malfunction), as well as hyperprolactinemia and hypothyroidism. Also, any history of a malignant disease as well as elevated levels of PSA (>4 mg/dL) and the wish for paternity led to exclusion.

		sleep apnea, estimated glomerular filtration rate , 30 mL/min, cardiac insufficiency (New York Heart Association score .2), active malignancy, unstable psychiatric disease, weight .135 kg (the weight limit for the dual-energy X-ray absorptiometry [DXA] scanner), current use of glucagonlike peptide-1 agonist therapy or very low-calorie diet, or an	BPH, and malignancy had been recently excluded, patients were eligible	elevated age-specific prostate-specific antigen (PSA).	range; patients with an American Urological Association questionnaire (used for symptoms of prostatism) score >22; and those with uncontrolled blood glucose levels—hemoglobin A1c (A1C) >10%				evidence of prostate enlargement or abnormalities.		> 4.0 lg/l) severe heart failure acute coronary event or procedure during the six months leading up to the study chronic obstructive lung disease hypothyroidism severe obstructive sleep apnea (OSA) active infection rheumatoid arthritis		
Treatments	250 mg testosterone cypionate (Watson	Intramuscular testosterone undecanoate 1,000 mg or a	Subjects were randomized to receive	Subjects were randomized (1:1) to	Testosterone cypionate (Cernos),	Patients were randomized to either supervised diet	Sustanon 200 mg (testosterone propionate	oral testosterone undecanoate	long-acting testosterone undecanoate	T-Gel at a dose of 50 mg per day	testosterone undecanoate	testosterone undecanoate 1000	intramuscular injection of testoster

	Pharmaceuticals, New Jersey; 200 mg/mL) or placebo (1.25 cc saline) intramuscularly in the buttock.	visually identical placebo injection (both in oily base) was injected into the upper outer quadrant of the buttock at 0, 6, 18, and 30 weeks	either TU 1,000 mg at week 0, week 6, week 18, administered by the practice nurse or GP over 5 minutes into the right or left upper outer buttock, or matching placebo	receive either 3 g metered-dose 2% testosterone gel (60 mg testosterone, Tostran [also known as Fortigel, Tostrex, Itnogen, Foresta; ProStrakan, Galashiels, Scotland, U.K.]) or placebo gel once daily	200 mg, a depot preparation of testosterone administered by deep intramuscular injection. Placebo was given as 0.9% isotonic saline	and exercise (D&E) alone or in combination with testosterone gel (50 mg once daily; Testo gel; Bayer Schering Pharma AG, Berlin, Germany)	30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/ml, Organon Laboratories, Cambridge, UK), a depot preparation.	(TU; AndriolÒ, Organon, Oss, The Netherlands) for 3 months, at a daily oral dosage of 120 mg, divided into 80 mg at breakfast and 40 mg at dinner (during the meals).	1000 mg intramuscular injections two years; according to the protocol every 10 weeks. Placebo arm patients were receiving placebo throughout the first year of this study and testosterone undecanoate 1000 mg intramuscular injections during second year.	mg intramuscular injections two years; according to the protocol every 10 weeks. Placebo arm patients were receiving placebo throughout the first year of this study and testosterone undecanoate 1000 mg intramuscular injections during second year.	one undecanoate (1000 mg) or placebo at baseline, 6 weeks, and then every 3 months for 2 years.

Primary Outcomes	The impact of HH on insulin resistance, inflammation, and body composition in men with type 2 diabetes	The primary outcome measure was the change across groups and time from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR).	The primary outcome measure was the change across groups and time from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR).	The primary end point was the difference between treatment groups in homeostasis model assessment (HOMA)-IR from baseline to months 6 and 12.	changes in the homeostasis model assessment (HOMA) index of IR, fasting blood glucose level, and A1C value.	The primary end point was the difference between treatment groups in homeostasis model assessment (HOMA)-IR from baseline to months 6 and 12	Changes in the homeostasis model assessment (HOMA) index of insulin resistance, fasting blood glucose and glycated haemoglobin.	changes in the homeostasis model assessment (HOMA) index of IR, fasting blood glucose level, and A1C value.	The primary outcome measure was the change across groups and time from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR).	The primary outcome measure was the change across groups and time from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR).	Effects of testosterone replacement therapy on glycaemic control - fasting plasma glucose (FPG) mmol/l, HbA1c, HOMA-IR, vascular function - change in flow mediated dilatation (FMD) %. vascular morphology - intima-media thickness (IMT)	Effects of testosterone replacement therapy on glycaemic control - fasting plasma glucose (FPG) mmol/l, HbA1c, HOMA-IR, vascular function - change in flow mediated dilatation (FMD) %. vascular morphology - intima-media thickness (IMT)	type 2 diabetes (2-h OGTT glucose ≥11·1 mmol/L) and mean change from baseline in 2-h OGTT glucose, assessed by intention to treat.

Secondary outcomes	-	The secondary outcome measure was the change across group and time in glycaemic control as measured by HbA1c. Other outcome measures were considered as explanatory variables.	The secondary outcome measure was the change across group and time in glycaemic control as measured by HbA1c. Other outcome measures were considered as explanatory variables.	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	changes in fasting lipids, anthropometric factors including BMI, waist circumference, and WHR, blood pressure, and androgen deficiency symptoms	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Changes in fasting lipids, blood pressure and anthropometric measurements including waist circumference, waist/ hip ratio, BMI and % body fat	changes in fasting lipids, anthropometric factors including BMI, waist circumference, and WHR, blood pressure, and androgen deficiency symptoms	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Effects of testosterone replacement therapy on non-alcoholic fatty liver disease (NAFLD), bone mineral density (BMD), total testosterone (TT), prostate specific antigen and haematocrit	Effects of testosterone replacement therapy on non-alcoholic fatty liver disease (NAFLD), bone mineral density (BMD), total testosterone (TT), prostate specific antigen and haematocrit	monitoring of haematocrit and prostate-specific antigen, and analysed prespecified serious adverse events
Follow up	24 weeks	40 weeks	52 weeks	12 months	7 months	52 weeks	7 months	3 months	3.4 years	9 months	1 year	2 years	2 years

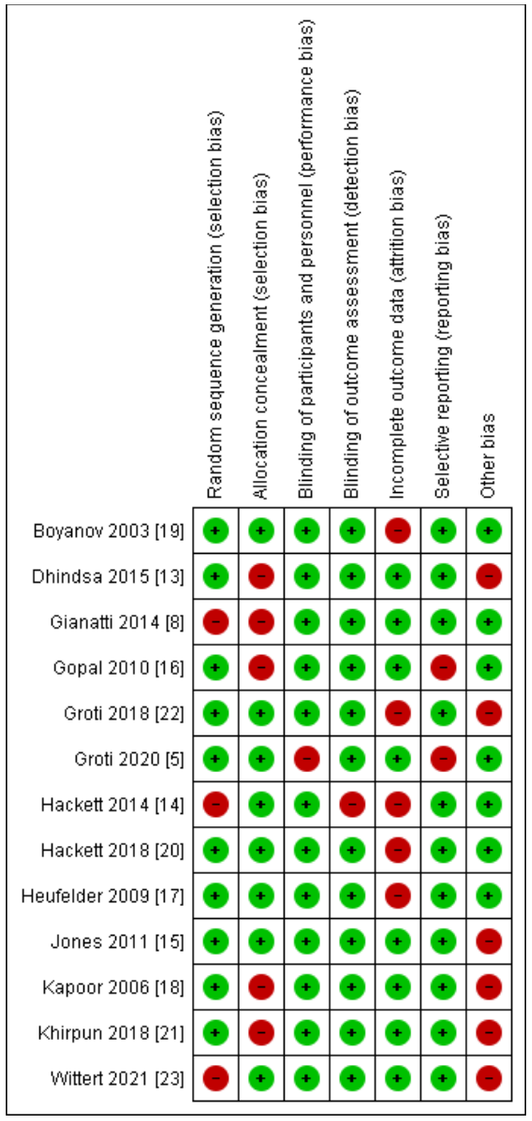
Supplementary Table S3: Characteristics of Observational Studies

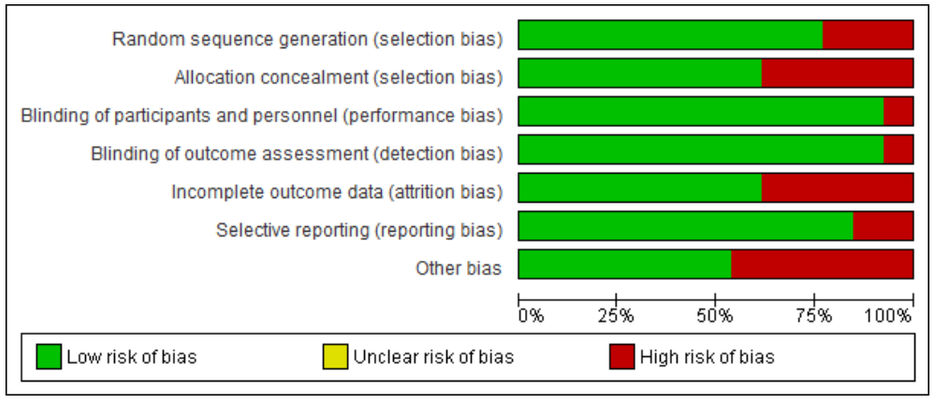
Characteristics	Yassin (2019) [12]	Haider (2020) [24]
Study name	Testosterone Therapy in Men with Hypogonadism Prevents Progression from Prediabetes to Type 2 Diabetes: Eight-Year Data from a Registry Study	Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study
Patients, n	316	356
Initiation	2011	2008
Completion	2018	2019
Year of publication	2019	2020
Population	Patients in this study were pooled from two ongoing urological registries. Ethical guidelines by the German Medical Association for observational studies in patients receiving standard treatment were followed	Patients with diabetes managed by the same local diabetes centre
Inclusion criteria	Prediabetes, defined as HbA1c 5.7–6.4% (39–46 mmol/mol), and total testosterone levels #12.1 nmol/L (;350 ng/dL) combined with symptoms of hypogonadism.	Patients with T2DM who had total testosterone levels ≤12.1 nmol/L (350 ng/dL) and symptoms of hypogonadism
Exclusion criteria	--	...
Primary Outcome	Anthropometric and metabolic parameters	glucose intolerance, with glycated haemoglobin (HbA1c) and insulin secretion

Supplementary Table S4: New Castle Ottawa scale to assess Publication bias in Observational studies

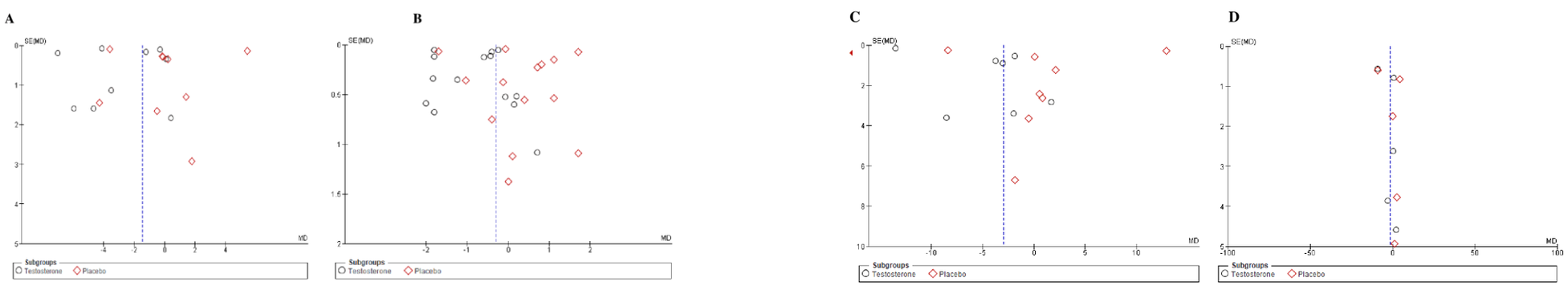
Study	Selection				Comparability	Outcomes			Total
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	
Yassin (2019) [12]	*	*	*	*	**	*	*	*	*********
Haider (2020) [24]	*	*	*	*	*	*	*	*	********

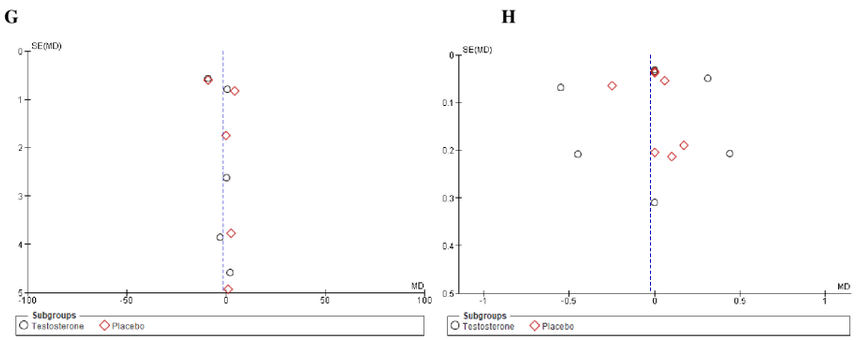
Supplementary Table S4: Cochrane risk of bias tool for assessing publication bias in Randomized controlled trials

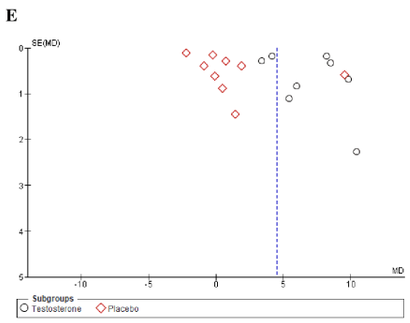


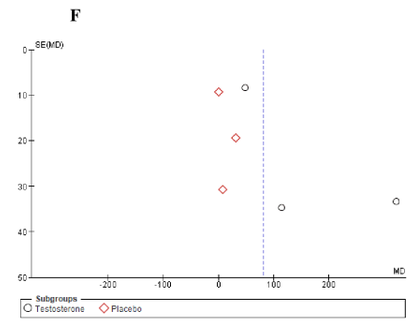


Supplementary Figure S1: Funnel Plots of primary outcomes









A: Homeostatic model assessment for insulin resistance (HOMA-IR), B: Fasting plasma glucose (FPG), C: Fasting serum insulin (FSI), D: Glycated hemoglobin (HbA1C), E: Total testosterone (TT), F: Free testosterone (FT), G: Sex hormone binding globulin (SHBG), H: Prostate specific antigen (PSA)