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DIABETES

Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies

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Background Accumulating evidence suggests a sex-dependent role of circulating testosterone in the metabolic syndrome (MetS).

Methods We conducted a meta-analysis of observational studies (PubMed and EMBASE—1 May 2010) relating MetS to determinants of testosterone status [total testosterone (TT), free testosterone (FT) and sex hormone-binding globulin (SHBG)].

Results A total of 52 studies were identified, comprising 22 043 men and 7839 women and presenting relative risk (RR) estimates or hormone levels for subjects with and without MetS. Endogenous TT and FT levels were lower in men with MetS [TT mean difference = −2.64 nmol/l, 95% confidence interval (CI) −2.95 to −2.32; FT standardized mean difference = −0.26 pmol/l, 95% CI −0.39 to −0.13] and higher in women with MetS (TT mean difference = 0.14 nmol/l, 95% CI 0.07–0.20; FT standardized mean difference = 0.52 pmol/l, 95% CI 0.33–0.71) compared with those without. Similarly, men with higher TT levels had a lower MetS risk (RR estimate = 0.38, 95% CI 0.28–0.50) whereas higher TT levels increased the risk of MetS in women (RR estimate = 1.68, 95% CI 1.15–2.45). In both sexes, higher SHBG levels were associated with a reduced risk (men: RR estimate = 0.29, 95% CI 0.21–0.41; women: RR estimate = 0.30, 95% CI 0.21–0.42).

Conclusion This meta-analysis supports the presence of a sex-dependent association between testosterone and MetS: TT and FT levels are lower in men with MetS, whereas they are higher in women with MetS. There are no indications for a sex-specific association between SHBG and MetS. In both men and women, MetS is associated with lower SHBG levels.

Keywords Testosterone, sex hormone-binding globulin, metabolic syndrome, systematic review, meta-analysis, observational studies

Introduction

The metabolic syndrome (MetS) is a constellation of metabolic risk factors (including hypertension, dyslipidaemia, abdominal obesity and impaired glucose metabolism), which is associated with a 2-fold increased risk of cardiovascular disease (CVD), and an even higher risk of type 2 diabetes.[1,2] Over the past years, various definitions of MetS have been introduced, of which those proposed by the National Cholesterol Education Program—Adult Treatment Panel III (NCEP ATP III),[3] the World Health Organization (WHO)[4] and the International Diabetes Federation (IDF)[5]—are the most widely used. The prevalence of MetS increases with age and is higher in men than in women.[6] MetS-associated risks seem to vary according to sex, with MetS being a stronger risk factor for CVD in women than men.[7,8]

Besides sex differences in prevalence and prognosis, factors associated with the occurrence of MetS may also vary by gender. Previous studies have suggested a role for sex hormones in the development of MetS. Androgen-deprivation therapy in prostate cancer patients,[9] and low total testosterone (TT) levels in hypogonadal men[10,11] have been associated with MetS. On the other hand, MetS and its individual components are common in hyperandrogenic conditions in women, such as the polycystic ovary syndrome (PCOS).[12,13] Sex hormone-binding globulin (SHBG), a testosterone transport protein that affects the circulating levels of free testosterone (FT), has also been linked to MetS. Low SHBG levels have been observed in both men and women with MetS.[14,15] However, little is known about possible sex differences in this association. Furthermore, several studies have examined the relationship between FT and MetS, although their findings have been inconsistent in men[16–18] and women.[15,19,20]

To systematically assess the associations of MetS with TT, SHBG and FT, and to investigate possible sex differences in these associations, we conducted a meta-analysis of observational studies relating endogenous TT, SHBG and/or FT levels to MetS in men and women separately.

Methods

Data sources and searches

We performed this meta-analysis according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology group.[21] A systematic search of PubMed and EMBASE (1966 to 1 May 2010) was conducted for English-language articles using the key words 'metabolic syndrome', 'insulin resistance syndrome' and 'syndrome X' combined with 'testosterone', 'sex hormone-binding globulin', 'shbg', 'androgens', 'sex hormones' and 'sex steroids'. In addition, reference lists of retrieved articles were searched.

Study selection

Studies were selected by two investigators (J.S.B. and Y.T.v.d.S.), using the following criteria. (i) Observational studies including TT, SHBG and/or FT as 'determinant' and MetS as 'outcome'. (ii) MetS defined as the presence of at least three of the following five components: obesity [based on waist circumference, waist-to-hip ratio or body mass index (BMI)], elevated triglyceride levels, low high-density lipoprotein cholesterol levels, impaired glucose metabolism (based on fasting glucose or insulin levels, presence of insulin resistance or diagnosis of diabetes) and hypertension (based on systolic and diastolic blood pressure measurements). (iii) Studies conducted in adults or adolescents. (iv) Availability of a measure of association [mean plus standard deviation (SD) of hormone levels in subjects with and without MetS and/or a relative risk (RR) estimate—odds ratio (OR), RR, hazard ratio (HR), prevalence ratio (PR)]. (v) Studies not selecting participants on the basis of existing diabetes mellitus or CVD.

If multiple reports used the same population for calculating association measures, we only included the analysis based on the largest number of participants.

Data extraction and quality assessment

The following data were extracted from each included study: (i) study characteristics [first author, year of publication, country of data collection, study design, length of follow-up if longitudinal (LO), MetS definition (and if applicable its modification), method of FT assessment, exclusion criterion regarding type 2 diabetes and variables incorporated in multivariable analyses]; (ii) study sample characteristics (sex, mean age and BMI, PCOS status in women, number of subjects with and without MetS, mean and SD of TT, SHBG and FT in subjects with and without MetS and RR estimates).

The primary measure of association was the mean difference in TT, SHBG and FT levels between subjects with and without MetS. For the calculation of mean differences, medians and geometric means were assumed to equal means. If studies provided ranges or interquartile ranges instead of SDs, approximate SDs were derived using the data extraction methods of Higgins[22] and Hozo *et al*.[23]

For studies relating TT, SHBG and FT to MetS risk, RR estimates were included as a secondary measure of association. ORs, RRs, HRs and PRs adjusted for the largest number of confounders were extracted. Adjustments for other hormones and components part of the MetS definition were omitted, as these might obscure true associations. Since individual studies reported RR estimates based on various cut-off levels (tertiles, quartiles or specific thresholds) or as a 1-SD increase in testosterone and SHBG, RR estimates were transformed to a uniform scale (comparing the highest vs lowest tertile of TT, SHBG and FT) using

the method of Danesh *et al*.[24] According to this method, the log RR estimate comparing the highest vs lowest tertile can be estimated as 2.18/2.54 times the log RR estimate comparing the highest vs lowest quartile, or assuming a normal distribution, as 2.18 times the log RR estimate for a 1-SD increase in TT, SHBG or FT. From the study of Laaksonen *et al*.,[25] log ORs for the highest vs lowest tertile were obtained by multiplying the dichotomized log ORs by 2.18/1.695.

The quality of each study was assessed against the following criteria: (i) population-based sample; (ii) exclusion of subjects on hormonal therapy; (iii) use of fasting blood samples for assessment of MetS components; (iv) adjusted analysis for potential confounders; (v) blood sample collection for hormonal assessment in the morning (this extra criterion was added for studies including men). Studies with a population-based sample were defined as those including subjects from the community, who were not institutionalized, clinic based or known to have MetS. Each criterion was graded as 'yes', 'no' or 'unclear'.

Attempts were made to contact authors when further information was needed for meta-analytic calculations. We contacted 13 authors for missing data of whom 9 provided additional data.[15,26–33]

Data synthesis and analysis

Measures of association were analysed for men and women separately, unless results showed no clear indications for an interaction by sex. To compare TT and SHBG levels between subjects with and without MetS, pooled analyses were performed using unstandardized mean differences of TT and SHBG. For the comparison of FT levels, standardized mean differences (mean differences divided by the pooled SD) were used, because individual studies used various methods for FT assessment.

Between-study heterogeneity was quantified by the I^2 statistic.[22] Random-effects models of DerSimonian and Laird[34] were applied in obtaining pooled estimates of association measures.

Univariable metaregression analyses including sex as covariate were conducted to assess sex differences in TT, SHBG and FT levels between subjects with and without MetS. Within each sex, univariable metaregression analyses for predetermined variables (age, BMI, MetS criteria, exclusion of type 2 diabetes, PCOS status, study design, adjustment for covariates and method of FT assessment) were performed to investigate their impact on the association measures and between-study heterogeneity. For these analyses, studies were stratified according to mean age (<55 vs $\geqslant 55$ years), mean BMI (<25 vs $\geqslant 25\,kg/m^2$), MetS definition used [NCEP ATP III vs other criteria (WHO, IDF, EGIR)], exclusion of diabetic patients (yes vs no), study design [cross-sectional (CS) vs LO], adjustment for covariates (yes vs no) and method of FT assessment (direct measurement vs algorithms). Age and BMI were also entered as continuous terms in metaregression analyses. In women, studies were further classified according to the number of PCOS patients included (<50 vs $\geqslant 50\%$). The prevalence of PCOS ranges from 5 to 10% in reproductive women, depending on ethnicity and the criteria being used.[35] In studies not excluding PCOS patients explicitly, the relative number of PCOS patients was assumed not to exceed this percentage range.

Multivariable metaregression analyses including sex and each of the predetermined variables (except for PCOS status) were conducted to investigate whether the interaction effect of sex changed after adjusting for age, BMI and control for age. Univariable and multivariable metaregression analyses were not considered when there were fewer than 10 studies available.

To investigate the impact of each quality parameter separately, sensitivity analyses were conducted in which studies not meeting the individual criteria were excluded. Since direct radioimmunoassay (RIA) is a less reliable method for measuring FT levels,[36] the impact of this assay was also investigated in sensitivity analyses. To assess the presence of possible publication bias, funnel plots were drawn and correlations between standardized association measures and their corresponding SEs were analysed using Egger's test.[37] To correct for publication bias, the 'trim and fill' method of Duval and Tweedie[38] was used. All analyses were conducted using STATA 11.1 (StataCorp., College Station, TX, USA).

Results

Study selection

The study selection process is described in Figure 1. Our initial search yielded 596 articles. Of these, 428 articles were excluded based on abstract review. After full-text review, an extra 116 studies were excluded because of lack of measure of interest ($n=91$), lack of standard MetS definition ($n=7$), inappropriateness of reported association measure for inclusion ($n=8$), multiple publication ($n=7$), unavailability of full text ($n=2$) and no correct stratification of MetS ($n=1$), leaving 52 studies eligible for inclusion, 32 including men, 19 including women and 1 study including both sexes.

Characteristics and quality of studies

Study characteristics are summarized in Tables 1–4. In men, 26 studies were CS, 5 were LO and 1 study used a case–control (CC) design. In women, 19 studies were CS and 1 study used a CC design. Nine studies included PCOS patients. Of these, five studies used the criteria from the National Institute of Child Health and Human Development (NICHD) conference to define PCOS,[73] three studies used the Rotterdam

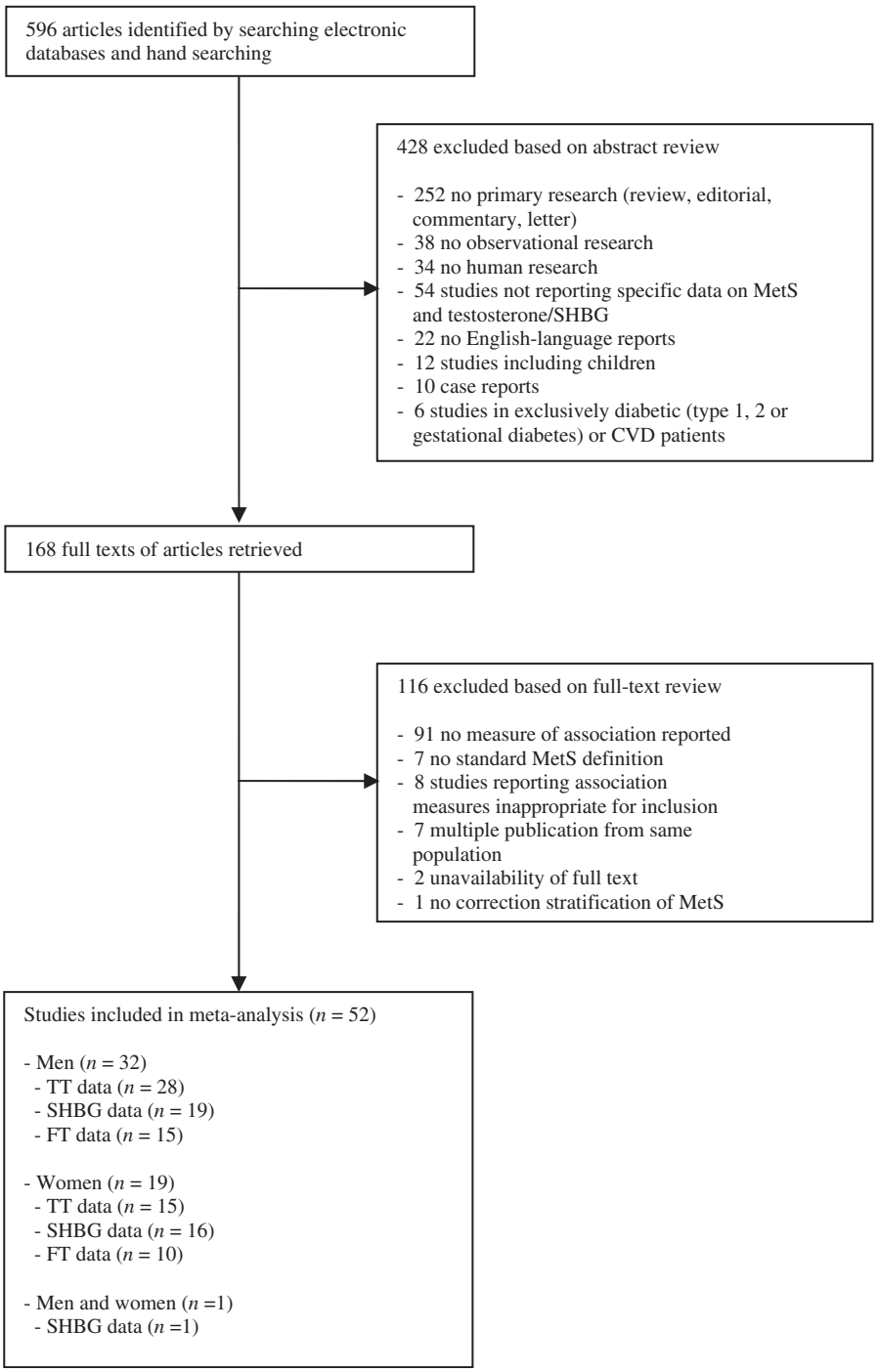

Figure 1 Flow diagram outlining the study selection process

criteria[74] and in one study PCOS criteria were not specified. Mean differences were derived from 45 studies and 17 studies provided RR estimates. Ten studies reported both measures of association (mean differences and RR estimates) and 4 studies provided mean differences for two populations separately. In analyses, these populations were considered as individual studies.

Most of the studies used the NCEP ATP III criteria to define MetS and some applied modified versions of criteria (Table S1, supplementary data are available at *IJE* online). Four studies reported mean differences for more than one MetS definition. From these studies, only the NCEP ATP III definition was considered in the pooled estimate of the mean difference. In analyses stratified by MetS criteria, mean

Table 1 Characteristics of studies reporting on TT, SHBG and/or FT levels in men with and without MetS

No.	Source	Country	Study design	Participants	Mean age (years)	Mean BMI (kg/m^2)	Adjusted for age	No. of MetS$^+$	No. of MetS$^-$	TT Mean (SD), nmol/l		SHBG Mean (SD), nmol/l		FT Mean (SD), pmol/l	
										MetS$^+$	MetS$^-$	MetS$^+$	MetS$^-$	MetS$^+$	MetS$^-$
1	Katabami *et al.*, 2010[39]	Japan	CS	Non-diabetic men	46	23.7	No	70	204					40.6 (13.9)[a]	51.01 (16.0)[a]
2	de Oya *et al.*, 2010[28,b]	Spain	CS	Adolescent boys	14	21.9	No	13	377			28.8 (15.2)	51.0 (34.6)		
3	Atlantis *et al.*, 2009[40 (1),c]	Australia	CS	Men from the Florey Adelaide Male Ageing Study	53		No	445	737	12.2 (4.9)	15.3 (5.6)	30.8 (14.0)	37.1 (17.1)		
	Atlantis *et al.*, 2009[40 (2),c]	Australia	CS	Men from the Florey Adelaide Male Ageing Study	53		No	498	691	12.1 (4.8)	15.5 (5.6)	31.2 (15.5)	37.2 (16.5)		
4	Coviello *et al.*, 2009[41(1),b]	USA	CS	Fathers of women with PCOS	57	30.2	No	89	122	12.8 (5.2)	15.6 (4.3)	72 (40)	80 (37)		
	Coviello *et al.*, 2009[41 (2),b]	USA	CS	Brothers of women with PCOS	29	28.7	No	13	45	15.0 (4.6)	18.8 (7.0)	46 (22)	55 (26)		
5	Demir *et al.*, 2009[42]	Turkey	CS	Men with lower urinary tract symptoms	60[d]	27.4[d]	No	60	130	14.0 (5.2)	16.0 (6.1)				
6	Haring *et al.*, 2009[43]	Germany	LO	Men from the Study of Health in Pomerania	49	26.4	No	480	524	15.5 (4.8)	17.7 (5.3)				
7	Chubb *et al.*, 2008[10]	Australia	CS	Non-diabetic men from the Health in Men Study	76[d]	26.2[d]	No	602	1900	14.0 (4.9)	16.7 (5.7)	36.8 (14.0)	45.5 (17.0)	274.6 (88.2)	291.2 (90.8)
8	Emmelot-Vonk *et al.*, 2008[44]	The Netherlands	CS	Non-diabetic men with low normal testosterone levels	67	27.3	No	62	160	12.7 (2.3)	13.5 (2.4)	28.9 (8.9)	34.4 (10.5)	376.5 (104.0)	345.4 (128.5)
9	Goncharov *et al.*, 2008[45 (1),c]	Russia	CS	Non-diabetic obese men	31	32.6	No	34	26	11.2 (4.0)	16.3 (6.8)	29.7 (21.5)	45.2 (32.0)	249.0 (94.0)	294.0 (129.0)
	Goncharov *et al.*, 2008[45 (2),c]	Russia	CS	Non-diabetic obese men	31	32.6	No	23	37	10.9 (4.4)	15.0 (6.3)	33.9 (27.2)	37.4 (28.0)	230.0 (95.0)	295.0 (120.0)
	Goncharov et *al.*, 2008[45 (3),c]	Russia	CS	Non-diabetic obese men	31	32.6	No	27	33	11.2 (4.6)	15.3 (6.3)	31.4 (22.3)	40.4 (30.7)	236.0 (85.0)	296.0 (125.0)
10	Laughlin *et al.*, 2008[31]	USA	CS	Men from the Rancho Bernardo Study	71	25.7	Yes	143	651	8.5 (2.8)	10.8 (3.4)				
11	Suetomi *et al.*, 2008[46]	Japan	CS	Men with erectile dysfunction	60	23.9[d]	No	25	108	15.3 (5.5)	16.0 (5.9)			33.7 (12.8)	36.1 (11.8)
12	Yeh *et al.*, 2008[47]	Taiwan	CS	Men with erectile dysfunction	58	24.9[d]	No	38	65	12.4 (5.8)	16.2 (5.9)				
13	Corona *et al.*, 2007[17 (1),c]	Italy	CS	Male patients with sexual dysfunction	52		No	348	738	13.6 (6.0)	17.4 (7.2)			34.8 (14.0)[a]	40.8 (13.7)[a]
	Corona *et al.*, 2007[17 (2),c]	Italy	CS	Male patients with sexual dysfunction	52		No	485	601	14.7 (7.4)	18.2 (6.0)			36.2 (14.1)[a]	42.5 (13.5)[a]
14	Guay and Jacobson, 2007[33 (1),c]	USA	CS	Men with erectile dysfunction	54	29.4	No	88	66					42.7 (18.4)[a]	49.3 (22.9)[a]
	Guay and Jacobson, 2007[33 (2),c]	USA	CS	Men with erectile dysfunction	54	29.4	No	54	100					39.6 (10.4)[a]	51.4 (22.9)[a]
15	Rodriguez *et al.*, 2007[48]	USA	CS[e]	Caucasian men from the Baltimore Longitudinal Study of Ageing	63	26.0	Yes	113	505	12.8 (0.2)	14.9 (0.1)	62.9 (2.8)	82.1 (1.6)		
16	Tang *et al.*, 2007[49]	Taiwan	CS	Men residing in a veterans' nursing home	79	23.8	No	101	280	13.3 (0.6)	16.2 (0.4)	39.9 (1.6)	53.9 (1.2)	194.5 (76.9)	205.4 (74.7)
17	Chen *et al.*, 2006[29]	Australia	CS	Non-diabetic men from the Australian Longitudinal Study of Ageing	76	26.0	No	20	140	12.1 (3.6)	14.2 (4.7)				
18	Gannagé-Yared *et al.*, 2006[50]	Lebanon	CS	Non-diabetic men	59	27.3	No	94	59	12.5 (3.8)	14.3 (4.0)	34.0 (13.7)	41.0 (15.5)		
19	Kaplan *et al.*, 2006[51]	USA	CS	Men with dyslipidaemia	52	27.4	No	265	597	14.0 (4.7)	16.1 (4.9)				
20	Kupelian *et al.*, 2006[18]	USA	CS[e]	Men from the Massachusetts Male Ageing Study	53[d]	27.1[d]	No	146	950	15.6 (6.4)	18.4 (5.9)	26.1 (11.8)	33.6 (16.1)	430.0 (190.0)	470.0 (180.0)
21	Maggio *et al.*, 2006[52]	Italy	CS	Men from the InCHIANTI study	75	26.6[d]	No	73	389	13.8 (4.8)	15.0 (4.5)	83.6 (30.8)	104.0 (46.1)	145.7 (48.8)	131.9 (56.6)
22	Mousavinasab *et al.*, 2006[53]	Finland	LO	Military service men on a high-caloric high-fat diet	17–28	24.3[d]	No	11	169			15.1 (6.6)	19.1 (10.2)		
23	Robeva *et al.*, 2006[54]	Bulgaria	CC	Non-diabetic, hyperinsulinaemic men with MetS and healthy age-matched controls	30	30.6	Yes	10	10	12.1 (3.7)	21.5 (7.5)				
24	Kalme *et al.*, 2005[55]	Finland	CS	Men from the Finish part of the Seven Countries Study	70–89		Yes	94	241	16.4 (9.4)	23.2 (9.9)	54.4 (27.1)	74.4 (31.0)		
25	Muller *et al.*, 2005[14]	The Netherlands	CS	Independently living men	60	26.3	No	96	304	15.7 (4.5)	19.4 (5.3)	34.7 (12.4)	42.4 (14.6)	321.1 (90.7)	364.7 (98.2)
26	Nuver *et al.*, 2005[56]	The Netherlands	CS	Testicular cancer patients treated with chemotherapy	38	25.4	No	22	62	18.3 (5.0)	20.0 (8.0)	20.0 (6.0)	26.0 (9.0)	442.0 (115.0)	495.0 (153.0)
27	Tong *et al.*, 2005[30 (1),b]	China	CS	Men from the Hong Kong Diabetes Family Study without a family history of diabetes	44	24.7	Yes	30	98	15.8 (4.0)	18.4 (6.1)	27.1 (9.3)	30.8 (13.2)		
	Tong *et al.*, 2005[30 (2),b]	China	CS	Men from the Hong Kong Diabetes Family Study with a family history of diabetes	39	25.9	Yes	70	109	16.0 (3.7)	18.3 (5.6)	21.2 (8.6)	27.4 (14.4)		
28	Laaksonen *et al.*, 2003[16]	Finland	CS	Non-diabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	53[c]	26.8[c]	No	345	1551	17.6 (6.8)	21.6 (7.4)	31.2 (13.0)	38.1 (15.6)	273.0 (79.0)	307.0 (75.0)

MetS$^+$, subjects with MetS; MetS$^-$, subjects without MetS. SI conversion factors: to convert testosterone (TT/FT) to ng/dl divide by 0.0347. To convert SHBG to μg/ml divide by 8.896.

[a]FT measured by RIA.

[b]Mean differences reported for two separate populations (1) and (2).

[c]Studies using multiple criteria to define the metabolic syndrome—Atlantis *et al.*[40]: (i) NCEP ATP III, (ii) IDF; Goncharov *et al.*[45]: (i) NCEP ATP III, (ii) WHO, (iii) IDF; Corona *et al.*[17]: (i) NCEP ATP III, (ii) IDF; Guay and Jacobson[33]: (i) NCEP ATP III modified, (ii) WHO.

[d]Mean age/BMI of study sample based on weighted means of age/BMI of subjects with and without MetS.

[e]LO study providing data on hormonal levels in subjects with and without MetS at baseline.

Table 2 Characteristics of studies reporting on TT, SHBG and/or FT levels in women with and without MetS

No.	Source	Country	Study design	Participants	Mean age (years)	Mean BMI (kg/m^2)	Adjusted for age	No. of MetS$^+$	No. of MetS$^-$	TT (mean (SD), nmol/l)		SHBG (mean (SD), nmol/l)		FT (mean (SD), pmol/l)	
										MetS$^+$	MetS$^-$	MetS$^+$	MetS$^-$	MetS$^+$	MetS$^-$
1	Alemzadeh *et al.*, 2010[57]	USA	CS	Obese adolescent girls with PCOS	16	36.2	No	35	68					48.6 (17.7)	38.5 (15.9)
2	Healy *et al.*, 2010[58]	Ireland	CS	Postmenopausal women with newly diagnosed breast cancer	68	28.3	No	42	63	1.14 (0.51)	1.07 (0.6)	49.4 (24.6)	57.0 (26.2)		
3	de Oya *et al.*, 2010[28,c]	Spain	CS	Adolescent girls	14	21.8	No	4	424			24.6 (11.2)	64.6 (34.9)		
4	de Sousa *et al.*, 2010[60]	Germany	CS	Obese postmenarcheal adolescent girls	15	32.6	No	48	112	1.8 (0.7)	1.5 (0.7)	19.1 (7.9)	37.9 (8.5)	49.0 (7.0)	40.0 (15.0)
5	Ni *et al.*, 2009[59]	China	CS	Women with PCOS	27	21.9	No	97	481	2.1 (0.8)	2.2 (0.9)	27.8 (25.6)	55.4 (38.7)	152.7 (97.7)	111.1 (72.0)
6	Janssen *et al.*, 2008[61]	USA	CS	Women from the SWAN study at time of their final menstruation period	51	26.9	No	130	819	1.5 (0.6)	1.3 (0.6)	34.1 (19.4)	45.0 (24.2)		
7	Maggio *et al.*, 2007[15]	Italy	CS	Women from the InCHIANTI Study 65 years and older	76	27.6[a]	No	145	367	2.3 (1.1)	2.1 (0.9)	97.5 (51.6)	131.2 (66.9)		
8	Park *et al.*, 2007[62]	Korea	CS	Women with PCOS	26	23.6	No	16	97	2.3 (0.9)	2.4 (1.1)	18.8 (8.9)	49.6 (40.6)	9.0 (2.8)[b]	5.9 (3.1)[b]
9	Coviello *et al.*, 2006[63]	USA	CS	Postmenarcheal adolescent girls with PCOS	17	32.0	No	18	31	2.8 (0.8)	2.5 (0.9)	33.0 (13.0)	77.0 (53.0)		
10	Ehrmann *et al.*, 2006[12]	USA	CS	Non-diabetic PCOS women who participated in a large multicentre national trial	28[a]	36.0[a]	No	123	245	2.2 (1.2)	2.2 (1.1)	32.8 (15.5)	43.8 (21.9)	41.8 (17.7)	37.8 (20.4)
11	Leibel *et al.*, 2006[19]	USA	CS	Postmenarcheal adolescent girls with PCOS	16	32.4[a]	No	10	26			8.4 (6.3)	15.4 (9.6)	90.2 (35.7)	67.0 (23.9)
12	Pasanisi *et al*, 2006[64]	Italy	CS	Postmenopausal women operated for breast cancer	57		No	16	94	1.7 (0.5)	1.4 (0.5)	46.3 (28.1)	67.8 (29.8)		
13	Weinberg *et al.*, 2006[32]	USA	CS	Postmenopausal women from the Women's Health Study (WHS)	65[a]	26.2[a]	Yes	108	104	0.8 (0.6)	0.6 (0.4)	32.6 (29.2)	55.8 (17.3)		
14	Apridonidze *et al.*, 2005[65]	USA	CS	Women with PCOS	30[a]	36.1[a]	No	46	60	2.5 (1.0)	2.1 (1.0)	26.2 (31.5)	36.5 (19.8)	55.9 (26.3)[b]	37.1 (28.1) [b]
15	Dokras *et al.*, 2005[66]	USA	CS	Women with PCOS	28		No	45	84	1.9 (1.0)	1.9 (1.2)	20.0 (11.1)	32.0 (31.5)	27.4 (15.2)	27.1 (26.0)
16	Golden *et al.*, 2004[67 (1),c]	USA	CS	Postmenopausal women from the ARIC study with minimal carotid atherosclerosis	62[a]	27.4[a]	No	60	121	0.9 (0.8)	0.7 (0.6)				
	Golden *et al.*, 2004[67 (2),c]	USA	CS	Postmenopausal women from the ARIC study with significant atherosclerosis	62[a]	27.9[a]	No	94	87	0.8 (0.6)	0.7 (0.5)				
17	Korhonen *et al.*, 2003[20]	Finland	CC	Premenopausal women from a community-based study	43[a]	28.3[a]	Yes	63	88	1.4 (0.5)	1.3 (0.6)	37.4 (22.2)	52.9 (25.3)	21.5 (9.5)	16.8 (6.6)

ARIC, Atherosclerosis Risk in Communities Study; MetS$^+$, subjects with MetS; MetS$^-$, subjects without MetS; SWAN, Study of Women's Health Across the Nation.
[a]Mean differences reported for two separate populations (1) and (2).
[b]Mean age/BMI of study sample based on weighted means of age/BMI of subjects with and without MetS.
[c]FT measured by RIA.

Table 3 Characteristics of studies presenting RR estimates for MetS according to TT, SHBG and/or FT levels in men

No.	Source	Country	Study design	Mean follow-up (years)	Participants	*N*	Variables adjusted for	RR estimate TT[a] (95% CI)	RR estimate SHBG[a] (95% CI)	RR estimate FT[a] (95% CI)
1	Akishita *et al.*, 2010[27]	Japan	CS	NA	Non-diabetic men	194	Age	OR 0.26 (0.11–0.59)		
2	Li *et al.*, 2010[68]	USA	CS	NA	Men from the Third National Health and Nutrition Examination Survey (NHANES-III)	1226	Age, smoking, alcohol consumption, physical activity, race, CRP, LDL cholesterol, HOMA-IR	PR 0.52 (0.38–0.69)	PR 0.51 (0.34–0.79)	PR 0.87 (0.63–1.20)
3	Haring *et al.*, 2009[43,b]	Germany	LO	5	Men from the Study of Health in Pomerania (SHIP) study	1004	None	RR 0.70 (0.59–0.83)		
4	Schneider *et al.*, 2009[26]	Germany	CS	NA	Men from the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential DATA for Commitment of Treatment (DETECT)	2719	None	OR 0.26 (0.21–0.32)		
5	Chubb *et al.*, 2008[10,b]	Australia	CS	NA	Non-diabetic men from the Health in Men study	2052	None	OR 0.28 (0.22–0.36)	OR 0.21 (0.16–0.28)	
6	Emmelot-Vonk *et al.*, 2008[44,b]	The Netherlands	CS	NA	Non-diabetic men with low normal testosterone levels	222	Age, smoking, alcohol consumption	OR 0.45 (0.21–0.95)	OR 0.25 (0.11–0.56)	OR 2.15 (1.00–4.57)
7	Kupelian *et al.*, 2008[69]	USA	CS	NA	Men from the Boston Area Community Health (BACH) survey	1885	Age, smoking, alcohol consumption, physical activity, ethnicity	OR 0.16 (0.10–0.27)	OR 0.13 (0.08–0.23)	OR 0.22 (0.13–0.37)
8	Rodriguez *et al.*, 2007[48,b]	USA	LO	5.8	Men from the Baltimore Longitudinal Study of Aging	417	Age, BMI	HR 0.46 (0.25–0.84)	HR 0.30 (0.17–0.58)	
9	Kupelian *et al.*, 2006[18,b]	USA	LO	14.4	Men from the Massachusetts Male Aging Study	950	None	RR 0.75 (0.55–0.97)	RR 0.50 (0.37–0.68)	RR 1.06 (0.81–1.41)
10	Muller *et al.*, 2005[14,b]	The Netherlands	CS	NA	Independently living men	400	Age, smoking, alcohol consumption, physical activity	OR 0.20 (0.10–0.38)	OR 0.17 (0.08–0.34)	OR 0.31 (0.15–0.63)
11	Tong *et al.*, 2005[30,b]	China	CS	NA	Men from the Hong Kong Diabetes Family Study	307	Age, smoking, family history of diabetes, CRP (TT and SHBG), IGF-1 (SHBG only)	OR 0.25 (0.12–0.52)	OR 0.17 (0.08–0.38)	
12	Laaksonen *et al.*, 2004[25]	Finland	LO	11	Non-diabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	702	Age, BMI, smoking, alcohol consumption, presence of CVD, socio-economic status	OR 0.43 (0.25–0.76)	OR 0.37 (0.21–0.64)	OR 0.56 (0.31–0.99)
13	Laaksonen *et al.*, 2003[16,b]	Finland	CS	NA	Non-diabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	1896	Age, BMI, smoking, alcohol consumption, presence of CVD, socio-economic status	OR 0.52 (0.36–0.75)	OR 0.54 (0.37–0.77)	OR 0.58 (0.41–0.83)

CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; NA, not applicable; LDL, low-density lipoprotein.
[a]RR estimates of MetS comparing highest vs lowest tertiles of TT, SHBG and FT.
[b]Studies reporting both measures of association (RR estimates and mean differences).

Table 4 Characteristics of studies presenting RR estimates for MetS according to TT and/or SHBG levels in women

No.	Source	Country	Study design	Participants	*N*	Variables adjusted for	RR estimate TT[a] (95% CI)	RR estimate SHBG[a] (95% CI)	RR estimate FT[a] (95% CI)
1	Patel *et al.*, 2009 [70]	USA	CS	Non-diabetic women 65 years and older from the Cardiovascular Health Study (CHS)	301	Age, race, estrogen use and number of ovaries removed	OR 2.49 (1.30–4.76)		OR 1.24 (0.67–2.32)
2	Maggio *et al.*, 2007 [15,b]	Italy	CS	Women from the InCHIANTI Study 65 years and older	589	None	OR 1.40 (0.91–2.16)	OR 0.31 (0.19–0.49)	
3	Chen *et al.*, 2006 [71]	Taiwan	CS	Women with PCOS not undergoing treatment	106	Age		OR 0.10 (0.01–0.89)	
4	Weinberg *et al.*, 2006 [32,b]	USA	CS	Postmenopausal women from the Women's Health Study	212	Age, BMI, smoking, alcohol consumption, physical activity, and the presence of CVD at follow-up	OR 3.20 (1.40–7.30)	OR 0.14 (0.05–0.37)	
5	Santoro *et al.*, 2005 [72]	USA	CS	Non-diabetic women from the Study of Women's Health Across the Nation (SWAN)	2961	Age, smoking, ethnicity, site	OR 1.25 (1.12–1.40)	OR 0.36 (0.29–0.43)	

SWAN, Study of Women's Health Across the Nation.
[a]RR estimates of MetS comparing highest vs lowest tertiles of TT, SHBG and FT.
[b]Studies reporting both measures of association (RR estimates and mean differences).

differences corresponding with all definitions were included. An overview of the study quality and methods of FT measurement are presented in Tables S2 and S3 (supplementary data are available at *IJE* online).

TT

Studies presenting TT levels in subjects with and without MetS included 14 319 men and 3904 women. Men with MetS had lower levels of TT (mean difference = −2.64 nmol/l, 95% CI −2.95 to −2.32), whereas women with MetS had higher levels of TT (mean difference = 0.14 nmol/l, 95% CI 0.07–0.20) compared with those without (Figure 2A). In multivariable metaregression analyses this sex-dependent association remained significant ($P < 0.001$) after adjusting for study level differences in age, BMI, diabetes status and control for age.

In men, there was evidence of substantial between-study heterogeneity ($I^2 = 89.1\%$), which was not explained by BMI, diabetes status, control for age or study design. However, in stratified and metaregression analyses TT mean differences were smaller in studies applying NCEP ATP III criteria ($P = 0.03$) (Table 5). Furthermore, metaregression analyses including age as continuous term showed a trend ($P = 0.08$) towards a stronger association in younger men. In women, no significant heterogeneity was observed ($I^2 = 28.5\%$), though the association between TT and MetS appeared to be stronger in women without PCOS ($P = 0.02$) (Table 5). In sensitivity analyses, differences in study quality did not influence associations between TT and MetS in both men and women.

Studies incorporating TT RR estimates comprised 13 974 men and 4063 women. Pooled analyses of RR estimates showed a reduced MetS risk with higher TT levels (RR estimate highest vs lowest TT tertile = 0.38, 95% CI 0.28–0.50) (Figure 3A). An opposite association was observed in women (RR estimate highest vs lowest TT tertile = 1.68, 95% CI 1.15–2.45). Although the number of studies on which the pooled RR estimates are based is small, these data are consistent with a sex difference in the association of MetS with TT. Substantial heterogeneity was observed among RR estimates in both men ($I^2 = 88.5\%$) and women ($I^2 = 66.6\%$). In men, analyses stratified for study design showed that associations were stronger in CS studies (RR estimate highest vs lowest TT tertile = 0.31, 95% CI 0.23–0.41) than LO studies (RR estimate highest vs lowest TT tertile = 0.64, 95% CI 0.53–0.79). In women, no sources of heterogeneity could be identified.

Funnel plots did not disclose publication bias among studies reporting mean differences (men: Egger's test = −1.21, 95% CI −2.49 to 0.06; women: Egger's test = −0.09, 95% CI −1.88 to 1.70) and RR estimates (men: Egger's test = −2.03, 95% CI −5.81 to 1.75; women: Egger's test = 2.05, 95% CI −0.60 to 4.70;

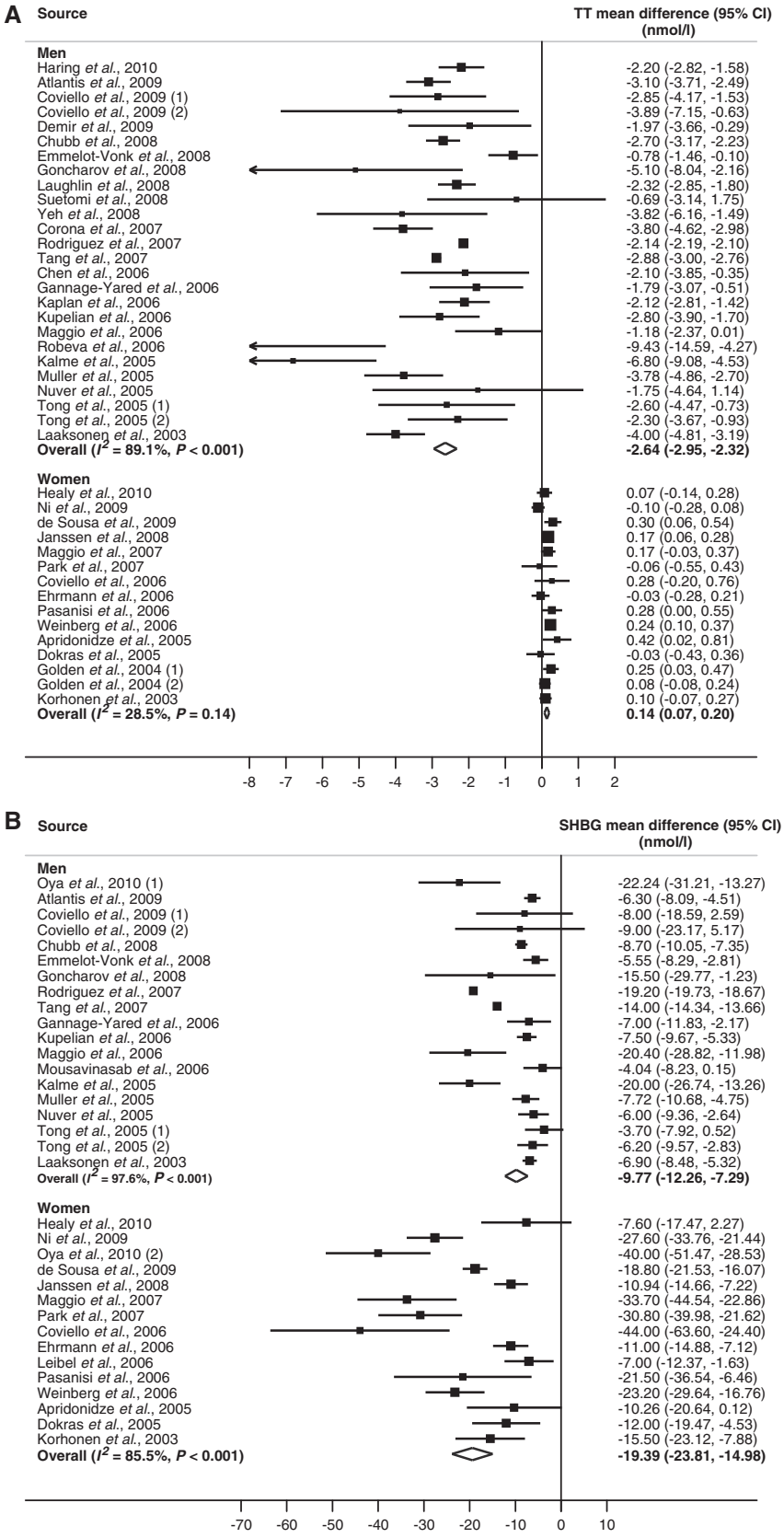

Figure 2 Random effects pooled mean difference of (A) TT, (B) SHBG and (C) FT levels between subjects with and without MetS, men and women**.** Negative values indicate lower (A) TT, (B) SHBG and (C) FT levels in subjects with MetS; positive values indicate higher TT (A), SHBG (B) and (C) FT levels in subjects with MetS. Sizes of squares represent the weight of each study

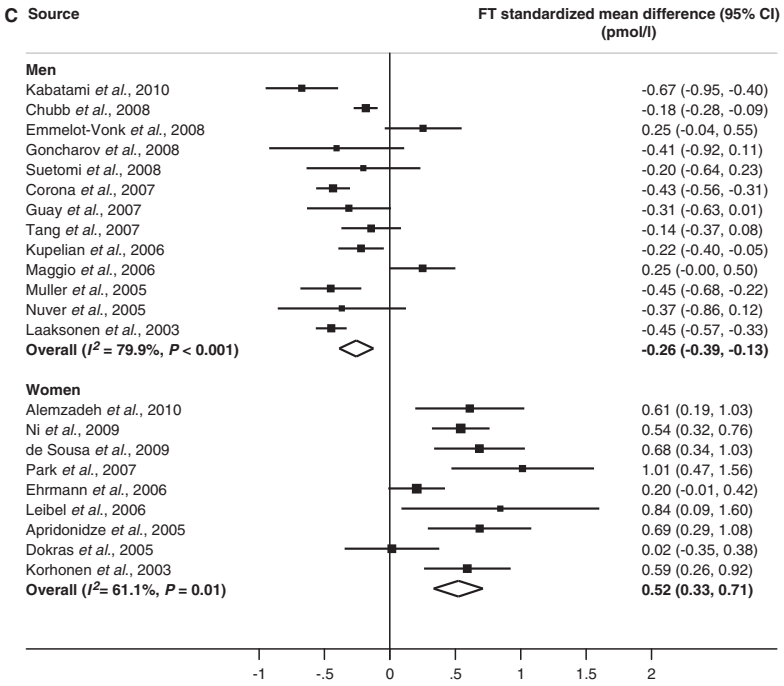

Figure 2 Continued

Figure S1A and B (supplementary data are available at *IJE* online). Although there was no strong evidence for publication bias in RR estimates, visual inspection of the funnel plot showed some asymmetry in women. Because of the small number of studies ($n = 4$), this plot was difficult to interpret.

SHBG

Studies reporting SHBG levels in subjects with and without MetS comprised 10 537 men and 4006 women. In both sexes, SHBG levels were lower in subjects with MetS (men: mean difference = −9.77 nmol/l, 95% CI −12.26 to −7.29; women: mean difference = −19.39 nmol/l, 95% CI −23.81 to −14.98) than in those without (Figure 2B). Overall, the inverse association between SHBG and MetS was stronger in women than men ($P = 0.003$). In multivariable metaregression analyses this sex difference remained consistent after adjusting for study level differences in age, BMI, diabetes status and control for age.

Substantial between-study heterogeneity was observed in both men ($I^2 = 97.6\%$) and women ($I^2 = 85.5\%$). In men, this heterogeneity was partly explained by differences in age. Univariable metaregression analyses including age as a dichotomous term showed that the association between SHBG and MetS tended to be more pronounced in men aged ⩾55 years ($P = 0.08$). This effect of age, however, disappeared when age was entered as a continuous term. In women, the association appeared to be stronger in those with a BMI <25 kg/m^2 (Table 5). This effect of BMI was also observed in metaregression analyses including BMI as a continuous term ($P = 0.04$). Sensitivity analyses showed no effect of study quality on the associations between SHBG and MetS in both men and women.

Studies providing data on SHBG RR estimates comprised 10 057 men and 3868 women. Analysis of RR estimates showed similar inverse associations between SHBG and MetS risk in men (RR estimate highest vs lowest SHBG tertile = 0.29, 95% CI 0.21–0.41) and women (RR estimate for highest vs lowest SHBG tertile = 0.30, 95% CI 0.21–0.42) (Figure 3B), without evidence of a sex difference ($P = 0.74$). There was heterogeneity among RR estimates in men ($I^2 = 80.7\%$), which remained unexplained in stratified and metaregression analyses. In women, no substantial heterogeneity was observed ($I^2 = 37.1\%$).

There were indications for publication bias among studies reporting mean differences in men (Egger's test = 3.73, 95% CI 0.18–7.27). Funnel plots showed asymmetry and pointed to missing studies in the lower left-hand corner, indicating a lack of studies reporting large SHBG differences with high precision (Figure S1A, supplementary data are available at *IJE* online). In women, no publication bias was observed (Egger's test = −2.03, 95% CI −4.92 to 0.86). Egger's test did not detect publication bias among studies reporting RR estimates (men: Egger's test = −1.87, 95% CI −6.50 to 2.88; women: Egger's test = −1.57, 95% CI −3.35 to 0.19), but in women the funnel plot showed some asymmetry (Figure S1B, supplementary data are available at *IJE* online).

Table 5 Mean differences of TT, SHBG and FT between subjects with and without MetS in men and women

	Men			Women		
	Studies (*n*)	TT mean difference (95% CI) (nmol/l)	I^2 (%) and (*P*)	Studies (*n*)	TT mean difference (95% CI) (nmol/l)	I^2 (%) and (*P*)
Overall random effects	26	−2.64 (−2.95 to −2.32)	89.1 (<0.001)	15	0.14 (0.07−0.20)	28.5 (0.14)
Age (years)						
<55	12	−3.03 (−3.60 to −2.45)	65.7 (<0.001)	9	0.10 (0.00−0.21)	42.6 (0.08)
⩾55	14	−2.38 (−2.78 to −1.99)	92.6 (<0.001)	6	0.18 (0.10−0,25)	0.0 (0.55)
BMI (kg/m^2)						
<25	4	−2.77 (−3.45 to −2.08)	20.7 (0.29)	2	−0.10 (−0.26 to 0.07)	0.0 (0.89)
⩾25	19	−2.42 (−2.78 to −2.06)	73.7 (<0.001)	11	0.16 (0.11−0.22)	0.0 (0.47)
PCOS status (women)						
Present	NA	NA	NA	6	0.03 (−0.13 to 0.18)	28.2 (0.22)
Absent	NA	NA	NA	9	0.17 (0.12−0.23)	0.0 (0.66)
MetS criteria[a]						
NCEP ATP III	20	−2.49 (−2.81 to −2.17)	89.8 (<0.001)	12	0.16 (0.10−0.22)	0.0 (0.52)
Other (WHO, IDF, EGIR)	10	−3.57 (−4.35 to −2.80)	62.4 (0.004)	3	0.08 (−0.14 to 0.30)	71.3 (0.03)
Control for age						
Adjusted for age	6	−2.87 (−3.68 to −2.05)	79.5 (<0.001)	2	0.18 (0.05−0.31)	36.3 (0.21)
Not adjusted for age	20	−2.62 (−3.00 to −2.23)	76.0 (<0.001)	13	0.13 (0.05−0.20)	30.2 (0.14)
Type 2 diabetes excluded						
Yes	7	−2.84 (−4.02 to −1.66)	87.9 (<0.001)	2	0.10 (−0.09 to 0.29)	54.8 (0.14)
No	19	−2.67 (−3.01 to −2.32)	89.9 (<0.001)	13	0.15 (0.07−0.22)	30.9 (0.14)
Study design						
CS	24	−2.64 (−2.97 to −2.32)	89.7 (<0.001)	14	0.14 (0.07−0.21)	32.7 (0.11)
CC	1	−9.43 (−14.59 to −4.27)	NA	1	0.10 (−0.07to 0.27)	NA
LO	1	−2.20 (−2.82 to −1.58)	NA			
	Studies (*n*)	SHBG mean difference (95% CI) (nmol/l)	I^2 (%) and (*P*)	Studies (*n*)	SHBG mean difference (95% CI) (nmol/l)	I^2 (%) and (*P*)
Overall random effects	19	−9.77 (−12.26 to −7.29)	97.6 (<0.001)	15	−19.39 (−23.81 to −14.98)	85.5 (<0.001)
Age (years)						
<55	10	−6.69 (−8,20 to −5,19)	48.9 (0.04)	11	−18.73 (−23.73 to −13.73)	87.3 (<0.001)
⩾55	9	−12.00 (−15.13 to −8.87)	98.2 (<0.001)	4	−21.42 (−31.76 to −11.09)	76.5 (0.01)
BMI (kg/m^2)						
<25	4	−10.36 (−17.50 to 3.23)	93.7 (<0.001)	3	−31.46 (−38.05 to −24.86)	42.7 (0.17)
⩾25	13	−9.52 (−13.96 to −5.08)	98.0 (<0.001)	11	−16.07 (−20.64 to −11.51)	83.2 (<0.001)
PCOS status (women)						
Present	NA	NA	NA	7	−18.57 (−26.33 to −10.82)	88.0 (<0.001)
Absent	NA	NA	NA	8	−20.41 (−26.15 to −14.67)	83.9 (<0.001)
MetS criteria[a]						
NCEP ATP IIII	13	−10.00 (−12.86 to −7.13)	98.0 (<0.001)	11	−17.94 (−23.01 to −12.88)	82.0 (<0.001)
Other (WHO, IDF, EGIR)	9	−7.85 (−10.50 to −5.21)	74.2 (<0.001)	4	−23.05 (−32.46 to −13.63)	87.6 (<0.001)
Control for age						
Adjusted for age	4	−12.19 (−21.34 to −3.05)	97.1 (<0.001)	2	−19.63 (−27.16 to −12.11)	56.3 (0.13)
Not adjusted for age	15	−9.02 (−11.70 to −6.33)	95.2 (<0.001)	13	−19.48 (−24,45 to −14.51)	87.0 (<0.001)
Type 2 diabetes excluded						
Yes	6	−7.04 (−8.59 to −5.49)	46.7 (0.10)	2	−10.97 (−13.65 to −8.28)	0.0 (0.98)
No	13	−11.03 (−13.89 to −8.17)	97.7 (<0.001)	13	−21.19 (−26.32 to −16.06)	83.6 (<0.001)
Study design						
CS	18	−10.11 (−12.65 to −7.57)	97.7 (<0.001)	14	−19.75 (−24.45 to −15.05)	86.6 (<0.001)
CC				1	−15.50 (−23.12 to −7.88)	NA
LO	1	−4.04 (−8.23 to 0.15)	NA			

(continued)

Table 5 Continued

	Studies (*n*)	FT standardized mean difference (95% CI) (pmol/l)	I^2 (%) and (*P*)	Studies (*n*)	FT standardized mean difference (95% CI) (pmol/l)	I^2 (%) and (*P*)
Overall random effects	13	−0.26 (−0.39 to −0.13)	79.9 (<0.001)	9	0.52 (0.33−0.71)	61.1 (0.01)
Age (years)						
<55	7	−0.41 (−0.51 to −0.31)	32.9 (0.18)	9	0.52 (0.33−0.71)	61.1 (0.01)
⩾55	6	−0.09 (−0.29 to 0.11)	79.3 (<0.001)			
BMI (kg/m^2)						
<25	3	−0.35 (−0.71 to 0,02)	77.2 (0.01)	2	0.71 (0.27−1.15)	59.8 (0.12)
⩾25	9	−0.20 (−0.36 to -0.04)	81.5 (0.001)	6	0.54 (0.33−0.76)	51.2 (0.07)
PCOS status (women)						
Present	NA	NA	NA	7	0.49 (0.26–0.73)	66.7 (0.01)
Absent	NA	NA	NA	2	0.64 (0.40–0.88)	0.0 (0.71)
MetS criteria[a]						
NCEP ATP III	11	−0.24 (−0.38 to −0.09)	80.0 (<0.001)	7	0.51 (0.25–0.76)	66.5 (0.01)
Other (WHO, IDF)	6	−0.46 (−0.54 to −0.38)	0.0 (0.69)	2	0.58 (0.40–0.77)	0.0 (0.49)
Control for age						
Adjusted for age				1	0.59 (0.26–0.92)	NA
Not adjusted for age	13	−0.26 (−0.39 to −0.13)	79.9 (<0.001)	8	0.52 (0.31–0.73)	64.9 (0.01)
Type 2 diabetes excluded						
Yes	5	−0.29 (−0.53 to −0.05)	87.8 (<0.001)	1	0.20 (−0.01 to 0.42)	NA
No	8	−0.23 (−0.40 to −0.07)	74.1 (<0.001)	8	0.58 (0.39–0.76)	45.8 (0.07)
Study design						
CS	13	−0.26 (−0.39 to −0.13)	79.9 (<0.001)	8	0.52 (0.31 to 0.73)	64.9 (0.01)
CC				1	0.59 (0.26–0.92)	NA
LO						
Method of FT assessment						
Direct measurement	3	−0.47 (−0.64 to −0.30)	38.0 (<0.20)	6	0.57 (0.34–0.80)	59.9 (0.03)
Algorithms	9	−0.18 (−0.34 to −0.03)	81.7 (<0.001)	3	0.44 (0.04–0.84)	75.1 (0.02)

CI, confidence interval; BMI, body mass index; FT, free testosterone; MetS, metabolic syndrome; No., number; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; TT, total testosterone; NA, not applicable.
[a]Stratification of MetS criteria without taking modifications into account: comparison of NCEP ATP II criteria versus other criteria (WHO, IDF, EGIR).

FT

Studies presenting FT levels in subjects with and without MetS included 8750 men and 1744 women in total. A sex difference was found ($P = 0.004$), such that women with MetS had higher FT levels (standardized mean difference = 0.52, 95% CI 0.33–0.71), whereas men with MetS had lower levels of FT than those without (standardized mean difference = −0.26, 95% CI −0.39 to −0.13) (Figure 2C). This sex-dependent association remained significant in multivariable analyses.

Substantial between-study heterogeneity was observed in both men ($I^2 = 79.9\%$) and women ($I^2 = 61.1\%$). In men, heterogeneity was partly explained by the different MetS criteria used across studies. As for TT, the inverse association with FT tended to be weaker among studies using NCEP ATP III criteria ($P = 0.08$) (Table 5). Furthermore, the association between MetS and FT differed according to the mean age of the study population ($P = 0.01$), with a stronger association being observed in younger men (Table 5). In women, no sources of heterogeneity were identified. In sensitivity analyses, exclusion of studies using RIA did not change the observed associations materially. Associations were also not affected by differences in study quality.

Studies reporting FT RR estimates comprised 7281 men. Consistent with the findings for TT, high FT levels were associated with a reduced MetS risk, albeit not statistically significant (RR estimate highest vs lowest FT tertile = 0.64, 95% CI 0.41–1.01) (Figure 3C). There was evidence of substantial between-study heterogeneity ($I^2 = 86.4\%$), of which no sources could be identified. One study in women reported an RR estimate for FT, albeit not significant (RR estimate highest vs lowest FT tertile = 1.24, 95% CI 0.67–2.31).

No publication bias was detected among studies providing FT mean differences in men (Egger's test = −1.19, 95% CI −3.25 to 0.88) and RR estimates in men (Egger's test = −2.69, 95% CI −10.55 to 5.16). In women, funnel plots disclosed publication bias among studies reporting mean differences (Egger's test = 2.36, 95% CI 0.51–4.21), indicating a lack of small studies reporting small FT differences (Figure S1A, supplementary data are available at *IJE* online).

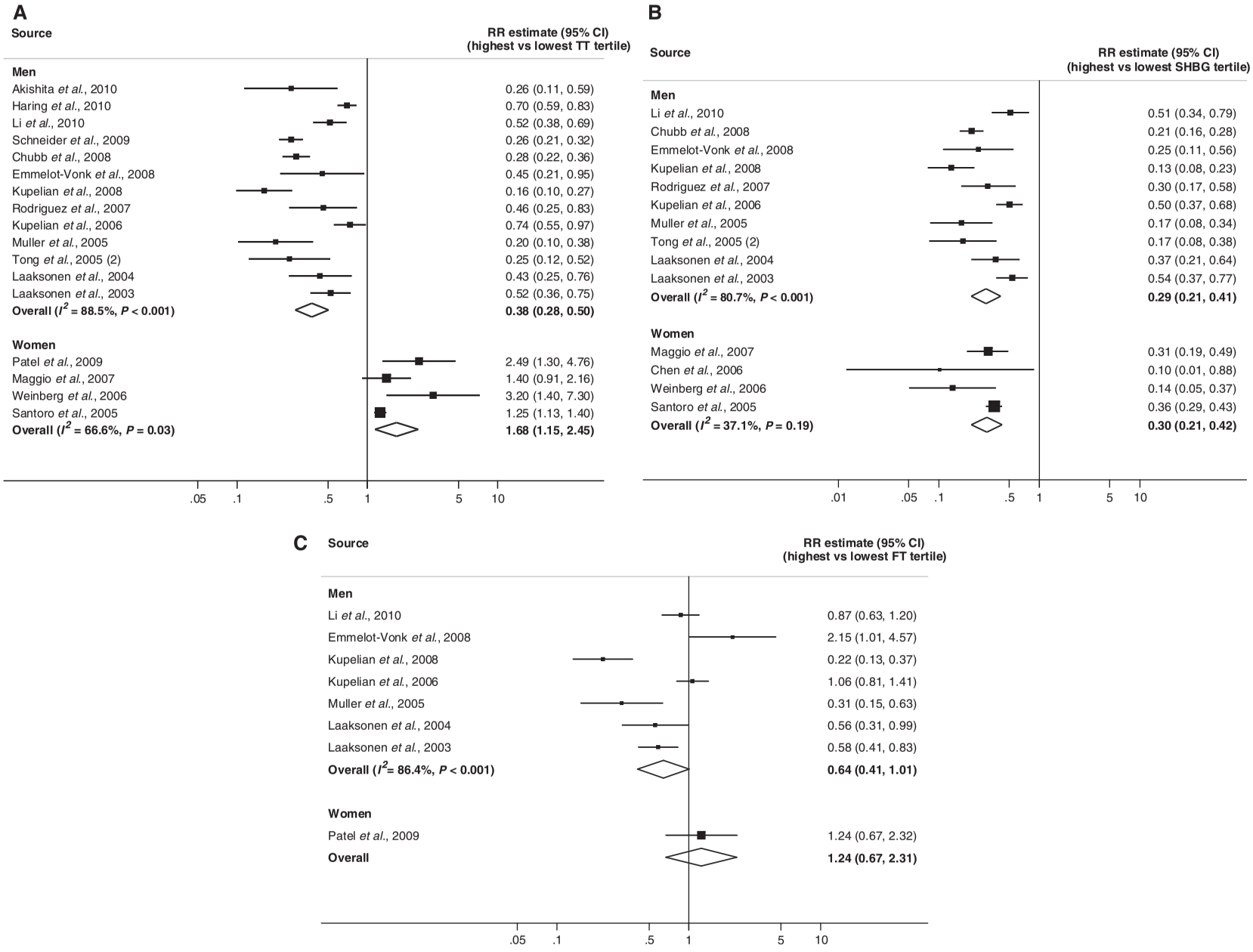

Figure 3 Random effects pooled RR estimate for MetS comparing highest vs lowest tertile of (A) TT, (B) SHBG and (C) FT, men and women. Sizes of squares represent the weight of each study

Discussion

Results of this meta-analysis support the presence of a sex-dependent association between endogenous testosterone and MetS. TT levels were lower in men with MetS, whereas they were higher in women with MetS. There was also some evidence for a sex-specific association between FT and MetS, with FT levels being lower in men with MetS and higher in women with MetS. Interestingly no sex-specific association was observed for SHBG. In both sexes, MetS was associated with lower SHBG levels. Although the mean difference in SHBG levels between those with and without MetS was larger in women, this sex difference was lost after taking potential confounders into account in pooled analyses of RR estimates.

Some limitations of our meta-analysis need to be considered while interpreting the findings. First of all, we could only partly explain between-study heterogeneity. In metaregression analyses we observed that at least some of the heterogeneity in men was explained by differences in age, MetS criteria and study design. In older men the associations of TT and FT with MetS tended to be less pronounced. This effect of age has been reported previously[43] and may be attributed to the age-related decline in testosterone, resulting in a lower contrast in TT and FT with increasing age. Associations of TT and FT with MetS were also weaker when NCEP ATP II criteria were used. These criteria differ from other criteria in degree of emphasis of the individual MetS components. While the NCEP ATP III criteria put equal emphasis on the five MetS components, other criteria assign greater value to a particular component: impaired glucose metabolism (WHO and EGIR) and presence of abdominal obesity (IDF). Therefore, this differential effect of MetS criteria suggests that abdominal obesity and impaired glucose metabolism are important mediators of the observed associations between testosterone and MetS in men. Furthermore, analyses stratified for study design showed stronger associations in CS studies. This may indicate that the 'rare disease assumption' does not apply to MetS, with ORs from CS studies overestimating the actual association. In women, the association between TT and MetS was weaker in PCOS patients. High baseline levels of testosterone in this specific patient population may result in lower inter-individual variation and low power to detect an association. Metaregression analyses further showed that the association between SHBG and MetS was more pronounced in leaner women, suggesting that in obesity SHBG is only one of the contributing factors. Another potential source of between-heterogeneity in both men and women is the variety of methods used for measuring FT levels.[81,82] FT values vary between different algorithms, and FT measurements by RIA have been criticized due to a lack of accuracy.[36] However, sensitivity analyses showed that the use of RIA did not have a major impact on the association between FT and MetS. In spite of material heterogeneity, we decided to pool the data from all studies. Although pooling of heterogeneous studies may affect the validity of the pooled estimates, the results of individual studies were largely compatible with the pooled estimates and pointed in the same direction as the overall estimate.

Another concern is the presence of potential publication bias among studies reporting SHBG mean differences in men and FT mean differences in women. However, evaluation of this publication bias by the 'trim and fill' method showed that imputation of missing studies did not significantly alter the observed associations of SHBG and FT with MetS. It is important to recognize that asymmetry is not necessarily the result of publication bias, but can also be caused by between-study heterogeneity.

A final limitation is the major contribution of CS studies to our meta-analysis, which precludes us from drawing firm conclusions about temporal associations. In men, findings from four LO studies[18,25,43,48] support a causal role for testosterone in MetS etiology. Experimental studies have demonstrated that testosterone has a beneficial effect on glucose and fat metabolism in male rats.[83–86] Moreover, intervention studies in hypogonadal have shown improvements in individual components[87,88] and even reversal of MetS following testosterone therapy.[89,90] However, associations in the opposite direction have been reported as well. In obese men, weight loss and maintenance cause an increase in testosterone and SHBG levels[91,92] and experimental data show suppressive effects of adiposity and insulin on testosterone production in men.[93–95] Furthermore, MetS has been associated with an increased risk of hypogonadism in middle-aged men.[96] Hence, complex, bidirectional relationships between testosterone and MetS seem to be plausible. In women, evidence for a causal role of testosterone in MetS is limited. This is reflected by the lack of LO studies in this meta-analysis. Nevertheless, some recent findings suggest that testosterone may be a risk factor in women as well. In a prospective study,[97] low SHBG and high testosterone levels at baseline were found to be associated with an increased MetS risk. Furthermore, high testosterone levels have been associated with increased risk of diabetes in postmenopausal women[98] and a decrease in insulin sensitivity in female rats.[99] On the other hand, metformin therapy and weight loss reduce androgen excess in women,[100,101] whereas insulin stimulates the ovarian production of testosterone.[102]

Since TT and SHBG are correlated, it is also unclear whether the observed associations between SHBG and MetS reflect an independent effect of SHBG. However, increasing evidence from epidemiological studies support the involvement of SHBG in MetS[10,25,97] and diabetes aetiology.[98,103,104] Moreover, single nucleotide polymorphisms (SNPs) in the *SHBG* gene have recently been shown to affect not only SHBG levels but also type 2 diabetes

risks in men as well as in women,[98,105] suggesting a potential causal role for SHBG in pathophysiological mechanisms.

Pooled estimates of our meta-analysis are comparable (regarding strength and direction) with those previously reported for type 2 diabetes by Ding *et al*.[106] This once more suggests a predominant role for glucose metabolism in the associations of testosterone with MetS and further indicates that the sex-dependent role of testosterone is not only restricted to type 2 diabetes, but also exists in preceding conditions such as MetS, and may even be found in earlier stages of disease. Although the exact mechanisms underlying the sex-specific associations between testosterone and MetS are not completely understood, similar sex-specific effects of testosterone have been observed in animal models. Low testosterone levels following castration in male rats, for instance, have been linked to obesity, insulin resistance and dyslipidaemia,[107,108] whereas prenatal and postnatal administration of testosterone has adverse effects on various MetS components in female rats.[109–111]

The lack of a sex-specific association between SHBG and MetS is not fully understood. Nevertheless, recent findings from genetic studies[112,113] provide some explanation. In these studies, one particular SHBG SNP, rs1799941, was found to have no effect on TT levels in women, whereas it raised testosterone levels in men. Based on these data, it has been hypothesized that women with genetically lower SHBG levels are exposed to proportionally more of the adverse effects of the biologically active unbound testosterone, such as increasing risk of MetS and diabetes. On the other hand, in men there is recent evidence that bound testosterone may be biologically active. If this is the case, then men with lower TT due to lower SHBG will be exposed to less of the protective metabolic effects of androgens, despite similar levels of unbound or FT and also experience higher risk of MetS and diabetes.[105] Thus, similar 'genetic' levels of SHBG may affect MetS risk in men and women differently, by altering the levels of testosterone in a sex-specific manner. Further research is necessary to elucidate the role of SHBG in the pathophysiology of MetS and diabetes.

In conclusion, findings of this meta-analysis support the presence of a sex-dependent association between TT and MetS, with high endogenous TT lowering MetS risk in men but increasing MetS risk in women. There are also indications for a sex difference in the association between FT and MetS. Higher SHBG levels are associated with a lower MetS risk in both men and women. Differences in age, BMI, MetS criteria, PCOS status and study design account for some of the variability observed. The comparability of our pooled estimates with those available for type 2 diabetes suggests a major contribution of impaired glucose metabolism to the observed associations. To further clarify the causal nature of the observed associations, more large-scale LO studies are required, particularly in women. However, LO studies are not perfect as early disease processes (before the actual diagnosis of MetS) may influence the level of testosterone and SHBG as well. Therefore, additional tools, such as Mendelian randomization studies and intervention studies, are needed to establish causation.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- Associations between endogenous testosterone and MetS are sex-specific, with TT and FT levels being lower in men with MetS, and higher in women with MetS.
- There are no indications for a sex-specific association between SHBG and MetS. In both men and women, MetS is associated with lower SHBG levels.
- The large contribution of cross-sectional studies (particularly in women), stresses the need for more LO studies, Mendelian randomization studies and intervention studies to establish the causal nature of the observed association between testosterone, SHBG and MetS.

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Commentary: Testosterone and the metabolic syndrome: cause or consequence?

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The Metabolic Syndrome (MetS), which affects approximately 15–25% of the adult population, comprises a cluster of cardiovascular risk factors that include central obesity, hypertension, hypertriglyceridaemia, glucose intolerance/insulin resistance and reduced high-density lipoprotein cholesterol levels. The presence