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Testosterone and depressive symptoms among men in the Diabetes Prevention Program

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Structured Abstract

Objective—We examined associations between randomization to intensive lifestyle intervention (ILS) and changes in testosterone and associations with mood among middle-aged men.

Design—Secondary analysis of men (n=886) participating in the Diabetes Prevention Program which randomized glucose-intolerant, overweight men to ILS, metformin, or placebo.

Main Outcome Measures—Changes in testosterone between baseline and 1-year follow-up and associations of these changes with mood measures (Beck Depression Inventory [BDI], Beck Anxiety Inventory [BAI])

Results—Median baseline testosterone was 10.98 nmol/l and 44% (n=385) had testosterone < 10.41 nmol/l or 300 ng/dl, a common threshold for biochemical hypogonadism. Testosterone increases were greater among men randomized to ILS vs. metformin vs. placebo (1.15 nmol/l vs. -0.12 nmol/l vs. -0.27 nmol/l, p<0.001). The association between changes in testosterone and mood differed by randomization arm (p<0.001 for interaction); there were no significant associations between changes in testosterone and mood changes among men randomized to ILS or

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placebo. Among men randomized to metformin, increases in testosterone were significantly associated with decreases in BDI (improved depressive symptoms) (β -coefficient -0.2336 , $p=0.0002$) indicating a 0.23 decrease in BDI for every 1 nmol/l increase in testosterone and decreases in BAI (improved anxiety symptoms) (β -coefficient -0.2147 , $p=0.0014$). Similar patterns were observed for bioavailable testosterone.

Conclusions—Among overweight middle-aged men with glucose-intolerance, ILS increased endogenous testosterone slightly but without significant improvements in mood. Metformin did not increase testosterone, but among participants randomized to metformin, testosterone increases were associated with improvements in mood. Thus, interventions that increase endogenous testosterone may not also improve mood.

Keywords

testosterone; androgens; mood; glucose-intolerance

Among older men, low testosterone concentrations are associated with depressed mood (1–4) and with incident depression (5,6). The extent to which testosterone is associated with mood independent of advancing age, and the relationships with weight changes and anti-depressant medication use, are not clear. On average, testosterone levels decline by approximately 0.8% per year beginning in middle-age, so that a man with a baseline value of 17.35 nmol/l (500 ng/dl) could have a decline of about 0.69 – 0.87 nmol/l (4–5 ng/dl) per year (7). Although average testosterone concentrations decline with age, variation across individuals is large, and some men experience minimal declines over years of follow-up (8). Comorbidities, particularly obesity, are strongly associated with reduced testosterone concentrations (8,9). In turn, older age (10) and greater weight (11) are associated with increased risk of depression.

Observational studies suggest that overweight and obese men who undergo lifestyle modification experience increases in testosterone (8,12–16). However, no randomized trials have examined whether lifestyle changes result in endogenous testosterone changes, and whether subsequent increases have beneficial effects upon mood. To our knowledge, no studies in men have examined whether testosterone levels change with randomization to metformin. Several observational studies suggest that metformin decreases testosterone levels along with weight (17,18), although another small observational study noted that testosterone increased after implementation of modifications to diet and increases in physical activity (19). Randomization to other antidiabetic medications such as pioglitazone has been reported to decrease total and bioavailable testosterone even with significant weight loss (20).

The Diabetes Prevention Program (DPP) was a randomized clinical trial which assigned overweight, glucose-intolerant individuals to intensive lifestyle intervention (ILS) vs. metformin vs. placebo with the goal of diabetes delay or prevention (21). Previous DPP reports have noted that participants reported a decline in depressive symptoms over the course of the study, largely attributable to the concurrent trend of increased anti-depressant medication use, but also due to weight loss (22). The DPP measured androgen levels at baseline and at one-year follow-up and concurrently assessed mood, anti-depressant

medication use, and weight. The majority of men were less than 65 years of age at baseline. Approximately 55% had total testosterone concentrations greater than 10.41 nmol/l (300 ng/dl) (23), a cutpoint commonly used to define hypogonadism (24). Thus, we were able to examine whether randomization to lifestyle or metformin altered testosterone and the magnitude of the association between changes in endogenous testosterone and concurrent changes in mood. Specifically, we addressed the following questions: 1) does randomization to a lifestyle intervention targeting weight loss or randomization to metformin alter testosterone compared to placebo among mid-life men, 2) are changes in endogenous testosterone associated with changes in mood in mid-life men, independent of age, race/ethnicity, weight, and anti-depressant medication use, 3) are changes in testosterone associated with mood changes in a cohort with a wide range of testosterone levels, including men whose testosterone levels were higher than levels considered to be hypogonadal?

Materials and Methods

The DPP study population has been previously described (21). The eligibility criteria included age at least 25 years, BMI at least 24 kg/m² (22 kg/m² in people of Asian descent), fasting plasma glucose 95–125 mg/dl, and glucose 2 hours after a 75-g oral glucose load of 140–199 mg/dl. All participants provided written informed consent, and each participating institution was overseen by its own ethics review board.

Eligible participants were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or ILS. The goals of ILS were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet plus moderate physical activity for at least 150 minutes per week. Weight and waist circumference were measured semiannually. Participants included in this report approved the use of their blood samples for secondary analyses. This cohort included male DPP participants with pre-randomization blood samples and blood samples one-year after randomization that were available for steroid sex hormone assays (Figure 1) and who did not report exogenous sex steroid use. We excluded one participant with a large increase in testosterone concentrations suggesting unreported hormone use, on the order of 34 nmol/l, (~1000 ng/dl) for a total of 886 participants.

Testosterone and SHBG measurements

As previously described,(23) sex steroids were measured using gas chromatography/mass spectrometry. The lower limits of quantification for testosterone was 0.1735 nmol/l. Interassay variation (coefficient of variation) at the lower limit of quantification for testosterone was 10.7%. Values were extrapolated below the lower limit of quantitation using Mass Hunter Workstation software (Agilent, Santa Clara, CA). Sex hormone binding globulin (SHBG) was assessed using an ELISA (Bioline) with interassay coefficients of variation of 7.8% and 5.0% at 18.2 and 63.1 nmol/l, respectively.

Mood assessments

Participants completed the Beck Depression Inventory (BDI) prior to randomization and at each annual visit (25). The BDI is a 21-item depression severity scale for adults. Higher

scores indicate more symptoms; while cut points vary, 0–13 indicates no or minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression. Although the minimal clinically important change in BDI score is controversial, clinically significant reductions are considered to be on the order of 2 points (26). Participants also brought all prescription medicines to each clinic visit, from which the use of antidepressants was recorded. Due to the mild nature of symptoms in the DPP cohort, significant depressive symptoms have been previously defined in the DPP as BDI scores 11 or use of anti-depressant medication (22). We also examined the relationship between androgen changes and other measurements of mood and well-being in the DPP, including the Beck Anxiety Inventory (BAI) (27) using a cut point of 8 to define significant anxiety, and the physical (PCS) and mental components (MCS) of the Medical Outcomes Study 36-item short form (SF-36) (28). The SF-36 is a 36-item generic health survey that has been widely validated and used in an international context to evaluate self-reported domains of health status. Scoring algorithms produce a standardized score for each of the two health dimensions by setting the general population mean at 50 ± 10 (mean $\pm$ 1 SD) (28), and increases in the numerical score indicate improved functioning. As with BDI, the minimally clinically significant change is controversial, although changes of at least 7 points are usually considered significant (29).

Statistical analysis

Baseline characteristics were described using percentages for categorical variables and means (SD) for normally distributed quantitative variables or median (Q1, Q3) for variables with skewed distributions. To assess whether change in each individual androgen measurement between baseline and year 1 follow-up was associated with change in each measure of mood between baseline and year 1 follow-up, we constructed a series of linear regression models. Initial models included the complete study population with adjustment for randomization arm, but significant interactions by randomization arm in the association between testosterone and mood were observed, so further analyses were stratified by randomization arm. Models were adjusted for variables previously reported to be associated with mood measurements in the DPP, including age, race/ethnicity, education level, weight loss, and use of anti-depressant medication. To determine whether associations were dependent on androgen level at baseline, additional models adjusted for baseline testosterone level were also performed. Similar models using logistic regression analysis were utilized to assess the effect of the change in testosterone on the presence of depression or anxiety or medication use at year 1 of follow-up. To determine whether bioavailable testosterone yielded a different pattern of associations, bioavailable testosterone was calculated according to the method described by Sodergard and colleagues taking into account the concentration of total testosterone and SHBG and assuming a fixed albumin concentration of 3.5 g/dl (30). In sensitivity analysis, we examined whether associations between changes in testosterone and changes in mood differed by baseline quartile of testosterone. The pattern of results was similar across baseline quartiles of testosterone (results not shown), and thus only the pooled results across all quartiles were included. The SAS analysis system was used for all analyses (SAS Institute, Cary, NC).

Results

Table 1 shows characteristics of male participants at enrollment. On average, men were 54 years of age and more than two-thirds of them were less than 60 years of age. Approximately 60% were Caucasian and about half had completed high school. Reflecting DPP inclusion criteria, the average BMI at entry was 32 kg/m². At baseline, about 55% had testosterone levels > 10.41 nmol/l, 9% met criteria for depression based on BDI score ≥ 11 or use of anti-depressant medication, and about 12% of men met criteria for anxiety based on BAI score ≥ 8 or use of medication. The MCS and PCS scores for the SF-36 were high (average 57 and 53, respectively), consistent with DPP inclusion criteria that required adequate function to enable participation in lifestyle intervention.

Table 2 shows changes in weight, total and bioavailable testosterone, SHBG, mood measures, and functioning over the initial study year. As has been previously reported for the entire DPP cohort (21), men randomized to lifestyle changes had significant declines in weight compared to placebo; men randomized to metformin also experienced significant weight loss but to a lesser extent than men randomized to ILS. Men randomized to ILS had small but significant increases in testosterone compared to participants randomized to placebo or metformin. Similar patterns were observed for bioavailable testosterone, although differences by randomization arm were not significant. Declines in SHBG were observed in all randomization arms, although men randomized to ILS had the smallest reductions. Men experienced small decreases in BDI and BAI indicating decreases in depressive symptoms and anxiety symptoms, although differences by randomization arm were not significant as noted in previous reports and the average change was < 2 points. Participants also had small increases in the PCS and decreases in the MCS component of the SF-36 score, although the average change was < 7 points.

Table 3 shows the association of changes in total and bioavailable testosterone with changes in mood and health status measures, stratified by randomization arm. Among men randomized to placebo, no significant associations were observed between testosterone and mood measures or SF-36 measures. Among men randomized to ILS, testosterone was not associated with changes in BDI, BAI, or PCS, although increases in testosterone were associated with decreases in MCS or declines in mental scores over year 1. Among men randomized to metformin, increases in total testosterone were associated with decreases in BDI score (improved depressive symptoms) and BAI score (improved anxiety symptoms) with associations persisting after adjustment for other variables, and independent of baseline testosterone associations (Table 3). Among men randomized to metformin, changes in testosterone (and bioavailable testosterone) were not associated with changes in SF-36 measures after adjustment.

Table 4 shows associations between changes in total and bioavailable testosterone, and presence of significant depressive symptoms (BDI ≥ 11), significant anxiety symptoms (BAI ≥ 8) or medication use at 1-year follow-up. Regardless of randomization arm, testosterone and bioavailable testosterone were not associated with significant depression or anxiety or use of anti-depressants at one-year follow-up after adjustment for other covariates.

Discussion

In this cohort of overweight, glucose-intolerant, middle-aged men, the majority of whom were eugonadal, men randomized to ILS had larger increases in testosterone than men randomized to metformin or placebo. Nevertheless, the increases in testosterone were small and were not associated with improved depression or anxiety scores. Randomization to metformin had minimal effect on testosterone compared to placebo. However, within this group, changes in testosterone were significantly and directly associated with changes in depression and anxiety scores. Among men randomized to placebo, there were no associations between changes in testosterone and changes in mood. Observed associations were robust to adjustment for demographic factors, weight loss and other factors associated with mood, such as anti-depressant medication use. These associations were also independent of baseline testosterone levels.

No randomized trials have previously examined whether lifestyle modification can improve testosterone. In the DPP, randomization to ILS led to significant weight loss compared to placebo, and weight loss subsequently delayed the onset of diabetes (21). This weight loss, approximately 7.9 kg compared to 0.12 kg weight loss among men randomized to placebo, resulted in fairly small increases in testosterone and non-significant increases in bioavailable testosterone. It is possible that larger increases in testosterone were not observed in the DPP because the participants were still overweight and glucose-intolerant even after successful lifestyle modification. It is also possible that other determinants of testosterone are more influential than weight, including comorbidities such as overall health status (16). While observational studies have noted that older age, heavier weight, and higher comorbidity correlate with lower testosterone levels and declines in testosterone levels (8,12–16), these studies included healthier and non-obese participants as well as obese participants with greater comorbidity (8,12–16).

No randomized trials have examined the impact of metformin upon testosterone in men, although small observational studies have suggested that metformin is associated with a decline in testosterone even as it is associated with a decline in weight (17,18), even as greater weight is also associated with lower testosterone levels. Given the conflicting evidence, we hypothesized that randomization to a weight loss intervention would lead to increases in testosterone. We found that among men randomized to ILS, the ratio of testosterone increase to weight decrease was 1.15 nmol/l to 7.87 kg, or the equivalent of 1 nmol/l of testosterone change per 6.8 kg of weight loss. Thus, it is possible that the weight loss in men randomized to metformin was too small to demonstrate significant associations with testosterone.

Regardless of randomization arm, increases in testosterone were not associated with the use of anti-depressant medication or the presence of clinically significant depression or anxiety at 1-year follow-up. In this respect, our results are similar to the lack of association noted in the Massachusetts Male Aging Study (8). Travison et al examined a mid-life population, (average baseline age of men approximately 55 years) in which the average depression score did not change significantly over time with testosterone. Like Travison et al, we examined a mid-life population who had minimal changes in depression scores over time. The DPP has

previously reported that weight loss (regardless of randomization assignment) was associated with a significant but small reduction in the likelihood of depression symptoms over the course of the randomized trial (22), although most of the improvement in depression symptoms was due to increased anti-depressant use over time rather than randomization assignment. Significant depression was an exclusion criteria, which may have minimized the impact of interventions upon depressive symptoms. Previous reports in other overweight, glucose-intolerant cohorts have also reported that intentional weight loss can lead to improved mood (31); the magnitude of weight loss associated with clinically significant improvements in mood scores has been large. In the Look AHEAD study, a randomized trial of lifestyle intervention among overweight and obese adults with diabetes, weight loss of approximately 8.6% of initial weight translated to a decrease of approximately 1.4 points on the BDI (31), a reduced incidence of elevated BDI scores (32), and a slight but significant increase in MCS and PCS scores on the SF-36 Short-Form Health Survey (33). (The relationship between testosterone and mood in that trial have not been reported). In the DPP, the magnitude of change observed in BDI scores with or without anti-depressant use was smaller, on the order of a decrease of 0.7 to 1.02 BDI units for approximately 3–7 kg of weight loss (22,34).

Although we found that randomization to ILS increased testosterone slightly, these increases were not associated with decreases in anxiety. Anxiety and depression are thought to commonly co-exist, but few studies have examined the association between testosterone and anxiety. In the Troms study, higher anxiety scores were associated with lower testosterone levels (4), but the anxiety symptoms did not reach a diagnostic threshold. Similar to the patterns observed for the BDI, we found that participants randomized to metformin overall had non-significant changes in their testosterone and BAI, but these changes were correlated. In one trial of testosterone therapy in hypogonadal men, testosterone lowered BDI scores but did not improve BAI scores (35). Thus, among men that have minimal amounts of depression and a significant proportion of whom are eugonadal, large changes in weight may not have similarly large impacts in testosterone or mood scores.

However, we observed that among men randomized to metformin, who did not have significant increases in testosterone compared to placebo, there were significant associations between increase in testosterone and declines in mood. Why the relationship between testosterone and mood would differ across randomization arms is speculative. Particular components of the ILS intervention apart from weight, such as physical activity (36), may have had a greater influence upon mood and thereby minimized the relationship between testosterone and mood. Alternatively, metformin may have as yet undocumented central effects that increase neurotransmitter or neuromodulator reactivity to testosterone.

This association between testosterone and mood among randomized to metformin is concordant with prior reports which have noted that low testosterone concentrations correlate with or predict depressive symptoms (1–3,6). These prior studies enrolled older men over the age of 65 at baseline and included only single measures of testosterone. In the Longitudinal Aging Study Amsterdam (LASA), the mean cohort age was approximately 75 years and baseline testosterone levels were 15.4 nmol/l. Men in the lowest bioavailable testosterone quartile were more likely to have depression as measured by the Center for

Epidemiologic Studies Depression Score (CES-D), before and after adjustment for age, weight, medication use, and other confounders (6). Similarly, significant associations between bioavailable testosterone and depression in the Rancho Bernardo Study (age > 65 years) (1) and the Health in Men Study (age > 71 years) (2) and between total testosterone and depression in the Health ABC Study (age > 70 years) (3) indicated that a single measure of testosterone correlated with depressive symptoms.

One report noted associations between endogenous testosterone and improved measures of quality of life and specifically MCS and PCS scores (37) and another noted correlations with the shorter 12-item summary (38). However, another report noted no association (39). We may not have observed associations between testosterone and SF-36 measures due to the small magnitude of improvement in SF-36 scores in the DPP: the DPP has previously reported that for every 5 kg weight loss, there was an improvement in PCS units of 0.64 and in MCS units of 0.28 (34).

Randomized trials examining exogenous testosterone for treatment of depressed mood have focused on hypogonadal men (40). However, off-label use of exogenous testosterone for mood and other symptoms has increased dramatically over the past decade among middle-aged men who do not meet laboratory criteria for hypogonadism (41). Thus, it is important to determine whether changes in endogenous testosterone in eugonadal middle-aged men correlate with improved mood, although we did not examine supplementation with exogenous testosterone. Strengths of this report include examination of this particular group of men, as well as its repeated measurement of endogenous testosterone and weight and the large amount of intentional weight loss achieved. In previous reports evaluating associations between mood and testosterone, the majority of participants were older than 65 years of age which assessed testosterone at a single point in time. Limitations include lack of longer-term follow-up. Both androgen measurements and depression scales have day-to-day variability, and it is possible that additional repeated measures minimized the small associations observed. The DPP cohort consisted of overweight glucose-intolerant men, and our results do not extend to men of with normal weight and glucose tolerance or to men with greater degrees of obesity and frank diabetes. It is possible that stronger associations would have been observed in men with more severe depression. Finally, we did not evaluate other measures of well-being commonly examined in the context of hypogonadism, such as strength and sexual dysfunction.

In conclusion, in this cohort of predominantly eugonadal middle-aged men with overweight or obesity and glucose-intolerance, randomization to a weight loss intervention was associated with small increases in testosterone, but these increases were not correlated with significant improvements in mood. While associations between testosterone and mood were observed among men randomized to metformin, the overall increases in testosterone among men randomized to this arm were not significant. Thus, our results do not support a central role for testosterone in the causal pathway between intentional weight loss and mood in a cohort of middle-aged men who are overweight and not depressed. As the DPP participants age, the role of testosterone in metabolic complications of glucose intolerance as well as function can be reexamined to determine how much these associations change in older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Flow chart of participants.

Table 1

Characteristics of participants at baseline (n=886), unless otherwise indicated. Mean (SD), median (Q1, Q3) or N (%) shown.

	Overall (n=886)	Placebo (n=278)	Metformin (n=315)	Lifestyle (n=293)	p-value*
Age (years)	54 (11)	53 (11)	54 (11)	55 (11)	0.25
Age group (%)					0.73
25-44	180 (20.3%)	59 (21.2%)	63 (20.0%)	58 (19.8%)	
45-59	436 (49.2%)	138 (49.6%)	161 (51.1%)	137 (46.8%)	
60+	270 (30.5%)	81 (29.1%)	91 (28.9%)	98 (33.4%)	
Race/ethnicity (%)					0.58
Caucasian	521 (58.8%)	155 (55.8%)	194 (61.6%)	172 (58.7%)	
Black	136 (15.4%)	47 (16.9%)	49 (15.6%)	40 (13.7%)	
Hispanic	153 (17.3%)	51 (18.3%)	51 (16.2%)	51 (17.4%)	
Asian	66 (7.4%)	21 (7.6%)	17 (5.4%)	28 (9.6%)	
American Indian	10 (1.1%)	4 (1.4%)	4 (1.3%)	2 (0.7%)	
Body mass index (kg/m ²)	32.0 (5.5)	32.1 (5.6)	32.0 (5.5)	31.8 (5.5)	0.83
Waist circumference (cm)	108 (13)	108 (13)	108 (13)	108 (14)	1.0
Total testosterone (nmol/l)	10.98 (8.59, 13.74)	10.49 (8.25, 13.44)	10.97 (8.59, 13.64)	11.64 (9.11, 14.40)	0.016
Testosterone < 10.41 nmol/l (%) [‡]	385 (44.0%)	134 (48.9%)	137 (44.3%)	114 (39.0%)	0.06
Bioavailable testosterone (nmol/l)	5.59 (4.48, 6.82)	5.58 (4.46, 6.72)	5.59 (4.25, 6.82)	5.68 (4.65, 6.86)	0.48
Sex hormone binding globulin (nmol/l)	39.79 (26.87, 56.33)	36.60 (26.35, 55.43)	40.03 (26.42, 57.36)	41.35 (28.80, 56.41)	0.26
Beck Depression Inventory (BDI) Score	2 (0, 5)	2 (0, 5)	2 (0, 5)	2 (0, 5)	0.96
BDI score ≥ 11 (%)	61 (7.0%)	20 (7.3%)	20 (6.4%)	21 (7.3%)	0.89
Antidepressant medication use (%)	18 (2.0%)	5 (1.8%)	6 (1.9%)	7 (2.4%)	0.87
BDI ≥ 11 or antidepressant use (%)	77 (8.8%)	25 (9.2%)	25 (8.0%)	27 (9.3%)	0.82
Beck Anxiety Inventory (BAI) Score	1 (0, 4)	1 (0, 4)	1 (0, 4)	1 (0, 4)	0.42
BAI Score ≥ 8 (%)	96 (11.0%)	25 (9.2%)	37 (11.9%)	34 (11.8%)	0.58
BAI ≥ 8 or antidepressant use	109 (12.5%)	29 (10.6%)	42 (13.5%)	38 (13.1%)	0.53
Mental Component Summary score	57.2 (52.9, 59.5)	57.2 (52.5, 59.6)	57.0 (53.1, 59.4)	57.2 (52.9, 59.5)	0.95
Physical Component Summary score	53.0 (49.0, 55.9)	52.9 (48.9, 55.9)	52.8 (49.0, 55.8)	53.1 (49.4, 55.9)	0.69

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* Comparison of three treatment groups
† 10.41 nmol/l is used as a cutpoint for hypogonadism

Changes in weight, hormones, and mood measures between baseline and year 1. A positive value indicates an increase and a negative value represents a decrease.

Table 2

	Overall (n=886)	Placebo (n=278)	Metformin (n=315)	Lifestyle (n=293)	p-value*
Change in weight (kg)	-3.61 (6.30)	-0.12 (4.42)	-2.73 (4.52)	-7.87 (7.02)	< 0.001
Change in Testosterone (nmol/l)	+0.26 (3.53)	-0.27 (3.09)	-0.12 (3.66)	+1.15 (3.63)	< 0.001
Change in bioavailable testosterone (nmol/l)	+0.83 (2.08)	+0.67 (2.01)	+0.78 (2.01)	+1.05 (2.20)	0.08
Change in sex hormone binding globulin (nmol/l)	-10.78 (20.14)	-11.97 (17.30)	-12.41 (20.15)	-7.91 (22.27)	0.011
Change in Beck Depression Inventory score	-0.57 (3.63)	-0.57 (3.50)	-0.48 (3.60)	-0.66 (3.79)	0.84
Change in Beck Anxiety Inventory score	-0.43 (3.50)	-0.05 (3.32)	-0.54 (3.87)	-0.69 (3.22)	0.08
Change in Mental Component Summary score	-0.26 (6.92)	-0.58 (6.93)	-0.32 (6.27)	0.11 (7.54)	0.49
Change in Physical Component Summary score	+0.31 (6.58)	-0.09 (6.73)	-0.06 (6.38)	+1.10 (6.60)	0.04

* Comparison of three treatment groups

Table 3

Association between change in testosterone and change in mood scores between baseline and year 1. Each coefficient represents the change in mood measure with an increase of 1 unit of hormone. A negative association indicates that an increase in testosterone is associated with a decrease in mood score i.e. improved mood.

	Lifestyle		Metformin		Placebo	
	β -coefficient	p-value	β -coefficient	p-value	β -coefficient	p-value
Association between change in testosterone (nmol/l) and change in Beck Depression Inventory (BDI)						
Unadjusted						
Model 1: Adjusted for age, race, ethnicity, and education	0.0046	0.94	-0.2598	<.0001	-0.0226	0.75
Model 2: Adjusted for model 1, and weight loss	-0.0061	0.92	-0.2515	<.0001	-0.0151	0.83
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.0426	0.53	-0.2505	<.0001	-0.0443	0.53
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0225	0.74	-0.2454	<.0001	-0.0466	0.51
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0194	0.78	-0.2336	0.0002	-0.0960	0.20
Association between change in bioavailable testosterone (nmol/l) and change in BDI						
Unadjusted						
Model 1: Adjusted for age, race, ethnicity, and education	0.0468	0.65	-0.3613	0.0004	0.0107	0.92
Model 2: Adjusted for model 1, and weight loss	0.0227	0.83	-0.3463	0.0007	0.0160	0.88
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.0640	0.55	-0.3399	0.0010	-0.0125	0.91
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0234	0.83	-0.3353	0.0011	-0.0150	0.89
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0064	0.96	-0.3323	0.0054	-0.1324	0.27
Association between change in testosterone (nmol/l) and change in Beck Anxiety Inventory (BAI)						
Unadjusted						
Model 1: Adjusted for age, race, ethnicity, and education	-0.0011	0.98	-0.2300	0.0001	0.0601	0.35
Model 2: Adjusted for model 1, and weight loss	-0.0056	0.92	-0.2199	0.0003	0.0826	0.20
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.0180	0.76	-0.1976	0.0012	0.0798	0.23
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0284	0.62	-0.1980	0.0012	0.0742	0.26
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0425	0.48	-0.2147	0.0014	0.0574	0.42
Association between change in bioavailable testosterone (nmol/l) and change in BAI						
Unadjusted						
Model 1: Adjusted for age, race, ethnicity, and education	0.0310	0.72	-0.3800	0.0005	0.1245	0.20
Model 2: Adjusted for model 1, and weight loss	0.0232	0.79	-0.3572	0.0012	0.1549	0.12
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.0441	0.63	-0.3273	0.0030	0.1512	0.13
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0658	0.48	-0.3270	0.0031	0.1450	0.15
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.1242	0.24	-0.3986	0.0019	0.1230	0.27

	Lifestyle		Metformin		Placebo	
	β -coefficient	p-value	β -coefficient	p-value	β -coefficient	p-value
<u>Association between change in testosterone (nmol/l) and change in Mental Component Summary Score (MCS)</u>						
Unadjusted	-0.0932	0.45	0.1779	0.069	0.0335	0.80
Model 1: Adjusted for age, race, ethnicity, and education	-0.0789	0.53	0.1816	0.066	0.0761	0.57
Model 2: Adjusted for model 1, and weight loss	-0.2359	0.08	0.1610	0.109	0.1271	0.35
Model 3: Adjusted for model 2, and baseline anti-depressant use	-0.2384	0.08	0.1570	0.12	0.1247	0.36
Model 4: Adjusted for model 3, and baseline testosterone concentration	-0.2894	0.038	0.2053	0.062	0.1193	0.41
<u>Association between change in bioavailable testosterone (nmol/l) and change in MCS</u>						
Unadjusted	-0.4226	0.04	0.3221	0.070	0.1012	0.62
Model 1: Adjusted for age, race, ethnicity, and education	-0.4020	0.056	0.3106	0.085	0.1789	0.39
Model 2: Adjusted for model 1, and weight loss	-0.5281	0.013	0.2839	0.12	0.2317	0.27
Model 3: Adjusted for model 2, and baseline anti-depressant use	-0.5382	0.012	0.2806	0.12	0.2314	0.26
Model 4: Adjusted for model 3, and baseline testosterone concentration	-0.6721	0.006	0.4416	0.04	0.1333	0.56
<u>Association between change in testosterone (nmol/l) and change in Physical Component Summary Score (PCS)</u>						
Unadjusted	0.0421	0.70	0.2272	0.02	-0.1716	0.20
Model 1: Adjusted for age, race, ethnicity, and education	0.0504	0.64	0.2049	0.04	-0.1822	0.18
Model 2: Adjusted for model 1, and weight loss	0.0259	0.83	0.1687	0.10	-0.2116	0.13
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.0220	0.85	0.1918	0.056	-0.2104	0.13
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.0326	0.79	0.1962	0.074	-0.2285	0.12
<u>Association between change in bioavailable testosterone (nmol/l) and change in PCS</u>						
Unadjusted	0.1564	0.39	0.2577	0.16	-0.2715	0.18
Model 1: Adjusted for age, race, ethnicity, and education	0.1594	0.39	0.2096	0.25	-0.2935	0.16
Model 2: Adjusted for model 1, and weight loss	0.1381	0.46	0.1625	0.38	-0.3209	0.13
Model 3: Adjusted for model 2, and baseline anti-depressant use	0.1329	0.49	0.1782	0.33	-0.3208	0.13
Model 4: Adjusted for model 3, and baseline testosterone concentration	0.1518	0.48	0.2974	0.16	-0.2433	0.30

Association between changes in testosterone and presence of depression or anxiety or medication use at year 1 follow-up. Depression defined as Beck depression Inventory score ≥ 11 or anti-depressant medication, and anxiety defined as Beck Anxiety Score ≥ 8 or anxiety medication use.

Table 4

	Lifestyle		Metformin		Placebo	
	OR	p-value	OR	p-value	OR	p-value
<u>Association between change in testosterone (nmol/l) and depression at year 1</u>						
Unadjusted	0.963	0.50	0.956	0.40	0.960	0.57
Model 1: Adjusted for age, race/ethnicity, and education	0.955	0.43	0.956	0.42	0.938	0.41
Model 2: Model 1, and adjusted for weight loss	0.998	0.98	0.965	0.54	0.903	0.17
Model 3: Model 2, and adjusted for baseline BDI ≥ 11 and ADM use	1.103	0.23	0.936	0.26	0.952	0.60
Model 4: Model 3, and adjusted for baseline testosterone	1.149	0.11	0.984	0.79	0.924	0.46
<u>Association between change in bioavailable testosterone (nmol/l) and depression at year 1</u>						
Unadjusted	0.984	0.86	0.938	0.51	1.076	0.53
Model 1: Adjusted for age, race/ethnicity, and education	0.971	0.75	0.936	0.52	1.065	0.62
Model 2: Model 1, and adjusted for weight loss	1.008	0.94	0.947	0.60	1.021	0.87
Model 3: Model 2, and adjusted for baseline BDI ≥ 11 and ADM use	1.117	0.34	0.942	0.56	1.134	0.40
Model 4: Model 3, and adjusted for baseline testosterone	1.352	0.056	1.007	0.95	0.958	0.81
<u>Association between change in testosterone (nmol/l) and anxiety at year 1</u>						
Unadjusted	1.019	0.73	0.889	0.013	0.986	0.81
Model 1: Adjusted for age, race/ethnicity, and education	1.016	0.79	0.888	0.014	0.975	0.69
Model 2: Model 1, and adjusted for weight loss	1.027	0.67	0.910	0.07	0.961	0.53
Model 3: Model 2, and adjusted for baseline BDI ≥ 11 and ADM use	1.066	0.32	0.894	0.06	1.000	0.99
Model 4: Model 3, and adjusted for baseline testosterone	1.091	0.20	0.874	0.06	0.998	0.98
<u>Association between change in bioavailable testosterone (nmol/l) and anxiety at year 1</u>						
Unadjusted	1.114	0.26	0.866	0.09	1.006	0.95
Model 1: Adjusted for age, race/ethnicity, and education	1.102	0.32	0.859	0.088	0.999	0.99
Model 2: Model 1, and adjusted for weight loss	1.115	0.28	0.883	0.18	0.984	0.87
Model 3: Model 2, and adjusted for baseline BDI ≥ 11 and ADM use	1.139	0.19	0.879	0.20	1.054	0.62
Model 4: Model 3, and adjusted for baseline testosterone	1.172	0.17	0.828	0.13	0.989	0.93