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Associations between testosterone and metabolic syndrome in depressed and non-depressed older men and women

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Objectives: Older age and major depressive disorder (MDD) are both risk factors for the development of cardiovascular diseases. Testosterone has been associated with MDD and metabolic syndrome (MetS) in men, although associations in women are less clear. Therefore, we investigated whether testosterone is associated with MetS and whether this association is different for depressed and non-depressed older men and women.

Methods: In this prospective cohort study, 478 participants (349 patients with MDD and 129 controls) aged between 60 and 93 years from the Netherlands Study of Depression in Older Persons were included. Total testosterone (TT) and sex-hormone binding globulin levels were measured using a second-generation radioimmune assay. Free testosterone (FT) was calculated based on TT. MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria.

Results: A higher risk for MetS was found in men with low FT and TT (odds ratio [OR]: 0.67, 95% confidence interval [95%CI]: 0.47-0.95 and OR: 0.51, 95%CI: 0.34-0.75), and in women with high FT (OR: 1.41, 95%CI: 1.08-1.82). Strong associations in the same direction were found with adiposity, glucose, and plasma lipid MetS components at baseline, but not with changes in these components at 2-year follow-up. The associations did not significantly differ between MDD patients and controls.

Conclusions: Independently of having MDD, low testosterone levels in men and, in contrast, high testosterone levels in women were significantly associated with MetS and its components.

KEYWORDS
depressive disorder, major, metabolic syndrome, older adults, testosterone

1 | INTRODUCTION

The older population shows the highest prevalence of the metabolic syndrome (MetS)[1] which puts this group at increased risk for cardiovascular diseases (CVD) and cardiovascular-related mortality.[2] Among the proposed

mechanisms to explain the association between age and MetS is the influence of testosterone. Testosterone levels decline during aging, especially in men, who have 10 times higher levels than women in younger adulthood.[3]

Low testosterone levels in men and high levels in women are thought to alter adipose tissue function, with effects on lipid

metabolism, insulin resistance, and fat mass expansion which may induce metabolic disadvantages.[4] However, this association is complex, as testosterone levels have both detrimental and beneficial effects depending on the type of tissue and sex.[4] Earlier research in men has shown that low testosterone levels may contribute to the development of MetS but that the magnitude of this effect is dependent on several other factors and that the relation may also be bidirectional.[5,6] In contrast to the findings in men, higher testosterone levels in women have been associated with MetS.[7] That said, prospective analyses are lacking and not all studies have found this association.[8]

In spite of a range of studies on this issue, many aspects of the complex relationship between testosterone and MetS remain unclear. This warrants further investigation into possible underlying pathophysiological processes, especially in the older population who are at the highest CVD mortality risk.[9] Influencing factors may include major depressive disorder (MDD), which has been associated with 80% to 90% elevated risk for CVD onset.[10] Additionally, the presence of MetS in depressed older adults has been associated with greater symptom severity of depression.[11] Dysregulations in the immune response and the hypothalamic-pituitary-adrenal axis seen in MDD[12] closely respond to alterations in the hypothalamic-pituitary-gonadal axis. This not only alters testosterone levels but also impacts its function.[4,13,14] Indeed, low testosterone levels have been associated with MDD in men,[15-18] although associations in women are inconsistent.[8,17,19,20]

Given these associations, we hypothesized that MDD or the use of antidepressants increases the vulnerability for testosterone level alterations. Therefore, we aimed to determine the associations between testosterone and MetS in older adults and test whether this association is stronger in depressed or antidepressant-using patients.

2 | MATERIALS AND METHODS

2.1 | Study population

Data for this study were obtained from Netherlands Study of Depression in Older Persons (NESDO). For methodological details, we refer to previously published work.[21,22] In short, this multicentre prospective cohort aims to study the course, predictors, and consequences of late-life depression. In total, 510 participants, aged 60 to 93 years, were recruited from 2007 to 2010. A group of 378 older persons with MDD, dysthymia, or minor depression was recruited from both general practitioners and mental health care facilities to cover a wide range of severities. The 132 controls without a history of depression were recruited via general practitioners. After baseline assessment, participants were invited for a second face-to-face interview with repeated measures of psychological, social, and physical functioning after 2 years.[23] During this period, 28 people died. Of the 482 participants who were still available for the study, 401 (83.4%) took part in the follow-up assessment. All participants gave their written and oral consent. The study protocol was approved by the Ethical Review Board of the VU Medical Center in Amsterdam, and subsequently by the local ethical review boards.

The presence or absence of depression was assessed by the Composite Interview Diagnostic Instrument[24] at baseline and after

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Key points

- Low free and total testosterone levels in men and in contrast high free testosterone levels in women are associated with the metabolic syndrome and its components in older adults.

- Depression does not alter the association between testosterone and metabolic syndrome.

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2 years of follow-up and was administered in face-to-face interviews. Depression diagnosis was present when participants met the criteria with a 6-month recency.

For the current study, we analysed MDD patients (N = 359) and healthy controls (N = 132). Thirteen participants were excluded due to missing data on plasma testosterone or sex-hormone binding globulin (SHBG). In total, 349 MDD patients (119 men and 230 women) and 129 controls (50 men and 79 women) were available for the baseline analyses. Ninety-nine participants (36 men and 63 women) dropped out between the baseline and the 2-year follow-up assessment (20.7% of baseline sample). Female non-responders suffered more often from MDD, and male non-responders were older compared with responders. MetS rates did not differ between responders and non-responders. In total, 266 MDD patients (91 men and 175 women) and 113 control participants (42 men and 71 women) were available for longitudinal analysis.

2.2 | Measurements

Predictors included testosterone (TT), free testosterone (FT), and SHBG. Blood was taken after an overnight fast at baseline (mean time of sampling 9:04 AM; range 8:10 to 10:45). EDTA plasma was stored at −80°C until determination of the androgenic markers. TT was measured using a second-generation testosterone assay without extraction (Architect i2000 analyzer; Abbott Diagnostics, Abbott Park, IL). In contrast to earlier radioimmune assays, second-generation testosterone assays suffer less from cross-reactivity with other steroid hormones and are less influenced by SHBG levels.[25,26] Strong correlation coefficients are reported between our radioimmunoassay and the gold standard ID-LC-MS/MS measurement in women (R = 0.95).[26] Intra- and inter-assay variations were between 4% and 10% at concentrations of 0.02, 2, and 20 nmol/L. The lower limit of quantification was 0.45 nmol/L. In 23 of 318 women (7.2%), the TT level was below the threshold and therefore imputed as 0.44 nmol/L as done before.[19] SHBG was measured using an automated immunometric assay (Architect i2000 analyzer). Intra- and inter-assay variations were between 4% and 6% over the whole range. The lower limit of detection for SHBG was 2 nmol/L. FT was calculated from TT, SHBG, and albumin levels using the formula published by Vermeulen.[27]

Outcome measures were MetS (as a dichotomous variable) and its individual components (as continuous variables) at baseline and after 2 years of follow-up. MetS was defined according to the adjusted National Cholesterol Education Program Adult Treatment Panel III

(ATP III) criteria.[2] To fulfil the diagnosis of MetS, at least three of the following criteria had to be met: blood pressure >130 mmHg systolic or >85 mmHg diastolic or antihypertensive medication; waist circumference >102 cm for men and >88 cm for women; fasting glucose levels >5.6 mmol/L (100 mg/dL) or anti-diabetic medication; high-density-lipoprotein (HDL) cholesterol levels <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or medication for reduced HDL cholesterol; and fasting triglycerides levels >1.7 mmol/L (150 mg/dL) or medication for hypertriglyceridemia.

Waist circumference was determined by measuring tape, measuring between the lower rib margin and the iliac crest following normal expiration, over light clothing. HDL cholesterol, triglycerides, and glucose levels were measured by standard laboratory methods after overnight fasting. Nineteen patients were set as missing value because they did not fast before the assessment. Blood pressure was measured in a supine position on the right arm by an electronic Omron sphygmomanometer and was averaged over two readings. HDL cholesterol levels, triglyceride levels, and fasting glucose levels were adjusted for medication effects.[28-30] When participants were using antihypertensive medication, 10 mmHg was added to the systolic blood pressure and 5 mmHg was added to the diastolic blood pressure.[31] When participants were using fibrates, 0.10 mmol/L [3.8 mg/dL] was subtracted from HDL cholesterol and 0.67 mmol/L [60 mg/dL] was added to triglycerides.[28,29] When participants were using anti-diabetic medication, when the glucose level was below 7 mmol/L [126 mg/dlL], a value of 7 mmol/L was given.[30] Body mass index (BMI) is not a MetS component but is often used as a weight measurement. Therefore, we included this variable as an outcome measure as well, to see whether both assessments are comparable. In general, waist circumference and BMI are highly correlated, independent of sex ($r = 0.93$, range 0.87-0.95).[32]

2.3 | Statistical analyses

All analyses were performed in strata separately for men and women. Data were analysed using IBM SPSS Statistics 24. A two-tailed P value <0.05 was considered statistically significant.

Characteristics were determined at baseline, using percentages, by chi-squared tests or means with SD by analysis of variance, dependent on the type of variable.

The first aim was to test the association between TT and FT with MetS diagnosis (dichotomous) and its individual components (continuous) at baseline and after 2-year follow-up. In the cross-sectional analyses, these associations were examined using logistic and linear multivariable regression analyses, when appropriate. All analyses were adjusted for age and for education, smoking status, alcohol use, number of chronic diseases, and testosterone-affecting medication in a second adjustment. Level of education was specified in years of education. Smoking status was dichotomized into non- and current smoker. Alcohol use was defined as daily alcohol intake in units. The number of chronic diseases was counted (including hypertension, range 0 through 8). Use of medication was considered as present when using Anatomical Therapeutic Chemical Classification (ATC) codes at least 50% of the days.[33] Out of the 478 participants, 33 were

taking medications that could influence their testosterone level; seven participants were taking sex hormones (ATC code G03), six participants were taking selective estrogen receptor modifiers (SERM) or aromatase inhibitors (ATC code L02B), and 21 participants were taking glucocorticoids (ATC code H02AB). All users of sex hormones, SERM's, or aromatase inhibitors were female. As none of them was using (anti-) androgens and their testosterone levels were within the reference intervals, we decided not to exclude these women. However, the main analyses were repeated in a sensitivity analysis with exclusion of this group. Nonlinear associations were analysed by adding squared TT and FT, respectively, to the model. FT was logarithmically transformed to reduce their positively skewed distributions. For interpretation purposes only, TT and FT were standardized (calculated z-scores) before entering the regression model calculating odds ratios (ORs) for MetS. In the prospective analyses, associations between standardized TT and FT with the change in MetS components over 2 years were examined using linear regression analyses. Two-year follow-up values of MetS components were subtracted from baseline values. Therefore, a positive delta score means a lowering of MetS components over 2 years. For waist circumference, triglycerides, blood pressure, glucose, and BMI, this would, in most cases, be associated with an improved metabolic profile. In contrast, a positive delta score for HDL would in most cases mean a worse metabolic profile. These delta scores were entered as outcomes in the regression model. Again, all analyses were adjusted for age first and adjusted for the other covariates afterwards as mentioned before.

To test whether the association between testosterone levels and MetS was similar for persons with and without MDD, interaction terms (ie, testosterone * MDD) were entered in the cross-sectional models. Next, the interaction term testosterone*antidepressant use was added to the regression models. When interactions were significant ($P < .05$), tests were run separately for MDD subgroups. All analyses were adjusted according to the previously mentioned models.

3 | RESULTS

3.1 | Findings in older men

The characteristics of the 169 men are shown in Table 1. Of our sample of men, 70% was currently depressed, and 46% was diagnosed with MetS. The mean plasma TT and FT levels were 16.7 ± (SD) 6.3 nmol/L and 307.1 ± 100.0 pmol/L.

3.1.1 | Cross-sectional associations between testosterone and MetS

Associations between TT and FT with MetS (components) and BMI are shown in Table 2 and Figures 1 and 2. Overall, both low TT and FT levels were associated with a higher risk for MetS (standardized OR: 0.51 CI95%; 0.34; 0.75 and OR: 0.67 CI95%; 0.47; 0.95). Low androgen levels were linearly associated with adverse MetS components except for blood pressure, with the strongest associations displayed for TT levels. After adjustment for all covariates, a 1SD (ie, 6.3 nmol/

TABLE 1 Baseline socio-demographic, lifestyle, and clinical characteristics of 169 men and 309 women

	Men (N = 169)	Women (N = 309)
Age (years)	69.6 ± 7.4	70.9 ± 7.3
Northern European ancestry	94.1%	94.5%
Education (years)	11.9 ± 3.8	10.5 ± 3.2
BMI (kg/m^2)	26.5 ± 3.7	26.4 ± 4.5
Smoking	19.5%	23.2%
Alcohol use (no. drinks/day)	0.9 ± 1.2	0.6 ± .8
Chronic disease	2.1 ± 1.5	2.5 ± 1.6
Testosterone affecting medication	4.1%	6.5%
Androgenic features		
Testosterone (nmol/L)	16.7 ± 6.3	0.96 ± 0.40
Free testosterone (pmol/L)	307.1 ± 100.0	14.1 ± 7.62
Outcome measures		
Metabolic syndrome diagnosis (adj. ATPIII)	45.6%	43.4%
Waist circumference (cm)	99.6 ± 11.4	91.8 ± 12.8
Triglycerides[a] (mmol/L)	1.5 ± 0.8	1.4 ± 0.7
HDL cholesterol[b] (mmol/L)	1.3 ± 0.3	1.7 ± 0.4
Systolic blood pressure (mmHg)	155.8 ± 20.8	151.3 ± 22.4
Diastolic blood pressure (mmHg)	86.3 ± 10.9	82.8 ± 11.3
Fasting glucose[c] (mmol/L)	6.1 ± 1.3	5.8 ± 1.3
Interactions		
Diagnosis of major depressive disorder	70.4%	74.4%
Use of antidepressants	49.7%	55.0%

Data are percentages or mean ± standard deviation (SD). *P*-values are based on chi-squared tests (for dichotomous and categorical variables) or t-tests for independent samples (for continuous variables). Triglyceride, HDL cholesterol, blood pressure, and fasting glucose values were adjusted for medication use (see measurements).

[a]To convert the values of triglycerides to milligrams per decilitre, divide by 0.01129.

[b]To convert the values for HDL cholesterol to milligrams per decilitre, divide by 0.02586.

[c]To convert the values of glucose to milligrams per decilitre, divide by 0.05551.

L) lower TT level was associated with a mean 3.5 cm higher waist circumference (*P* < .001), a mean 0.18 mmol/L higher triglycerides (*P* = .006), a mean 0.04 mmol/L lower HDL (*P* = .01), a mean 0.23 mmol/L higher fasting glucose (*P* = .03), and a mean 0.96 kg/m^2 higher BMI (*P* < .001). SHBG showed ORs and standardized betas in same direction as for TT and FT (data not shown).

3.1.2 | Longitudinal associations between testosterone and MetS

Associations between TT and FT with 2-year changes in MetS components and BMI are shown in Table 3. In contrast to the cross-sectional analyses, neither baseline TT nor FT levels were associated with changes in MetS components over 2 years, except for fasting glucose. A higher FT level was associated with lower fasting glucose levels after 2 years (*P* = .02).

3.1.3 | Moderating effects of MDD

Although associations were slightly stronger in the MDD group than in controls (Figure 1), they were not statistically significantly different. For the MetS components, there was only one exception. The adverse effects of lower TT levels on systolic blood pressure were stronger in depressed patients compared with controls (standardized β for interaction −0.46 (*P* = .04), for MDD patients −0.20 (*P* = .02) and for controls 0.14 (*P* = .43).

3.2 | Findings in older women

The characteristics of the 309 women are shown in Table 1. Of our female sample, 72% was currently depressed, and 43% was diagnosed with MetS. The mean plasma TT and FT levels were 0.96 nmol/L ± 0.40 nmol/L and 14.1 pmol/L ± 7.62 pmol/L (mean ± SD).

3.2.1 | Associations between testosterone and MetS

Association between TT and FT with MetS (components) and BMI are shown in Table 2 and Figures 1 and 2. Overall, high FT levels were associated with a higher risk for MetS (standardized OR: 1.41; 95%CI: 1.08-1.82; *P* = .01). After adjustment for all covariates, high FT, but not TT, levels were linearly associated with MetS as well as adverse MetS components, except for systolic and diastolic blood pressure. In contrast to men, a 1-SD (7.62 pmol/L) higher FT level was associated with a mean 2.4 cm higher waist circumference (*P* < .001), a mean 0.18 mmol/L higher triglycerides (*P* < .001), a mean 0.05 mmol/L higher HDL (*P* = .02), a mean 0.18 mmol/L higher fasting glucose (*P* = .02), and a mean 1.0 kg/m^2 higher BMI (*P* < .001). SHBG showed standardized betas in opposite direction as for FT. The exclusion of 13 women using aromatase inhibitors, SERM, estrogens, or progestagens did not remarkably change the results (standardized OR: 1.40; 95%CI: 1.07-1.82; *P* = .01).

3.2.2 | Longitudinal associations between testosterone and MetS

Associations between TT and FT with a 2-year change in MetS components and BMI are shown in Table 3. As in men, neither TT nor FT were associated with changes in MetS components over 2 years.

3.2.3 | Moderating effects of MDD

Similar to older men, associations were slightly stronger in the MDD group than in controls (Figure 1), although not statistically significantly different. Only women with MDD and high levels of FT showed a higher mean waist circumference and BMI compared with controls (standardized β for interaction 1.13 [*P* = .03] and 1.05 [*P* = .045]), for MDD participants 0.24 (*P* < .001) and 0.29 (*P* < .001) and for controls −.04 (*P* = .77) and.02 (*P* = .88).

TABLE 2 Associations of TT and FT levels with MetS diagnosis and components in 169 men and 309 women

	MetS diagnosis		Waist		Triglycerides		HDL		Systolic BP		Diastolic BP		Glucose		BMI	
	OR (95%CI)	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Men																
Testosterone																
Age adjusted	0.52 (0.36–0.76)	<.001	−0.34	<.001	−0.21	.005	0.23	.002	−0.13	.08	−0.09	.22	−0.18	.02	−0.29	<.001
Fully adjusted[a]	0.51 (0.34–0.75)	<.001	−0.33	<.001	−0.22	.006	0.19	.01	−0.11	.13	−0.09	.22	−0.18	.03	−0.26	<.001
Free testosterone																
Age adjusted	0.66 (0.46–0.92)	.02	−0.31	<.001	−0.15	.06	0.12	.13	−0.03	.67	−0.04	.65	−0.16	.05	−0.29	<.001
Fully adjusted[a]	0.67 (0.47–0.95)	.02	−0.30	<.001	−0.15	.06	0.09	.21	−0.02	.79	−0.04	.58	−0.14	.09	−0.27	<.001
Women																
Testosterone																
Age adjusted	0.89 (0.70–1.12)	.33	−0.03	.66	0.02	.67	0.06	.34	0.07	.23	0.08	.18	−0.02	.77	0.02	.69
Fully adjusted[c]	0.92 (0.71–1.19)	.53	−0.01	.92	0.02	.69	0.08	.19	0.08	.19	0.10	.08	−0.01	.86	0.06	.28
Free testosterone																
Age adjusted	1.31 (1.04–1.66)	.02	0.19	.002	0.25	<.001	−0.12	.04	0.09	.11	0.09	.11	0.16	.01	0.22	<.001
Fully adjusted[a]	1.41 (1.08–1.82)	.01	0.19	.001	0.25	<.001	−0.13	.02	0.11	.07	0.10	.08	0.14	.02	0.23	<.001

Data are standardized odds ratios (OR) with 95% CI or standardized betas determined by (log) linear regression. As the independent variables were naturally log-transformed in the logistic regression analyses, a one-unit change in FT or TT will not be a constant effect in the odds but will vary with FT and TT itself. The dependent and independent variables were therefore standardized, in order for the effect sizes of the ORs to become comparable among the different models. The standardized ORs and beta coefficients refer to how many SD the dependent variable will change per SD increase in the independent variable.

[a]Adjusted for age, education, smoking status, alcohol use, number of chronic diseases, and testosterone affecting medication.

Abbreviation: BP, blood pressure.
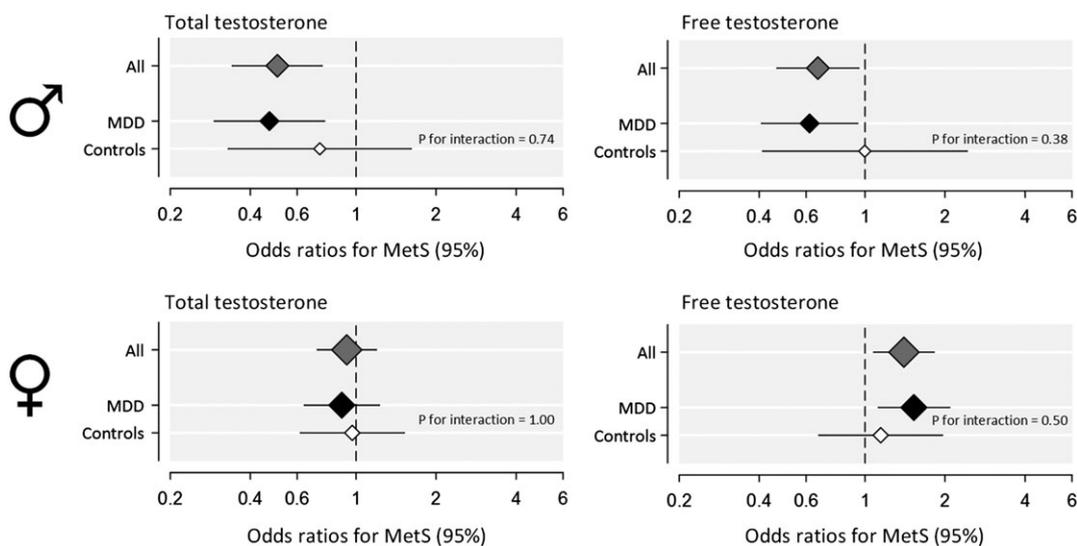
FIGURE 1 Relationship between plasma total and free testosterone and metabolic syndrome in 169 men and 309 women. Adjusted odds ratios for metabolic syndrome are shown for all participants and separately for depressed and controls on a logarithmic scale. Interaction terms for free testosterone and total testosterone with major depressive disorder are shown as well, but were not significant. Total testosterone and free testosterone levels were standardized before analysis. The size of the diamonds is proportional to the number of participants. Error bars represent standard errors (*SE*)

4 | DISCUSSION

In this study, we aimed to investigate whether plasma testosterone is associated with MetS and whether this association is different for depressed and non-depressed older men and women. Strong associations between lower levels of TT and FT in men and, in contrast, higher levels of FT in women with MetS and its components were found. However, the association in depressed older people did not differ significantly from healthy controls.

Our findings in men of an inverse association between testosterone and MetS are in line with earlier findings in men aged older than 60[8,34,35] as were the relationships with MetS components in one study,[35] but not in the other study.[8] In contrast, relationships of largely the opposite direction were found in our sample of older
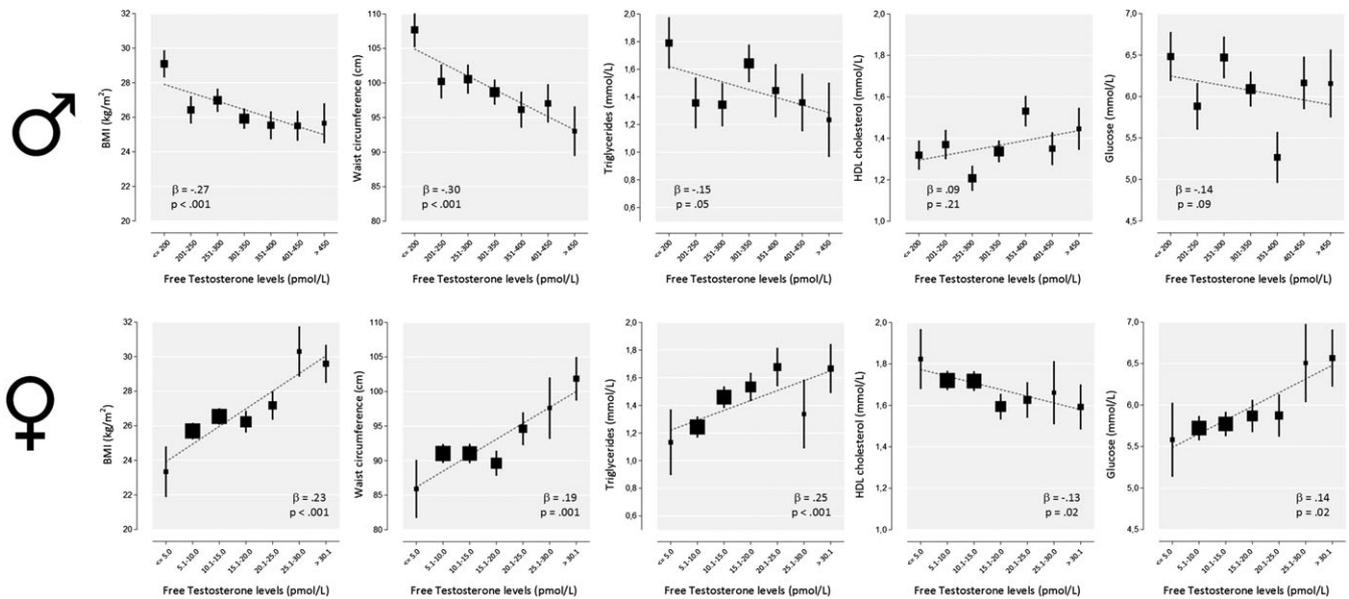
FIGURE 2 Relationship between plasma free testosterone and metabolic syndrome components in 169 men and 309 women. Free testosterone levels were categorized for visualization purposes only, as all analyses were carried out with continuous data. Free testosterone levels were log$_e$-transformed before analysis, and back-transformed geometric mean levels are presented on logarithmic scales. Error bars represent standard errors (SE). The sizes of the boxes are proportional to the number of participants

TABLE 3 Associations of TT and FT levels with delta changes in MetS components in 133 men and 246 women over 2 years

	ΔWaist		ΔTriglycerides		ΔHDL		ΔSystolic BP		ΔDiastolic BP		ΔGlucose		ΔBMI	
	β	p	β	p	β	p	β	β	β	p	β	p	β	p
Men														
Testosterone														
Age adjusted	−0.09	.31	0.06	.53	0.03	.76	0.06	.53	0.00	.99	0.15	.11	−0.08	.36
Fully adjusted[a]	−0.10	.26	0.07	.47	−0.01	.90	0.05	.63	0.01	.94	0.15	.10	−0.12	.20
Free testosterone														
Age adjusted	−0.05	.57	0.12	.21	−0.03	.74	0.07	.46	0.04	.70	0.22	.02	−0.09	.30
Fully adjusted[a]	−0.07	.48	0.13	.17	−0.06	.49	0.07	.44	0.05	.62	0.22	.02	−0.14	.14
Women														
Testosterone														
Age adjusted	−0.05	.50	0.01	.86	0.11	.14	−0.05	.43	−0.00	.97	−0.01	.84	−0.03	.61
Fully adjusted[a]	−0.05	.47	0.02	.81	0.10	.14	−0.05	.47	0.00	.99	−0.02	.81	−0.03	.70
Free testosterone														
Age adjusted	0.01	.84	0.12	.09	0.07	.36	−0.03	.72	0.05	.61	0.00	.96	−0.06	.35
Fully adjusted[a]	−0.02	.76	0.12	.10	0.05	.48	−0.03	.68	0.04	.61	−0.01	.88	−0.05	.48

Data are standardized betas determined by linear regression. As the independent variables were naturally log-transformed in the logistic regression analyses, a one-unit change in FT or TT will not be a constant effect in the odds but will vary with FT and TT itself. The dependent and independent variables were therefore standardized, in order for the effect sizes of the beta's to become comparable among the different models. The standardized beta coefficients refer to how many SD the dependent variable will change per SD increase in the independent variable.

[a]Adjusted for age, education, smoking status, alcohol use, number of chronic diseases, and testosterone affecting medication.

Abbreviation: BP, blood pressure.

women. Higher levels of FT (but not of TT) were associated with MetS and its components, which is also in line with previous studies of postmenopausal women.[7,36-38] Similarly, in younger women with polycystic ovarian syndrome (PCOS), high FT and TT levels have also been linked to MetS,[13] whereas such data are largely lacking in postmenopausal women with PCOS.[13] Caution should be taken when interpreting findings with calculated FT in epidemiological research, as the formula is importantly dependent on age.[39]

Sex-hormone binding globulin may explain why women, in contrast to men, are particularly sensitive to FT and not to TT levels. In our study, the associations for SHBG with MetS were in the same direction for both sexes, which is remarkable given the contrasting

results for FT and TT. SHBG binds to androgens and determines for a large part the amount of FT. However, it also has metabolic effects and helps to protect women against exposure to excessively high testosterone levels. The occupancy of SHBG steroid-binding sites by androgens is sex dependent with an occupation rate of only 18% in women and up to 56% in men. This possibly leads to a more swift response to increased or decreased androgen levels in women,[40] which might explain our strong findings with FT but not with TT.

In line with other studies, we found no longitudinal associations between TT and FT and the incidence of MetS in older people.[41-43] Any changes in (components of) the MetS may have already taken place years before our baseline assessment, as a high or low androgen status may have been present since puberty—exerting its metabolic effects over decades. Moreover, a single measurement of testosterone could have been insufficient to detect associations. However, as suggested before,[43] the case of reverse causation might be true as well supposing TT and FT can be considered as a marker of MetS, but any potential causal role should be investigated during longer follow-up periods and/or in experimental designs. In supplementation studies, testosterone may help to improve lipid profiles, body composition, and insulin sensitivity in older and hypogonadal men, whereas anti-androgenic treatment had similar effects in women with PCOS.[4] Unfortunately, experimental studies in older women are scarce.[44]

Despite being the subject of many studies, the underlying mechanisms of the relationship between MDD and MetS remain largely unclear. Several mechanisms, like unhealthy lifestyle habits and immune-inflammatory dysregulation, may be involved, which all influence androgen levels.[4,13] We could not confirm, however, that the relationship between androgenic markers and MetS is moderated by MDD or antidepressant use in older people, since associations were similar in depressed and non-depressed older people. Given the complexity of the relationship between androgenic markers and MetS and the heterogeneity of MDD, it is possible that the interaction terms that were tested were too crude to be informative. Regarding antidepressants, effects on immune-inflammatory dysregulation but also obesity might be medication-type specific.[45] Moreover, certain subtypes of MDD might be more vulnerable for testosterone alterations. In addition, the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis are closely linked, as the end-products steroid hormones of both systems have the same backbone, being derived from cholesterol. Furthermore, these two systems crosstalk, with stimulating and inhibiting effects from both sides.[46]

Some limitations of our study need to be discussed. TT was measured at one time point, which limits its merit to reflect the androgenic status of the participants. However, TT gradually declines with age and may be too small to be measurable and of clinical importance over a period of 2 years for both men and women.[43,47] Previous studies generally also measured the androgenic status at one time point. In addition, a radioimmune assay was used to determine testosterone levels, which is less reliable than liquid chromatography with tandem mass spectrometry (LC-MS/MS) analyses, in particular at the lower concentrations generally measured in women (<5 nmol/L).[48,49] However, as stated in the method section, good correlations have been reported between this radioimmunoassay we used and the ID-LC-MS/MS measurement of testosterone.[26] A strength of our study is its design with measurements of MetS components at two time points, which enabled us to study testosterone not only as a marker but also as a predictor for changes in MetS components. Finally, we studied the association in a well-characterized sample of older subjects with standardized assessment of psychiatric disorders.

In conclusion, our study showed that lower TT and FT levels in older men and higher levels of FT in older women were associated with MetS. Remarkably, testosterone had opposite adverse effects on the metabolic phenotype among the sexes. However, this association was not moderated by MDD or antidepressant use. Therefore, TT and FT could not explain the previously reported relationship between MDD and MetS in older people.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.W., E.G., M.B., F.B., and R.S. conceived the research question. A. W. did the data analysis with help from E.G. All authors contributed to the interpretation of the results. A.W. wrote the first draft of the paper, which was further refined by all other authors. All authors revised the article critically and gave their approval for the version to be published. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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