



HAL
open science

Testosterone, SHBG and the metabolic syndrome: a systematic review and meta-analysis of observational studies.

Judith S.M. Brand, Ingeborg van Der Tweel, Diederick E Grobbee, Marielle H Emmelot-Vonk, Yvonne T van Der Schouw

► **To cite this version:**

Judith S.M. Brand, Ingeborg van Der Tweel, Diederick E Grobbee, Marielle H Emmelot-Vonk, Yvonne T van Der Schouw. Testosterone, SHBG and the metabolic syndrome: a systematic review and meta-analysis of observational studies.. International Journal of Epidemiology, 2010, <10.1093/ije/DYQ158>. <hal-00625943>

HAL Id: hal-00625943

<https://hal.science/hal-00625943v1>

Submitted on 23 Sep 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Testosterone, SHBG and the metabolic syndrome: a systematic review and meta-analysis of observational studies.

Journal:	<i>International Journal of Epidemiology</i>
Manuscript ID:	IJE-2009-09-0813.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	24-Jul-2010
Complete List of Authors:	Brand, Judith; UMC Utrecht, Julius Centre van der Tweel, Ingeborg; UMC Utrecht, Julius Centre Grobbee, Diederick; UMC Utrecht, Julius Centre Emmelot-Vonk, Marielle; UMC Utrecht, Julius Centre van der Schouw, Yvonne; UMC Utrecht, Julius Centre
Key Words:	Testosterone, SHBG, metabolic syndrome, systematic review, meta-analysis, observational studies

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Testosterone, SHBG and the metabolic syndrome: a systematic review and meta-analysis of**
2 **observational studies.**

3
4
5 **Judith S. Brand, Ingeborg van der Tweel, Diederick E. Grobbee, Marielle H. Emmelot-Vonk,**
6 **Yvonne T. van der Schouw**

7
8
9 Julius Center for Health Sciences and Primary Care (J.S.B., I.v.d.T, D.E.G., Y.T.v.d.S.), University
10 Medical Center Utrecht, Utrecht, The Netherlands.
11 Department of Geriatric Medicine (M.H.E-V.), University Medical Center Utrecht, Utrecht, The
12 Netherlands.

13
14
15 Corresponding author (to whom reprint requests should be addressed): Prof. Yvonne T. van der
16 Schouw, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht,
17 Room STR 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands. Phone: +31-88-756 8165, Fax:
18 +31-88-755 5485; E-mail: y.t.vanderschouw@umcutrecht.nl

19
20 Short title: meta-analysis of testosterone, SHBG and the metabolic syndrome.

21
22 Word count: 4523.

23
24 Funding: This study did not receive any funding or support.

25
26 Disclosure statement: The authors have nothing to declare.

1
2
3 **Abstract**
4

5
6 **Background:** Accumulating evidence suggests a sex-dependent role of circulating testosterone in the
7
8
9 metabolic syndrome (MetS).

10
11 **Methods:** We conducted a meta-analysis of observational studies (PubMed and EMBASE – May 1,
12
13 2010) relating MetS to determinants of testosterone status [total testosterone (TT), free testosterone
14
15 (FT) and sex hormone-binding globulin (SHBG)].
16

17
18 **Results:** Fifty-two studies were identified, comprising 22 043 men and 7839 women and presenting
19
20 relative risk (RR) estimates or hormone levels for subjects with and without MetS. Endogenous TT
21
22 and FT levels were lower in men with MetS (TT mean difference = -2.64 nmol/L; 95% CI, -2.95, -
23
24 2.32, FT standardized mean difference = -0.26 pmol/L; 95% CI, -0.39, -0.13) and higher in women
25
26 with MetS (TT mean difference = 0.14 nmol/L; 95% CI, 0.07, 0.20, FT standardized mean difference
27
28 = 0.52 pmol/L; 95% CI, 0.33, 0.71) compared with those without. Similarly, men with higher TT
29
30 levels had a lower MetS risk (RR estimate = 0.38; 95% CI, 0.28, 0.50) while TT increased the risk of
31
32 MetS in women (RR estimate = 1.68; 95% CI, 1.15, 2.45). In both sexes, higher SHBG levels were
33
34 associated with a reduced risk (men: RR estimate = 0.29; 95% CI, 0.21, 0.41, women: RR estimate =
35
36 0.30; 95% CI, 0.21, 0.42).
37
38

39
40 **Conclusion:** This meta-analysis supports the presence of a sex-dependent association between
41
42 testosterone and MetS: TT and FT levels are lower in men with MetS, whilst they are higher in
43
44 women with MetS. There are no indications for a sex-specific association between SHBG and MetS.
45
46 In both men and women, MetS is associated with lower SHBG levels.
47

48
49 **Key words:** Testosterone, SHBG, metabolic syndrome, systematic review, meta-analysis,
50
51 observational studies
52
53

54
55
56
57
58
59
60

1 Introduction

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

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

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

25
26
27

1 **Methods**

2 ***Data Sources and Searches***

3 We performed this meta-analysis according to the guidelines of the Meta-analysis of Observational
4 Studies in Epidemiology group ²¹. A systematic search of PubMed and EMBASE (1966 – May 1,
5 2010) was conducted for English-language articles using the key words *metabolic syndrome*, *insulin*
6 *resistance syndrome* and *syndrome X* combined with *testosterone*, *sex hormone-binding globulin*,
7 *shbg*, *androgens*, *sex hormones* and *sex steroids*. In addition, reference lists of retrieved articles were
8 searched.

10 ***Study Selection***

11 Studies were selected by two investigators (J.S.B., Y.T.v.d.S.), using the following criteria: 1.
12 observational studies including TT, SHBG and/or FT as *determinant* and MetS as *outcome*. 2. MetS
13 defined as the presence of at least 3 of the following 5 components: obesity (based on waist
14 circumference, waist to hip ratio or BMI), elevated triglyceride levels, low high density lipoprotein
15 cholesterol levels, impaired glucose metabolism (based on fasting glucose or insulin levels, presence
16 of insulin resistance or diagnosis of diabetes) and hypertension (based on systolic and diastolic blood
17 pressure measurements). 3. studies conducted in adults or adolescents. 4. availability of a measure of
18 association (mean plus SD of hormone levels in subjects with and without MetS and/or a relative risk
19 estimate (odds ratio (OR), relative risk (RR), hazard ratio (HR), prevalence ratio (PR)). 5. studies not
20 selecting participants on the basis of existing diabetes mellitus or cardiovascular disease.

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

24 ***Data Extraction and Quality Assessment***

25 The following data were extracted from each included study: 1. study characteristics (first author, year
26 of publication, country of data collection, study design, length of follow-up if longitudinal, MetS
27 definition (and if applicable its modification), method of free testosterone assessment, exclusion

1 criterion regarding type 2 diabetes and variables incorporated in multivariable analyses); 2. study
2 sample characteristics (sex, mean age and BMI, PCOS status in women, number of subjects with and
3 without MetS, mean and SD (derived if SE or 95% CI reported) of TT, SHBG and FT in subjects with
4 and without MetS and relative risk (RR) estimates).

5 The primary measure of association was the mean difference in TT, SHBG and FT levels between
6 subjects with and without MetS. For the calculation of mean differences, medians and geometric
7 means were assumed to equal means. If studies provided ranges or interquartile ranges instead of SDs,
8 approximate SDs were derived using data extraction methods of Higgins²² and Hozo²³ et al.

9 For studies relating TT, SHBG and FT to MetS risk, RR estimates were included as a secondary
10 measure of association. ORs, RRs, HRs and PRs adjusted for the largest number of confounders were
11 extracted. Adjustments for other hormones and components part of the MetS definition were omitted,
12 as these might obscure true associations. Since individual studies reported RR estimates based on
13 various cut-off levels (tertiles, quartiles or specific thresholds) or as a 1 SD increase in testosterone
14 and SHBG, RR estimates were transformed to a uniform scale (comparing the highest versus lowest
15 tertile of TT, SHBG and FT) using the method of Danesh et al.²⁴. According to this method, the log
16 relative risk estimate comparing the highest versus lowest tertile can be estimated as 2.18/2.54 times
17 the log relative risk estimate comparing the highest versus lowest quartile, or assuming a normal
18 distribution, as 2.18 times the log relative risk estimate for a 1 SD increase in TT, SHBG or FT. From
19 the study of Laaksonen et al²⁵ log ORs for the highest versus lowest tertile were obtained by
20 multiplying the dichotomized log ORs by 2.18/1.695.

21 The quality of each study was assessed against the following criteria: 1. population-based sample. 2.
22 exclusion of subjects on hormonal therapy. 3. use of fasting blood samples for assessment of MetS
23 components. 4. adjusted analysis for potential confounders. An extra criterion was added for studies
24 including men: 5. blood sample collection for hormonal assessment in the morning. Studies with a
25 population based sample were defined as those including subjects from the community, who were not
26 institutionalized, clinic based or known to have MetS. Each criterion was graded as 'yes', 'no' or
27 'unclear'.

1 Attempts were made to contact authors when further information was needed for meta-analytic
2 calculations. We contacted 13 authors for missing data of whom 9 provided additional data ^{15,26-33}

4 *Data Synthesis and Analysis*

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

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

13 Univariable metaregression analyses including sex as covariate were conducted to assess sex
14 differences in TT, SHBG and FT levels between subjects with and without MetS. Within each sex,
15 univariable metaregression analyses for predetermined variables (age, BMI, MetS criteria, exclusion
16 of type 2 diabetes, PCOS status, study design, adjustment for covariates and method of FT
17 assessment) were performed to investigate their impact on the association measures and between-
18 study heterogeneity. For these analyses, studies were stratified according to mean age (< 55 years vs ≥
19 55 years), mean BMI (< 25 kg/m² vs ≥ 25 kg/m²), MetS definition used (NCEP ATP III vs other
20 criteria (WHO, IDF, EGIR)), exclusion of diabetic patients (yes vs no), study design (cross-sectional
21 (CS) vs longitudinal (LO)), adjustment for covariates (yes vs no) and method of FT assessment (direct
22 measurement vs algorithms). Age and BMI were also entered as continuous terms in metaregression
23 analyses. In women, studies were further classified according to the number of PCOS patients
24 included (< 50% vs ≥ 50%). The prevalence of PCOS ranges from 5 to 10% in reproductive women,
25 depending on ethnicity and the criteria being used ³⁵. In studies not excluding PCOS patients
26 explicitly, the relative number of PCOS patients was assumed not to exceed this percentage range.

27 Multivariable metaregression analyses including sex and each of the predetermined variables (except
28 for PCOS status) were conducted to investigate whether the interaction effect of sex changed after

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 adjusting for age, BMI and control for age. Univariable and multivariable meta-regression analyses
2 were not considered when there were fewer than 10 studies available.
3 To investigate the impact of each quality parameter separately, sensitivity analyses were conducted in
4 which studies not meeting the individual criteria were excluded. Since direct radioimmunoassay
5 (RIA) is a less reliable method for measuring free testosterone levels ³⁶, the impact of this assay was
6 also investigated in sensitivity analyses. To assess the presence of possible publication bias, funnel
7 plots were drawn and correlations between standardized association measures and their corresponding
8 SEs were analyzed using Egger's test ³⁷. In case of publication bias, the "trim and fill" method of
9 Duval and Tweedie ³⁸ was used to correct for this bias. All analyses were conducted using STATA
10 11.1 (StataCorp., College Station, Tex., U.S.A.).

For Review Only

27

1 **Results**

2 *Study selection*

3 The study selection process is described in Figure 1. Our initial search yielded 596 articles. Of these,
4 428 articles were excluded based on abstract review. After full text review, an extra 116 studies were
5 excluded because of lack of measure of interest (n = 91), lack of standard MetS definition (n = 7),
6 inappropriateness of reported association measure for inclusion (n = 8), multiple publication (n = 7),
7 unavailability of full text (n = 2) and no correct stratification of MetS (n = 1), leaving 52 studies
8 eligible for inclusion, 32 including men, 19 including women and 1 study including both men and
9 women.

11 *Characteristics and quality of studies*

12 Study characteristics are summarized in Tables 1 and 2. In men, 26 studies were cross-sectional, 5
13 were longitudinal and 1 study used a case-control design. In women, 19 studies were cross-sectional
14 and 1 study used a case-control design. Nine studies included PCOS patients. Of these, 5 studies used
15 the NICHD criteria to define PCOS⁷³, 3 studies used the Rotterdam criteria⁷⁴ and in 1 study PCOS
16 criteria were not specified. From 45 studies mean differences were derived; 17 studies provided
17 relative risk estimates. Ten studies included both measures of association and 4 studies provided mean
18 differences for two populations separately. In analyses, these populations were considered as
19 individual studies.

20 Most of the studies used the NCEP ATP III criteria to define MetS and some applied modified
21 versions of criteria (Supplementary Table 1). Four studies reported mean differences for more than
22 one MetS definition. From these studies, only the NCEP ATP III definition was considered in the
23 pooled estimate of the mean difference. In univariable metaregression analyses, mean differences
24 corresponding with all definitions were included. An overview of the study quality and methods of FT
25 measurement is presented in Supplementary Tables 2 and 3.

1 **Total Testosterone**

2 Studies presenting TT levels in subjects with and without MetS included 14 319 men and 3904
3 women in total. Men with MetS had lower levels of TT (mean difference = -2.64 nmol/L; 95% CI, -
4 2.95, -2.32), whereas women with MetS had higher levels of TT (mean difference = 0.14 nmol/L;
5 95% CI, 0.07, 0.20) compared with those without (Figure 2A). In multivariable metaregression
6 analyses this sex-dependent association remained significant ($P < 0.001$) after adjusting for study level
7 differences in age, BMI, diabetes status and control for age.

8 In men, there was evidence of substantial between-study heterogeneity ($I^2 = 89.1\%$), which was not
9 explained by BMI, diabetes status, control for age or study design. However, in stratified and
10 metaregression analyses TT mean differences were smaller in studies applying NCEP ATP III criteria
11 ($P = 0.03$) (Table 3). Furthermore, metaregression analyses including age as continuous term showed
12 a trend ($P = 0.08$) towards a stronger association in younger men. In women, no significant
13 heterogeneity was observed ($I^2 = 28.5\%$), though the association between TT and MetS appeared to be
14 stronger in women without PCOS ($P = 0.02$) (Table 3). In sensitivity analyses, differences in study
15 quality did not influence associations between TT and MetS in both men and women.

16 Studies incorporating TT relative risk estimates comprised 13 974 men and 4063 women. Pooled
17 analyses of RR estimates showed a reduced MetS risk with increasing TT levels (RR estimate highest
18 versus lowest TT tertile = 0.38; 95% CI, 0.28, 0.50) (Figure 3A). An opposite association was
19 observed in women (RR estimate highest versus lowest TT tertile = 1.68; 95% CI, 1.15, 2.45).

20 Although the number of studies on which the pooled RR estimates are based are small, these data are
21 consistent with a sex difference in the association of MetS with TT. Substantial heterogeneity was
22 observed among RR estimates in both men ($I^2 = 88.5\%$) and women ($I^2 = 66.6\%$). In men, analyses
23 stratified for study design showed that associations were stronger in cross-sectional studies (RR
24 estimate highest versus lowest TT tertile = 0.31; 95% CI, 0.23, 0.41) than longitudinal studies (RR
25 estimate highest versus lowest TT tertile = 0.64; 95% CI, 0.53, 0.79). In women, no sources of
26 heterogeneity could be identified.

27 Funnel plots did not disclose publication bias among studies reporting mean differences (men: Egger's
28 test = -1.21; 95% CI, -2.49, 0.06 and women: Egger's test = -0.09; 95% CI, -1.88, 1.70) and RR

1 estimates (men: Egger's test = -2.03; 95% CI, -5.81, 1.75 and women: Egger's test = 2.05; 95% CI, -
 2 0.60, 4.70) (Supplementary Figures 1A and 1B). Although there was no strong evidence for
 3 publication bias in RR estimates, visual inspection of the funnel plot showed some asymmetry in
 4 women. Because of the small number of studies (N = 4), this plot was difficult to interpret.

6 ***Sex Hormone-Binding Globulin***

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

14 Substantial between-study heterogeneity was observed in both men ($I^2 = 97.6\%$) and women ($I^2 =$
 15 85.5%). In men, this heterogeneity was partly explained by differences in age. Univariable
 16 meta-regression analyses including age as a dichotomous term showed that the association between
 17 SHBG and MetS tended to be more pronounced in men aged 55 years and older ($P = 0.08$). This effect
 18 of age, however, disappeared when age was entered as a continuous term. In women, the association
 19 appeared to be stronger in those with a BMI < 25 kg/m² (Table 3). This effect of BMI was also
 20 observed in meta-regression analyses including BMI as a continuous term ($P = 0.04$) Sensitivity
 21 analyses showed no effect of study quality on the associations between SHBG and MetS in both men
 22 and women.

23 Studies providing data on SHBG relative risk estimates comprised 10 057 men and 3868 women.
 24 Analysis of RR estimates showed similar inverse associations between SHBG and MetS risk in men
 25 (RR estimate highest versus lowest SHBG tertile = 0.29; 95% CI, 0.21, 0.41) and women (RR
 26 estimate for highest versus lowest SHBG tertile = 0.30; 95% CI, 0.21, 0.42) (Figure 3B), without
 27 evidence of a sex difference ($P = 0.74$). There was heterogeneity among RR estimates in men ($I^2 =$

1 80.7%) which remained unexplained in stratified and metaregression analyses. In women, no
2 substantial heterogeneity was observed ($I^2 = 37.1\%$).

3 There were indications for publication bias among studies reporting mean differences in men (Egger's
4 test = 3.73; 95% CI, 0.18, 7.27). Funnel plots showed asymmetry and pointed to missing studies in the
5 lower left-handed corner, indicating a lack of studies reporting large SHBG differences with high
6 precision (Supplementary Figure 1A). In women, no publication bias was observed (Egger's test = -
7 2.03; 95% CI, -4.92, 0.86). Egger's test did not detect publication bias among studies reporting RR
8 estimates (men: Egger's test = -1.87; 95% CI, -6.50, 2.88, women: Egger's test = -1.57; 95% CI, -
9 3.35, 0.19), but in women the funnel plot showed some asymmetry (Supplementary Figure 1B).

11 ***Free Testosterone***

12 Studies presenting FT levels in subjects with and without MetS included 8750 men and 1744 women
13 in total. A sex difference was found ($P = 0.004$), such that women with MetS had higher FT levels
14 (mean difference = 0.52; 95% CI, 0.33, 0.71), while men with the metabolic syndrome had lower
15 levels of FT than those without (mean difference = -0.26; 95% CI, -0.39, -0.13) (Figure 2C). This sex-
16 dependent association remained significant in multivariable analyses.

17 Substantial between-study heterogeneity was observed in both men ($I^2 = 79.9\%$) and women ($I^2 =$
18 61.1%). In men, heterogeneity was partly explained by the different MetS criteria used across studies.
19 As for TT, the inverse association with FT tended to be weaker among studies using NCEP ATP III
20 criteria ($P = 0.08$) (Table 3). Furthermore, the association between MetS and FT differed according to
21 the mean age of the study population ($P = 0.01$), with a stronger association being observed in
22 younger men (Table 3). In women, no sources of heterogeneity were identified. In sensitivity analyses,
23 exclusion of studies using RIA did not change the observed associations materially. Associations were
24 also not affected by differences in study quality.

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

1 study in women reported a RR estimate for FT, albeit not significant (RR estimate highest versus
2 lowest FT tertile = 1.24; 95% CI, 0.67, 2.31).

3 No publication bias was detected among studies providing FT mean differences in men (Egger's test =
4 -1.19; 95% CI, -3.25, 0.88) and RR estimates in men (Egger's test = -2.69; 95% CI, -10.55, 5.16). In
5 women, funnel plots disclosed publication bias among studies reporting mean differences (Egger's
6 test = 2.36; 95% CI, 0.51, 4.21), indicating a lack of small studies reporting small FT differences
7 (Supplementary Figure 1A).

8

9

10 Discussion

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

19 Some limitations of our meta-analysis need to be considered while interpreting the findings. First of
20 all, we could only partly explain between-study heterogeneity. In metaregression analyses we
21 observed that at least some of the heterogeneity in men was explained by differences in age, MetS
22 criteria and study design. In older men the associations of TT and FT with MetS tended to be less
23 pronounced. This effect of age has been reported previously⁴³ and may be attributed to the age-related
24 decline in testosterone, resulting in a lower contrast in TT and FT with increasing age. Associations of
25 TT and FT with MetS were also weaker when NCEP ATP II criteria were used. These criteria differ
26 from other criteria in degree of emphasis of the individual MetS components. While the NCEP ATP
27 III criteria put equal emphasis on the five MetS components, other criteria assign greater value to a
28 particular component: impaired glucose metabolism (WHO and EGIR) and presence of abdominal

1 obesity (IDF). Therefore, this differential effect of MetS criteria suggests that abdominal obesity and
2 impaired glucose metabolism are important mediators of the observed associations between
3 testosterone and MetS in men. Furthermore, analyses stratified for study design showed stronger
4 associations in cross-sectional studies. This may indicate that the 'rare disease assumption' does not
5 apply to the metabolic syndrome, with odds ratios from cross-sectional studies overestimating the
6 actual association. In women, the association between TT and MetS was weaker in PCOS patients
7 High baseline levels of testosterone in this specific patient population may result in lower
8 interindividual variation and low power to detect an association. Metaregression analyses further
9 showed that the association between SHBG and MetS was more pronounced in leaner women,
10 suggesting that in obesity SHBG is only one of the contributing factors. Another potential source of
11 between-heterogeneity in both men and women is the variety of methods used for measuring free
12 testosterone levels^{81,82}. FT values vary between different algorithms and FT measurements by RIA
13 have been criticized due to a lack of accuracy³⁶. However, sensitivity analyses showed that the use of
14 RIA did not have a major impact on the association between FT and MetS. In spite of material
15 heterogeneity, we decided to pool the data from all studies. While pooling of heterogeneous studies
16 may affect the validity of the pooled estimates, the results of individual studies were largely
17 compatible with the pooled estimates and pointed in the same direction as the overall estimate.
18 Another concern is the presence of potential publication bias among studies reporting SHBG mean
19 differences in men and FT mean differences in women. However, evaluation of this publication bias
20 by the "trim and fill" method showed that imputation of missing studies did not significantly alter the
21 observed associations of SHBG and FT with MetS. It is important to recognize that asymmetry is not
22 necessarily the result of publication bias, but can also be caused by between-study heterogeneity.
23 A final limitation is the major contribution of cross-sectional studies to our meta-analysis, which
24 precludes us from drawing firm conclusions about temporal associations. In men, findings from four
25 longitudinal studies^{18,25,43,48} support a causal role for testosterone in the MetS etiology. Experimental
26 studies have demonstrated that testosterone has beneficial effect on glucose and fat metabolism in
27 male rats⁸³⁻⁸⁶. Moreover, intervention studies in hypogonadal have shown improvements in individual
28 components^{87,88} and even reversal of MetS following testosterone therapy^{89,90}. However, associations

1 in the opposite direction have been reported as well. In obese men, weight loss and maintenance cause
2 an increase in testosterone and SHBG levels ^{91,92} and experimental data show suppressive effects of
3 adiposity and insulin on testosterone production in men ⁹³⁻⁹⁵. Furthermore, MetS has been associated
4 with an increased risk of hypogonadism in middle aged men ⁹⁶. Hence, complex, bidirectional
5 relationships between testosterone and MetS seem to be plausible. In women, evidence for a causal
6 role of testosterone in MetS is limited. This is reflected by the lack of longitudinal studies in this
7 meta-analysis. Nevertheless, some recent findings suggest that testosterone may be a risk factor in
8 women as well. In a prospective study ⁹⁷, low SHBG and high testosterone levels at baseline were
9 found to be associated with an increased MetS risk. Furthermore, high testosterone levels have been
10 associated with increased risk of diabetes in postmenopausal women ⁹⁸ and a decrease in insulin
11 sensitivity in female rats ⁹⁹. On the other hand, metformin therapy and weight loss reduce androgen
12 excess in women ^{100,101}, while insulin stimulates the ovarian production of testosterone ¹⁰².

13 Since TT and SHBG are correlated, it is also unclear whether the observed associations between
14 SHBG and MetS reflect an independent effect of SHBG. However, increasing evidence from
15 epidemiological studies support the involvement of SHBG in MetS ^{10,25,97} and diabetes
16 etiology^{98,103,104}. Moreover, polymorphisms in the SHBG gene have recently been shown to affect not
17 only SHBG levels but also type 2 diabetes risks in men as well as in women ^{98,105}, suggesting a
18 potential causal role for SHBG in pathophysiological mechanisms.

19 Pooled estimates of our meta-analysis are comparable (regarding strength and direction) with those
20 previously reported for type 2 diabetes by Ding et al. ¹⁰⁶. This once more suggests a predominant role
21 for glucose metabolism in the associations of testosterone with MetS and further indicates that the
22 sex-dependent role of testosterone is not restricted to type 2 diabetes, but also exist in preceding
23 conditions such as MetS, and may even be found in earlier stages of disease. Although the exact
24 mechanisms underlying the sex specific associations between testosterone and MetS are not
25 completely understood, similar sex-specific effects of testosterone have been observed in animal
26 models. Low testosterone levels following castration in male rats, for instance, have been linked to
27 obesity, insulin resistance and dyslipidemia ^{84,107,108}. Whereas prenatal and postnatal administration of
28 testosterone has adverse effects on various MetS components in female rats ¹⁰⁹⁻¹¹¹.

1
2
3 1 The lack of a sex specific association between SHBG and MetS is not fully understood. Nevertheless,
4
5 2 recent findings from genetic studies ^{112,113} provide some explanation. In these studies, one particular
6
7 3 SHBG SNP, rs1799941, was found to have no effect on total testosterone levels in women while
8
9 4 raising testosterone levels in men. Based on these data, it has been hypothesized that women with
10
11 5 genetically lower SHBG levels are exposed to proportionally more of the adverse effects of the
12
13 6 biologically active unbound testosterone, such as increasing risk of MetS and diabetes in women. On
14
15 7 the other hand, in men there is recent evidence that bound testosterone may be biologically active. If
16
17 8 this is the case, then men with lower total testosterone due to lower SHBG will be exposed to less of
18
19 9 the protective metabolic effects of androgens, despite similar levels of unbound or free testosterone
20
21 10 and also experience higher risk of MetS and diabetes ¹⁰⁵. Thus similar 'genetic' levels of SHBG may
22
23 11 affect MetS risk in men and women differently, by altering the levels of testosterone in a sex-specific
24
25 12 manner. Further research is necessary to elucidate the role of SHBG in the pathophysiology of MetS
26
27 13 and diabetes.

28
29
30
31 14 In conclusion, findings of this meta-analysis support the presence of a sex-dependent association
32
33 15 between TT and MetS, with high endogenous TT lowering MetS risk in men, while increasing MetS
34
35 16 risk in women. There are also indications for a sex difference in the association between FT and MetS.
36
37 17 Higher SHBG levels are associated with a lower MetS risk in both men and women. Differences in
38
39 18 age, BMI, MetS criteria, PCOS status and study design account for some of the variability observed.
40
41 19 The comparability of our pooled estimates with those available for type 2 diabetes suggests a major
42
43 20 contribution of impaired glucose metabolism to the observed associations. To further clarify the causal
44
45 21 nature of the observed associations, more large-scale longitudinal studies are required, in women in
46
47 22 particular. However, longitudinal studies are not perfect as early disease processes before the actual
48
49 23 diagnosis of MetS may influence the level of testosterone and SHBG as well. Therefore, additional
50
51 24 tools, such as Mendelian randomization studies and intervention studies, are needed to establish
52
53 25 causation.
54
55
56
57
58
59
60

28

1
2
3 1 **Key messages**
4

- 5 2 1. Associations between endogenous testosterone and the metabolic syndrome (MetS) are sex-
6 specific with total and free testosterone levels being lower in men with MetS, while being
7 3 higher in women with MetS.
8 4
9 5 2. There are no indications for a sex-specific association between SHBG and MetS. In both men
10 6 and women MetS is associated with lower SHBG levels.
11 7
12 8 3. The large contribution of cross-sectional studies (particularly in women), stresses the need for
13 9 more longitudinal studies, Mendelian randomization studies and intervention studies to
14 establish the causal nature of the observed association between testosterone, SHBG and MetS.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Acknowledgements**

2 We thank all investigators who kindly provided additional information from their studies.

For Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 References

- 2 ¹ Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with
3 the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005; **28**: 1769-78.
- 4 ² Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008; **28**: 629-
5 36.
- 6 ³ Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.
7 Executive Summary of The Third Report of The National Cholesterol Education Program
8 (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In
9 Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486-97.
- 10 ⁴ Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its
11 complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a
12 WHO consultation. *Diabet Med* 1998; **15**: 539-53.
- 13 ⁵ Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The
14 metabolic syndrome--a new worldwide definition. *Lancet* 2005; **366**: 1059-62.
- 15 ⁶ Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic
16 syndrome and their role for cardiovascular disease. *Clin Res Cardiol* 2006; **95**: 136-47.
- 17 ⁷ Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk:
18 Northern Manhattan Study. *Stroke* 2008; **39**: 30-5.
- 19 ⁸ Takahashi K, Bokura H, Kobayashi S, Iijima K, Nagai A, Yamaguchi S. Metabolic
20 syndrome increases the risk of ischemic stroke in women. *Intern Med* 2007; **46**: 643-8.
- 21 ⁹ Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer
22 and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 2008; **93**: 2042-9.
- 23 ¹⁰ Chubb SA, Hyde Z, Almeida OP, et al. Lower sex hormone-binding globulin is more
24 strongly associated with metabolic syndrome than lower total testosterone in older men: the
25 Health in Men Study. *Eur J Endocrinol* 2008; **158**: 785-92.
- 26 ¹¹ Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in
27 Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes*
28 *Care* 2006; **29**: 1591-8.
- 29 ¹² Ehrmann DA, Liljenquist DR, Kasza K, et al. Prevalence and predictors of the metabolic
30 syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006; **91**: 48-
31 53.
- 32 ¹³ Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of
33 metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome.
34 *Metabolism* 2003; **52**: 908-15.

- 1
2
3 1 ¹⁴ Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous
4 2 sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab* 2005; **90**:
5 3 2618-23.
6
7
8 4 ¹⁵ Maggio M, Lauretani F, Ceda GP, et al. Association of hormonal dysregulation with
9 5 metabolic syndrome in older women: data from the InCHIANTI study. *Am J Physiol*
10 6 *Endocrinol Metab* 2007; **292**: E353-8.
11
12
13 7 ¹⁶ Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the
14 8 metabolic syndrome: a population-based study. *Eur J Endocrinol* 2003; **149**: 601-8.
15
16
17 9 ¹⁷ Corona G, Mannucci E, Petrone L, et al. A comparison of NCEP-ATPIII and IDF
18 10 metabolic syndrome definitions with relation to metabolic syndrome-associated sexual
19 11 dysfunction. *J Sex Med* 2007; **4**: 789-96.
20
21 12 ¹⁸ Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex
22 13 hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are
23 14 associated with development of the metabolic syndrome in nonobese men. *J Clin Endocrinol*
24 15 *Metab* 2006; **91**: 843-50.
25
26
27 16 ¹⁹ Leibel NI, Baumann EE, Kocherginsky M, Rosenfield RL. Relationship of adolescent
28 17 polycystic ovary syndrome to parental metabolic syndrome. *J Clin Endocrinol Metab* 2006;
29 18 **91**: 1275-83.
30
31
32 19 ²⁰ Korhonen S, Hippelainen M, Vanhala M, Heinonen S, Niskanen L. The androgenic sex
33 20 hormone profile is an essential feature of metabolic syndrome in premenopausal women: a
34 21 controlled community-based study. *Fertil Steril* 2003; **79**: 1327-34.
35
36
37 22 ²¹ Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
38 23 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in
39 24 Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-12.
40
41
42 25 ²² Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-
43 26 analyses. *BMJ* 2003; **327**: 557-60.
44
45
46 27 ²³ Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median,
47 28 range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13.
48
49
50 29 ²⁴ Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein,
51 30 albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective
52 31 studies. *JAMA* 1998; **279**: 1477-82.
53
54
55 32 ²⁵ Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding
56 33 globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care*
57 34 2004; **27**: 1036-41.
58
59
60 35 ²⁶ Schneider HJ, Sievers C, Klotsche J, et al. Prevalence of low male testosterone levels in
36 primary care in Germany: cross-sectional results from the DETECT study. *Clin Endocrinol*
37 (*Oxf*) 2009; **70**: 446-54.

- 1
2
3 1 ²⁷ Akishita M, Fukai S, Hashimoto M, et al. Association of low testosterone with metabolic
4 2 syndrome and its components in middle-aged Japanese men. *Hypertens Res* 2010; **33**: 587-
5 3 91.
6
7
8 4 ²⁸ de Oya I, Schoppen S, Lasuncion MA, et al. Sex hormone-binding globulin levels and
9 5 metabolic syndrome and its features in adolescents. *Pediatr Diabetes* 2010; **11**: 188-94.
10
11 6 ²⁹ Chen RY, Wittert GA, Andrews GR. Relative androgen deficiency in relation to obesity
12 7 and metabolic status in older men. *Diabetes Obes Metab* 2006; **8**: 429-35.
13
14
15 8 ³⁰ Tong PC, Ho CS, Yeung VT, et al. Association of testosterone, insulin-like growth factor-I,
16 9 and C-reactive protein with metabolic syndrome in Chinese middle-aged men with a family
17 10 history of type 2 diabetes. *J Clin Endocrinol Metab* 2005; **90**: 6418-23.
18
19
20 11 ³¹ Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in
21 12 older men. *J Clin Endocrinol Metab* 2008; **93**: 68-75.
22
23
24 13 ³² Weinberg ME, Manson JE, Buring JE, et al. Low sex hormone-binding globulin is
25 14 associated with the metabolic syndrome in postmenopausal women. *Metabolism* 2006; **55**:
26 15 1473-80.
27
28
29 16 ³³ Guay AT, Jacobson J. The relationship between testosterone levels, the metabolic
30 17 syndrome (by two criteria), and insulin resistance in a population of men with organic erectile
31 18 dysfunction. *J Sex Med* 2007; **4**: 1046-55.
32
33
34 19 ³⁴ DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-
35 20 88.
36
37
38 21 ³⁵ Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet* 2007;
39 22 **370**: 685-97.
40
41
42 23 ³⁶ Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the
43 24 estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999; **84**: 3666-72.
44
45
46 25 ³⁷ Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a
47 26 simple, graphical test. *BMJ* 1997; **315**: 629-34.
48
49
50
51 27 ³⁸ Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and
52 28 adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**: 455-63.
53
54
55 29 ³⁹ Katabami T, Kato H, Asahina T, et al. Serum free testosterone and metabolic syndrome in
56 30 Japanese men. *Endocr J* 2010; **57**: 533-9.
57
58
59 31 ⁴⁰ Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA, Members of the Florey
60 32 Adelaide Male Ageing Study. Inverse associations between muscle mass, strength, and the
33 metabolic syndrome. *Metabolism* 2009; **58**: 1013-22.
34
35
36 34 ⁴¹ Coviello AD, Sam S, Legro RS, Dunaif A. High prevalence of metabolic syndrome in first-
35 degree male relatives of women with polycystic ovary syndrome is related to high rates of
36 obesity. *J Clin Endocrinol Metab* 2009; **94**: 4361-6.

- 1
2
3 1 42 Demir O, Akgul K, Akar Z, et al. Association between severity of lower urinary tract
4 2 symptoms, erectile dysfunction and metabolic syndrome. *Aging Male* 2009; **12**: 29-34.
5
6
7 3 43 Haring R, Volzke H, Felix SB, et al. Prediction of metabolic syndrome by low serum
8 4 testosterone levels in men: results from the study of health in Pomerania. *Diabetes* 2009; **58**:
9 5 2027-31.
10
11
12 6 44 Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone
13 7 supplementation on functional mobility, cognition, and other parameters in older men: a
14 8 randomized controlled trial. *JAMA* 2008; **299**: 39-52.
15
16
17 9 45 Goncharov NP, Katsya GV, Chagina NA, Gooren LJ. Three definitions of metabolic
18 10 syndrome applied to a sample of young obese men and their relation with plasma
19 11 testosterone. *Aging Male* 2008; 1-5.
20
21
22 12 46 Suetomi T, Kawai K, Hinotsu S, et al. Negative impact of metabolic syndrome on the
23 13 responsiveness to sildenafil in Japanese men. *J Sex Med* 2008; **5**: 1443-50.
24
25
26 14 47 Yeh HC, Wang CJ, Lee YC, et al. Association among metabolic syndrome, testosterone
27 15 level and severity of erectile dysfunction. *Kaohsiung J Med Sci* 2008; **24**: 240-7.
28
29
30 16 48 Rodriguez A, Muller DC, Metter EJ, et al. Aging, androgens, and the metabolic syndrome
31 17 in a longitudinal study of aging. *J Clin Endocrinol Metab* 2007; **92**: 3568-72.
32
33
34 18 49 Tang YJ, Lee WJ, Chen YT, Liu PH, Lee MC, Sheu WH. Serum testosterone level and
35 19 related metabolic factors in men over 70 years old. *J Endocrinol Invest* 2007; **30**: 451-8.
36
37
38 20 50 Gannage-Yared MH, Khalife S, Semaan M, Fares F, Jambart S, Halaby G. Serum
39 21 adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and
40 22 somatotrophic axis in healthy non-diabetic elderly men. *Eur J Endocrinol* 2006; **155**: 167-76.
41
42
43 23 51 Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly
44 24 exacerbated in obese men with the metabolic syndrome. What are the implications for the
45 25 relatively high incidence of erectile dysfunction observed in these men? *J Urol* 2006; **176**:
46 26 1524,7; discussion 1527-8.
47
48
49 27 52 Maggio M, Lauretani F, Ceda GP, et al. Association between hormones and metabolic
50 28 syndrome in older Italian men. *J Am Geriatr Soc* 2006; **54**: 1832-8.
51
52
53 29 53 Mousavinasab F, Tahtinen T, Jokelainen J, et al. The Pro12Ala polymorphism of the PPAR
54 30 gamma 2 gene influences sex hormone-binding globulin level and its relationship to the
55 31 development of the metabolic syndrome in young Finnish men. *Endocrine* 2006; **30**: 185-90.
56
57
58 32 54 Robeva R, Kirilov G, Tomova A, Kumanov P. Low testosterone levels and unimpaired
59 33 melatonin secretion in young males with metabolic syndrome. *Andrologia* 2006; **38**: 216-20.
60
61
62 34 55 Kalme T, Seppala M, Qiao Q, et al. Sex hormone-binding globulin and insulin-like growth
63 35 factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and
64 36 mortality in elderly men. *J Clin Endocrinol Metab* 2005; **90**: 1550-6.

- 1
2
3 1 ⁵⁶ Nuver J, Smit AJ, Wolffenbuttel BH, et al. The metabolic syndrome and disturbances in
4 hormone levels in long-term survivors of disseminated testicular cancer. *J Clin Oncol* 2005;
5 **23**: 3718-25.
6
7
8 4 ⁵⁷ Alemzadeh R, Kichler J, Calhoun M. Spectrum of metabolic dysfunction in relationship
9 with hyperandrogenemia in obese adolescent girls with polycystic ovary syndrome. *Eur J*
10 *Endocrinol* 2010; **162**: 1093-9.
11
12
13 7 ⁵⁸ Healy LA, Ryan AM, Carroll P, et al. Metabolic syndrome, central obesity and insulin
14 resistance are associated with adverse pathological features in postmenopausal breast cancer.
15 *Clin Oncol (R Coll Radiol)* 2010; **22**: 281-8.
16
17
18 10 ⁵⁹ Ni RM, Mo Y, Chen X, Zhong J, Liu W, Yang D. Low prevalence of the metabolic
19 syndrome but high occurrence of various metabolic disorders in Chinese women with
20 polycystic ovary syndrome. *Eur J Endocrinol* 2009; **161**: 411-8.
21
22
23 13 ⁶⁰ de Sousa G, Brodoswki C, Kleber M, Wunsch R, Reinehr T. Association between
24 androgens, intima-media thickness and the metabolic syndrome in obese adolescent girls.
25 *Clin Endocrinol (Oxf)* 2010; **72**: 770-4.
26
27 16 ⁶¹ Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the
28 metabolic syndrome: the Study of Women's Health Across the Nation. *Arch Intern Med* 2008;
29 **168**: 1568-75.
30
31
32 19 ⁶² Park HR, Choi Y, Lee HJ, Oh JY, Hong YS, Sung YA. The metabolic syndrome in young
33 Korean women with polycystic ovary syndrome. *Diabetes Res Clin Pract* 2007; **77 Suppl 1**:
34 S243-6.
35
36
37 22 ⁶³ Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have
38 an increased risk of the metabolic syndrome associated with increasing androgen levels
39 independent of obesity and insulin resistance. *J Clin Endocrinol Metab* 2006; **91**: 492-7.
40
41
42 25 ⁶⁴ Pasanisi P, Berrino F, De Petris M, Venturelli E, Mastroianni A, Panico S. Metabolic
43 syndrome as a prognostic factor for breast cancer recurrences. *Int J Cancer* 2006; **119**: 236-8.
44
45
46 27 ⁶⁵ Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the
47 metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*
48 2005; **90**: 1929-35.
49
50
51 30 ⁶⁶ Dokras A, Bochner M, Hollinrake E, Markham S, Vanvoorhis B, Jagasia DH. Screening
52 women with polycystic ovary syndrome for metabolic syndrome. *Obstet Gynecol* 2005; **106**:
53 131-7.
54
55
56 33 ⁶⁷ Golden SH, Ding J, Szklo M, Schmidt MI, Duncan BB, Dobs A. Glucose and insulin
57 components of the metabolic syndrome are associated with hyperandrogenism in
58 postmenopausal women: the atherosclerosis risk in communities study. *Am J Epidemiol* 2004;
59 **160**: 540-8.
60

- 1
2
3 1 ⁶⁸ Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-
4 2 binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes Care*
5 3 2010; **33**: 1618-24.
6
7
8 4 ⁶⁹ Kupelian V, Hayes FJ, Link CL, Rosen R, McKinlay JB. Inverse association of testosterone
9 5 and the metabolic syndrome in men is consistent across race and ethnic groups. *J Clin*
10 6 *Endocrinol Metab* 2008; **93**: 3403-10.
11
12 7 ⁷⁰ Patel SM, Ratcliffe SJ, Reilly MP, et al. Higher serum testosterone concentration in older
13 8 women is associated with insulin resistance, metabolic syndrome, and cardiovascular disease.
14 9 *J Clin Endocrinol Metab* 2009; **94**: 4776-84.
15
16
17 10 ⁷¹ Chen MJ, Yang WS, Yang JH, Hsiao CK, Yang YS, Ho HN. Low sex hormone-binding
18 11 globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome
19 12 in women with PCOS. *Hum Reprod* 2006; **21**: 2266-71.
20
21
22 13 ⁷² Santoro N, Torrens J, Crawford S, et al. Correlates of circulating androgens in mid-life
23 14 women: the study of women's health across the nation. *J Clin Endocrinol Metab* 2005; **90**:
24 15 4836-45.
25
26
27 16 ⁷³ Zawadzki J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a
28 17 rational approach. In: Dunaif A, Givens J, Haseltine F, Merriam G, editors. Polycystic ovary
29 18 syndrome.: Boston Blackwell Scientific; 1992. p. 377-384.
30
31
32 19 ⁷⁴ Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003
33 20 consensus on diagnostic criteria and long-term health risks related to polycystic ovary
34 21 syndrome. *Fertil Steril* 2004; **81**: 19-25.
35
36
37 22 ⁷⁵ Balkau B, Charles MA. Comment on the provisional report from the WHO consultation.
38 23 European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999; **16**: 442-3.
39
40
41 24 ⁷⁶ Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic
42 25 syndrome phenotype in adolescents: Findings from the Third National Health and Nutrition
43 26 Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003; **157**: 821-7.
44
45
46 27 ⁷⁷ Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and
47 28 adolescents. *N Engl J Med* 2004; **350**: 2362-74.
48
49
50 29 ⁷⁸ Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and
51 30 adolescents - an IDF consensus report. *Pediatr Diabetes* 2007; **8**: 299-306.
52
53
54 31 ⁷⁹ Nanjee MN, Wheeler MJ. Plasma free testosterone--is an index sufficient? *Ann Clin*
55 32 *Biochem* 1985; **22 (Pt 4)**: 387-90.
56
57
58 33 ⁸⁰ Anderson DC. Sex-hormone-binding globulin. *Clin Endocrinol (Oxf)* 1974; **3**: 69-96.
59
60
61 34 ⁸¹ de Ronde W, van der Schouw YT, Pols HA, et al. Calculation of bioavailable and free
62 35 testosterone in men: a comparison of 5 published algorithms. *Clin Chem* 2006; **52**: 1777-84.

- 1
2
3 1 ⁸² Ho CK, Stoddart M, Walton M, Anderson RA, Beckett GJ. Calculated free testosterone in
4 2 men: comparison of four equations and with free androgen index. *Ann Clin Biochem* 2006;
5 3 **43**: 389-97.
6
7
8 4 ⁸³ Grillo ML, Jacobus AP, Scalco R, et al. Testosterone rapidly stimulates insulin release
9 5 from isolated pancreatic islets through a non-genomic dependent mechanism. *Horm Metab*
10 6 *Res* 2005; **37**: 662-5.
11
12 7 ⁸⁴ Xu XF, De Pergola G, Bjorntorp P. Testosterone increases lipolysis and the number of
13 8 beta-adrenoceptors in male rat adipocytes. *Endocrinology* 1991; **128**: 379-82.
14
15 9 ⁸⁵ Singh R, Artaza JN, Taylor WE, et al. Testosterone inhibits adipogenic differentiation in
16 10 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-
17 11 cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription
18 12 factors. *Endocrinology* 2006; **147**: 141-54.
19
20 13 ⁸⁶ Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in
21 14 subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens. *J*
22 15 *Clin Endocrinol Metab* 1995; **80**: 239-43.
23
24 16 ⁸⁷ Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves
25 17 insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in
26 18 hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 2006; **154**: 899-906.
27
28 19 ⁸⁸ Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2
29 20 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003; **6**: 1-7.
30
31 21 ⁸⁹ Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and
32 22 exercise plus transdermal testosterone reverses the metabolic syndrome and improves
33 23 glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma
34 24 testosterone. *J Androl* 2009; **30**: 726-33.
35
36 25 ⁹⁰ Haider A, Gooren LJ, Padungtod P, Saad F. Improvement of the metabolic syndrome and
37 26 of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral
38 27 testosterone undecanoate. *Exp Clin Endocrinol Diabetes* 2010; **118**: 167-71.
39
40 28 ⁹¹ Kaukua J, Pekkarinen T, Sane T, Mustajoki P. Sex hormones and sexual function in obese
41 29 men losing weight. *Obes Res* 2003; **11**: 689-94.
42
43 30 ⁹² Niskanen L, Laaksonen DE, Punnonen K, Mustajoki P, Kaukua J, Rissanen A. Changes in
44 31 sex hormone-binding globulin and testosterone during weight loss and weight maintenance in
45 32 abdominally obese men with the metabolic syndrome. *Diabetes Obes Metab* 2004; **6**: 208-15.
46
47 33 ⁹³ Pitteloud N, Hardin M, Dwyer AA, et al. Increasing insulin resistance is associated with a
48 34 decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab* 2005; **90**:
49 35 2636-41.
50
51 36 ⁹⁴ Isidori AM, Caprio M, Strollo F, et al. Leptin and androgens in male obesity: evidence for
52 37 leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab* 1999; **84**: 3673-80.
53
54
55
56
57
58
59
60

- 1
2
3 1 ⁹⁵ Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone
4 (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in
5 hypogonadism of obese men. *J Clin Endocrinol Metab* 1993; **76**: 1140-6.
6
7
8 4 ⁹⁶ Laaksonen DE, Niskanen L, Punnonen K, et al. The metabolic syndrome and smoking in
9 relation to hypogonadism in middle-aged men: a prospective cohort study. *J Clin Endocrinol*
10 *Metab* 2005; **90**: 712-9.
11
12
13 7 ⁹⁷ Torrens JI, Sutton-Tyrrell K, Zhao X, et al. Relative androgen excess during the
14 menopausal transition predicts incident metabolic syndrome in midlife women: study of
15 Women's Health Across the Nation. *Menopause* 2009; **16**: 257-64.
16
17
18 10 ⁹⁸ Ding EL, Song Y, Manson JE, et al. Sex hormone-binding globulin and risk of type 2
19 diabetes in women and men. *N Engl J Med* 2009; **361**: 1152-63.
20
21
22 12 ⁹⁹ Holmang A, Larsson BM, Brzezinska Z, Bjorntorp P. Effects of short-term testosterone
23 exposure on insulin sensitivity of muscles in female rats. *Am J Physiol* 1992; **262**: E851-5.
24
25 14 ¹⁰⁰ Cho L, Kilpatrick E, Keevil B, Coady A, Atkin S. Effect of metformin, orlistat and
26 pioglitazone treatment on mean insulin resistance and its biological variability in polycystic
27 ovary syndrome. *Clin Endocrinol (Oxf)* 2008;.
28
29
30 17 ¹⁰¹ Crave JC, Fimbel S, Lejeune H, Cugnardey N, Dechaud H, Pugeat M. Effects of diet and
31 metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute
32 and obese women. *J Clin Endocrinol Metab* 1995; **80**: 2057-62.
33
34 20 ¹⁰² Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin stimulates
35 androgen accumulation in incubations of ovarian stroma obtained from women with
36 hyperandrogenism. *J Clin Endocrinol Metab* 1986; **62**: 904-10.
37
38
39 23 ¹⁰³ Vikan T, Schirmer H, Njolstad I, Svartberg J. Low testosterone and sex hormone-binding
40 globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men.
41 *Eur J Endocrinol* 2010; **162**: 747-54.
42
43
44 26 ¹⁰⁴ Lakshman KM, Bhasin S, Araujo AB. Sex hormone-binding globulin as an independent
45 predictor of incident type 2 diabetes mellitus in men. *J Gerontol A Biol Sci Med Sci* 2010; **65**:
46 503-9.
47
48
49 29 ¹⁰⁵ Perry JR, Weedon MN, Langenberg C, et al. Genetic evidence that raised sex hormone
50 binding globulin (SHBG) levels reduce the risk of type 2 diabetes. *Hum Mol Genet* 2010; **19**:
51 535-44.
52
53
54 32 ¹⁰⁶ Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk
55 of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; **295**: 1288-99.
56
57 34 ¹⁰⁷ Holmang A, Bjorntorp P. The effects of testosterone on insulin sensitivity in male rats.
58 *Acta Physiol Scand* 1992; **146**: 505-10.
59
60

- 1
2
3 1 ¹⁰⁸ Haug A, Hostmark AT, Spydevold O, Eilertsen E. Hypercholesterolaemia,
4 2 hypotriacylglycerolaemia and increased lipoprotein lipase activity following orchidectomy in
5 3 rats. *Acta Endocrinol (Copenh)* 1986; **113**: 133-9.
- 6
7
8 4 ¹⁰⁹ Alexanderson C, Eriksson E, Stener-Victorin E, et al. Postnatal testosterone exposure
9 5 results in insulin resistance, enlarged mesenteric adipocytes, and an atherogenic lipid profile
10 6 in adult female rats: comparisons with estradiol and dihydrotestosterone. *Endocrinology*
11 7 2007; **148**: 5369-76.
- 12
13
14 8 ¹¹⁰ Demissie M, Lazic M, Foecking EM, Aird F, Dunaif A, Levine JE. Transient Prenatal
15 9 Androgen Exposure Produces Metabolic Syndrome in Adult Female Rats. *Am J Physiol*
16 10 *Endocrinol Metab* 2008;.
- 17
18
19 11 ¹¹¹ Nilsson C, Niklasson M, Eriksson E, Bjorntorp P, Holmang A. Imprinting of female
20 12 offspring with testosterone results in insulin resistance and changes in body fat distribution at
21 13 adult age in rats. *J Clin Invest* 1998; **101**: 74-8.
- 22
23
24 14 ¹¹² Dunning AM, Dowsett M, Healey CS, et al. Polymorphisms associated with circulating
25 15 sex hormone levels in postmenopausal women. *J Natl Cancer Inst* 2004; **96**: 936-45.
- 26
27 16 ¹¹³ Ahn J, Schumacher FR, Berndt SI, et al. Quantitative trait loci predicting circulating sex
28 17 steroid hormones in men from the NCI-Breast and Prostate Cancer Cohort Consortium
29 18 (BPC3). *Hum Mol Genet* 2009; **18**: 3749-57.
- 30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Nr.	Source	Country	Study design	Participants	Mean age	Mean BMI	Adjusted for age	MetS No.		Mean (SD), nmol/L				Mean (SD), pmol/L	
								Yes	No	Total Testosterone		SHBG		Free Testosterone	
										MetS ⁺	MetS ⁻	MetS ⁺	MetS ⁻	MetS ⁺	MetS ⁻
1	Katabami et al, 2010 ³⁹	Japan	CS	Nondiabetic men	46	23.7	No	70	204	-	-	-	-	40.6 (13.9) ^c	51.01 (16.0) ^c
2	de Oya et al, 2010 ^{28 d}	Spain	CS	Adolescent boys	14	21.9	No	13	377	-	-	28.8 (15.2)	51.0 (34.6)	-	-
3	Atlantis et al, 2009 ⁴⁰	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	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	U.S.A.	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	U.S.A.	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 ^a	27.4 ^a	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	Nondiabetic men from the Health in Men Study	76 ^a	26.2 ^a	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	Netherlands	CS	Nondiabetic 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	Russia	CS	Nondiabetic 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	Russia	CS	Nondiabetic 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	Russia	CS	Nondiabetic 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	U.S.A.	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 ^a	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 ^a	No	38	65	12.4 (5.8)	16.2 (5.9)	-	-	-	-
13	Corona et al, 2007 ¹⁷	Italy	CS	Male patients with sexual dysfunction	52	-	No	348	738	13.6 (6.0)	17.4 (7.2)	-	-	34.8 (14.0) ^c	40.8 (13.7) ^c
	Corona et al, 2007 ¹⁷	Italy	CS	Male patients with sexual dysfunction	52	-	No	485	601	14.7 (7.4)	18.2 (6.0)	-	-	36.2 (14.1) ^c	42.5 (13.5) ^c
14	Guay et al, 2007 ³³	U.S.A.	CS	Men with erectile dysfunction	54	29.4	No	88	66	-	-	-	-	42.7 (18.4) ^c	49.3 (22.9) ^c
	Guay et al, 2007 ³³	U.S.A.	CS	Men with erectile dysfunction	54	29.4	No	54	100	-	-	-	-	39.6 (10.4) ^c	51.4 (22.9) ^c
15	Rodriguez et al, 2007 ⁴⁸	U.S.A.	CS ^e	Caucasian men from the Baltimore Longitudinal Study of Aging	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	Nondiabetic men from the Australian Longitudinal Study of Aging	76	26.0	No	20	140	12.1 (3.6)	14.2 (4.7)	-	-	-	-
18	Gannagé-Yared et al, 2006 ⁵⁰	Lebanon	CS	Nondiabetic 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	U.S.A.	CS	Men with dyslipidemia	52	27.4	No	265	597	14.0 (4.7)	16.1 (4.9)	-	-	-	-
20	Kupelian et al, 2006 ¹⁸	U.S.A.	CS ^e	Men from the Massachusetts Male Aging Study	53 ^a	27.1 ^a	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 ^a	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)

Table 1A Continued

Nr.	Source	Country	Study design	Participants	Mean age	Mean BMI	Adjusted for age	No.		Mean (SD), nmol/L				Mean (SD), pmol/L Free Testosterone	
								MetS ⁺	MetS ⁻	Total Testosterone		SHBG		MetS ⁺	MetS ⁻
22	Mousavinasab et al, 2006 ⁵³	Finland	LO	Military service men on a high-caloric high-fat diet	17-28	24.3 ^a	No	11	169	-	-	15.1 (6.6)	19.1 (10.2)	-	-
23	Robeva et al, 2006 ⁵⁴	Bulgaria	CC	Nondiabetic, 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	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	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) ^d	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) ^d	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	Nondiabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	53 ^b	26.8 ^b	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)

BMI, body mass index; CC, case-control; CS, cross-sectional; LO, longitudinal; MetS, metabolic syndrome; MetS⁺, subjects with the metabolic syndrome; MetS⁻, subjects without the metabolic syndrome; No., number; SHBG, sex hormone-binding globulin; -, not applicable.

^a mean age/BMI of study sample based on weighted means of age/BMI of subjects with and without MetS.

^b studies using multiple criteria to define the metabolic syndrome (Atlantis et al, 2009: (1) NCEP ATP III, (2) IDF; Goncharov et al, 2008: (1) NCEP ATP III, (2) WHO, (3) IDF; Corona et al, 2007: (1) NCEP ATP III, (2) IDF; Guay et al, 2007: (1) NCEP ATP III modified, (2) WHO).

^c free testosterone measured by radioimmunoassay.

^d mean differences reported for two separate populations (1) and (2).

^e longitudinal study providing data on hormonal levels in subjects with and without MetS at baseline.

SI conversion factors: to convert testosterone (total testosterone/free testosterone) to ng/dL divide by 0.0347. To convert SHBG to µg/mL divide by 8.896.

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

Nr.	Source	Country	Study design	Participants	Mean age	Mean BMI	Adjusted for age	Mean (SD), nmol/L						Mean (SD), pmol/L	
								No.		Total Testosterone		SHBG		Free Testosterone	
								MetS ⁺	MetS ⁻	MetS ⁺	MetS ⁻	MetS ⁺	MetS ⁻	MetS ⁺	MetS ⁻
1	Alemzadeh et al, 2010 ⁵⁷	U.S.A.	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 ^{28c}	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	U.S.A.	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	U.S.A.	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	U.S.A.	CS	Nondiabetic PCOS women who participated in a large multicenter 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	U.S.A.	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	U.S.A.	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	U.S.A.	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	U.S.A.	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}	U.S.A.	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)	-	-	-	-
17	Golden et al, 2004 ^{67(2)c}	U.S.A.	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; BMI, body mass index; CS, cross-sectional; LO, longitudinal; MetS, metabolic syndrome; MetS⁺, subjects with the metabolic syndrome; MetS⁻, subjects without the metabolic syndrome; No., number; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; SWAN, Study of Women's Health Across the Nation; -, not applicable.

^a mean age/BMI of study sample based on weighted means of age/BMI of subjects with and without MetS;

^b free testosterone measured by radioimmunoassay.

^c mean differences reported for two separate populations (1) and (2).

Table 2A Characteristics of studies presenting relative risk estimates for MetS according to TT, SHBG and/or FT levels, men

Nr.	Source	Country	Study design	Mean follow-up	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	-	Nondiabetic men	194	Age	OR 0.26 (0.11 - 0.59)	-	-
2	Li et al, 2010 ⁶⁸	U.S.A	CS	-	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	5.0 yr	Men from the Study of Health in Pomerania (SHIP) study	1004	-	RR 0.70 (0.59 - 0.83)	-	-
4	Schneider et al, 2009 ²⁶	Germany	CS	-	Men from the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential DATA for Commitment of Treatment (DETECT)	2719	-	OR 0.26 (0.21 - 0.32)	-	-
5	Chubb et al, 2008 ^{10 b}	Australia	CS	-	Nondiabetic men from the Health in Men study	2052	-	OR 0.28 (0.22 - 0.36)	OR 0.21 (0.16 - 0.28)	-
6	Emmelot-Vonk et al, 2008 ^{44 b}	Netherlands	CS	-	Nondiabetic 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	U.S.A.	CS	-	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}	U.S.A.	LO	5.8 yr	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}	U.S.A.	LO	14.4 yr	Men from the Massachusetts Male Aging Study	950	-	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}	Netherlands	CS	-	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	-	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	11.0 yr	Nondiabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	702	Age, BMI, smoking, alcohol consumption, presence of CVD, socioeconomic 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	-	Nondiabetic men from the Kuopio Ischaemic Heart Disease Risk Factor Study	1896	Age, BMI, smoking, alcohol consumption, presence of CVD, socioeconomic status	OR 0.52 (0.36 - 0.75)	OR 0.54 (0.37 - 0.77)	OR 0.58 (0.41 - 0.83)

BMI, body mass index; CI, confidence interval; CS, cross-sectional; CVD, cardiovascular disease; CRP, C-reactive protein; FT, free testosterone; HR, hazard ratio; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; LO, longitudinal; MetS, metabolic syndrome; OR, odds ratio; PR, prevalence ratio; RR, relative risk; SHBG, sex hormone-binding globulin; TT, total testosterone; yr, year; -, not applicable.

^a relative risk estimates of MetS comparing highest versus lowest tertiles of TT, SHBG and FT.

^b studies reporting both measures of association (relative risk estimates and mean differences).

Table 2B Characteristics of studies presenting relative risk estimates for MetS according to TT and/or SHBG levels, women

Nr.	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	U.S.A.	CS	Nondiabetic 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	-	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}	U.S.A.	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	U.S.A.	CS	Nondiabetic 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)	-

BMI, body mass index; CI, confidence interval; CS, cross-sectional; CVD, cardiovascular disease; FT, free testosterone; MetS, metabolic syndrome; OR, odds ratio; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; SWAN, Study of Women's Health Across the Nation; TT, total testosterone; -, not applicable.

^a relative risk estimates of MetS comparing highest versus lowest tertiles of TT, SHBG and FT.

^b studies reporting both measures of association (relative risk estimates and mean differences).

Table 3 Mean differences of TT, SHBG and FT between subjects with and without the MetS, men and women.

	Studies No.	Men TT mean difference (95% CI) (nmol/L)	I ²	Studies No.	Women TT mean difference (95% CI) (nmol/L)	I ²
Overall random effects	26	-2.64 (-2.95, -2.32)	89.1 % (p< 0.001)	15	0.14 (0.07, 0.20)	28.5 % (p = 0.14)
Age						
- Age < 55 years	12	-3.03 (-3.60, -2.45)	65.7% (p < 0.001)	9	0.10 (0.00, 0.21)	42.6% (p = 0.08)
- Age ≥ 55 years	14	-2.38 (-2.78, -1.99)	92.6% (p< 0.001)	6	0.19 (0.10, 0.25)	0.0% (p = 0.55)
BMI						
- BMI < 25 kg/m ²	4	-2.77 (-3.45, -2.08)	20.7% (p = 0.29)	2	-0.10 (-0.26, 0.07)	0.0% (p = 0.89)
- BMI ≥ 25 kg/m ²	19	-2.42 (-2.78, -2.06)	73.7% (p < 0.001)	11	0.16 (0.11, 0.22)	0.0% (p = 0.47)
PCOS status (women)						
- PCOS (women)	-	-	-	6	0.03 (-0.13, 0.18)	28.2% (p = 0.22)
- no PCOS (women)	-	-	-	9	0.17 (0.12, 0.23)	0.0 % (p = 0.66)
MetS criteria †						
- NCEP ATP III	16	-2.43 (-2.79, -2.08)		12	0.16 (0.10, 0.22)	
- Other (WHO, IDF, EGIR)	8	-3.90 (-4.83, -2.96)		0	-	
Control for age						
- adjusted for age	6	-2.87 (-3.68, -2.05)	79.5% (p < 0.001)	2	0.18 (0.05, 0.31)	36.3% (p = 0.21)
- not adjusted for age	20	-2.62 (-3.00, -2.23)	76.0% (p < 0.001)	13	0.13 (0.05, 0.20)	30.2% (p = 0.14)
Type 2 diabetes excluded						
- yes	7	-2.84 (-4.02, -1.66)	87.9% (p < 0.001)	2	0.10 (-0.09, 0.29)	54.8% (p = 0.14)
- no	19	-2.67 (-3.01, -2.32)	89.9% (p < 0.001)	13	0.15 (0.07, 0.22)	30.9% (p = 0.14)
Study design						
- cross-sectional	24	-2.64 (-2.97, -2.32)	89.7% (p< 0.001)	14	0.14 (0.07, 0.21)	32.7% (p = 0.11)
- case-control	1	-9.43 (-14.59, -4.27)	-	1	0.10 (-0.07, 0.27)	-
- longitudinal	1	-2.20 (-2.82, -1.58)	-	-	-	-
	Studies No.	SHBG mean difference (95% CI) (nmol/L)	I ²	Studies No.	SHBG mean difference (95% CI) (nmol/L)	I ²
Overall random effects	19	-9.77 (-12.26, -7.29)	97.6% (p< 0.001)	15	-19.39 (-23.81, -14.98)	85.5% (p<0.001)
Age						
- Age < 55 years	10	-6.69 (-8.20, -5.19)	48.9% (p = 0.04)	11	-18.73 (-23.73, -13.73)	87.3% (p<0.001)
- Age ≥ 55 years	9	-12.00 (-15.13, -8.87)	98.2% (p< 0.001)	4	-21.42 (-31.76, -11.09)	76.5% (p = 0.01)
BMI						
- BMI < 25 kg/m ²	4	-10.36 (-17.50, 3.23)	93.7% (p<0.001)	3	-31.46 (-38.05, -24.86)	42.7% (p = 0.17)
- BMI ≥ 25 kg/m ²	13	-9.52 (-13.96, -5.08)	98.0% (p<0.001)	11	-16.07 (-20.64, -11.51)	83.2% (p < 0.001)
PCOS status (women)						
- PCOS (women)	-	-	-	7	-18.57 (-26.33, -10.82)	88.0% (p<0.001)
- no PCOS (women)	-	-	-	8	-20.41 (-26.15, -14.67)	83.9% (p < 0.001)
MetS criteria †						
- NCEP ATP III	10	-10.55 (-13.57, -7.53)		11	-17.94 (-23.01, -12.88)	
- Other (WHO, IDF, EGIR)	7	-7.17 (-10.25, -4.09)		0	-	
Control for age						
- adjusted for age	4	-12.19 (-21.34, -3.05)	97.1% (p<0.001)	2	-19.63 (-27.16, -12.11)	56.3% (p = 0.13)
- not adjusted for age	15	-9.02 (-11.70, -6.33)	95.2% (p<0.001)	13	-19.48 (-24.45, -14.51)	87.0% (p<0.001)
Type 2 diabetes excluded						
- yes	6	-7.04 (-8.59, -5.49)	46.7% (p = 0.10)	2	-10.97 (-13.65, -8.28)	0.0% (p = 0.98)
- no	13	-11.03 (-13.89, -8.17)	97.7% (p<0.001)	13	-21.19 (-26.32, -16.06)	83.6% (p<0.001)
Study design						
- cross-sectional	18	-10.11 (-12.65, -7.57)		14	-19.75 (-24.45, -15.05)	86.6% (p < 0.001)
- case-control	-	-	97.7% (p<0.001)	-	-	-
- longitudinal	1	-4.04 (-8.23, 0.15)	-	1	-15.50 (-23.12, -7.88)	-

Table 3 Continued

	Studies No.	FT standardized mean difference (95% CI) (pmol/L)	I ²	Studies No.	FT standardized mean difference (95% CI) (pmol/L)	I ²
Overall random effects	13	-0.26 (-0.39; -0.13)	79.9% (p<0.001)	9	0.52 (0.33, 0.71)	61.1% (p=0.01)
Age						
- Age < 55 years	7	-0.41 (-0.51, -0.31)	32.9% (p = 0.18)	9	0.52 (0.33, 0.71)	61.1% (p = 0.01)
- Age ≥ 55 years	6	-0.09 (-0.29, 0.11)	79.3% (p<0.001)	0	-	
BMI						
- BMI < 25	3	-0.35 (-0.71, 0.02)	77.2% (p = 0.01)	2	0.71 (0.27, 1.15)	59.8% (p = 0.12)
- BMI ≥ 25 kg/m ²	9	-0.20 (-0.36, -0.04)	81.5% (p<0.001)	6	0.54 (0.33, 0.76)	51.2% (p = 0.07)
PCOS status (women)						
- PCOS (women)	-	-		7	0.49 (0.26, 0.73)	66.7% (p = 0.01)
- no PCOS (women)	-	-		2	0.64 (0.40, 0.88)	0% (p = 0.71)
MetS criteria †						
- NCEP ATP III	10	-0.19 (-0.34, -0.05)		6	0.50 (0.21, 0.79)	
- Other (WHO, IDF)	5	-0.47 (-0.55, -0.39)		0	-	
Control for age						
- adjusted for age	0	-		1	0.59 (0.26, 0.92)	
- not adjusted for age	13	-0.26 (-0.39, -0.13)	79.9% (p< 0.001)	8	0.52 (0.31, 0.73)	64.9% (p = 0.01)
Type 2 diabetes excluded						
- yes	5	-0.29 (-0.53, 0.05)	87.8% (p<0.001)	3	0.50 (0.08, 0.91)	
- no	8	-0.23 (-0.40, -0.07)	74.1% (p<0.001)	2	0.31 (-0.26, 0.87)	
Study design						
- cross-sectional	13	-0.26 (-0.39; -0.13)	79.9% (p<0.001)	8	0.52 (0.31, 0.73)	64.9% (p = 0.01)
- case-control	0	-		1	0.59 (0.26, 0.92)	
- longitudinal	0	-		0	-	
Method of FT assessment						
- Direct measurement	3	-0.47 (-0.64, -0.30)	38.0% (p < 0.20)	6	0.57 (0.34, 0.80)	59.9% (p = 0.03)
- Algorithms	9	-0.18 (-0.34, -0.03)	81.7% (p< 0.001)	3	0.44 (-0.04, 0.84)	75.1% (p = 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; -, not applicable.

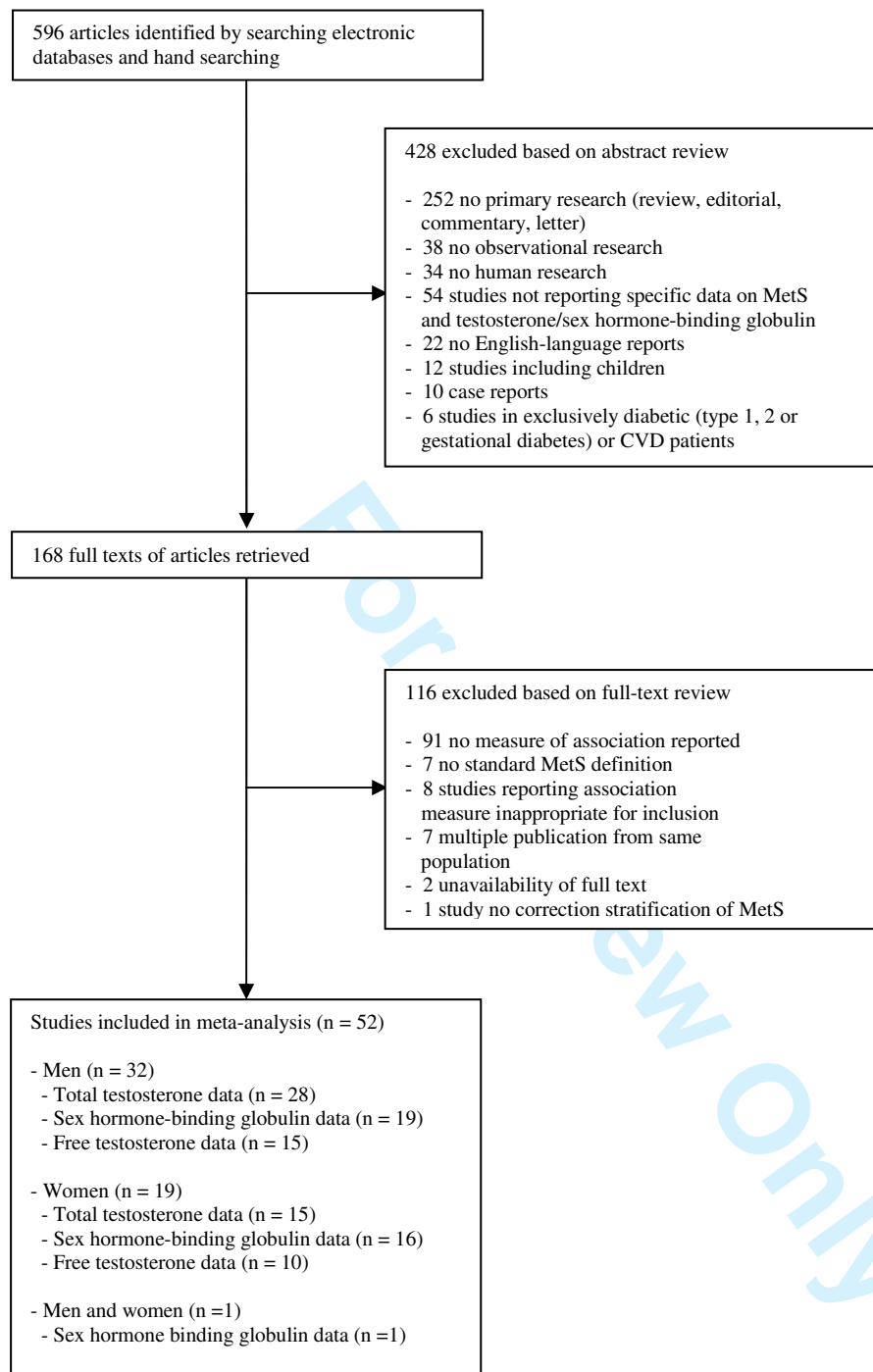


Figure 1 Flow diagram outlining the study selection process. MetS, metabolic syndrome; CVD, cardiovascular disease.

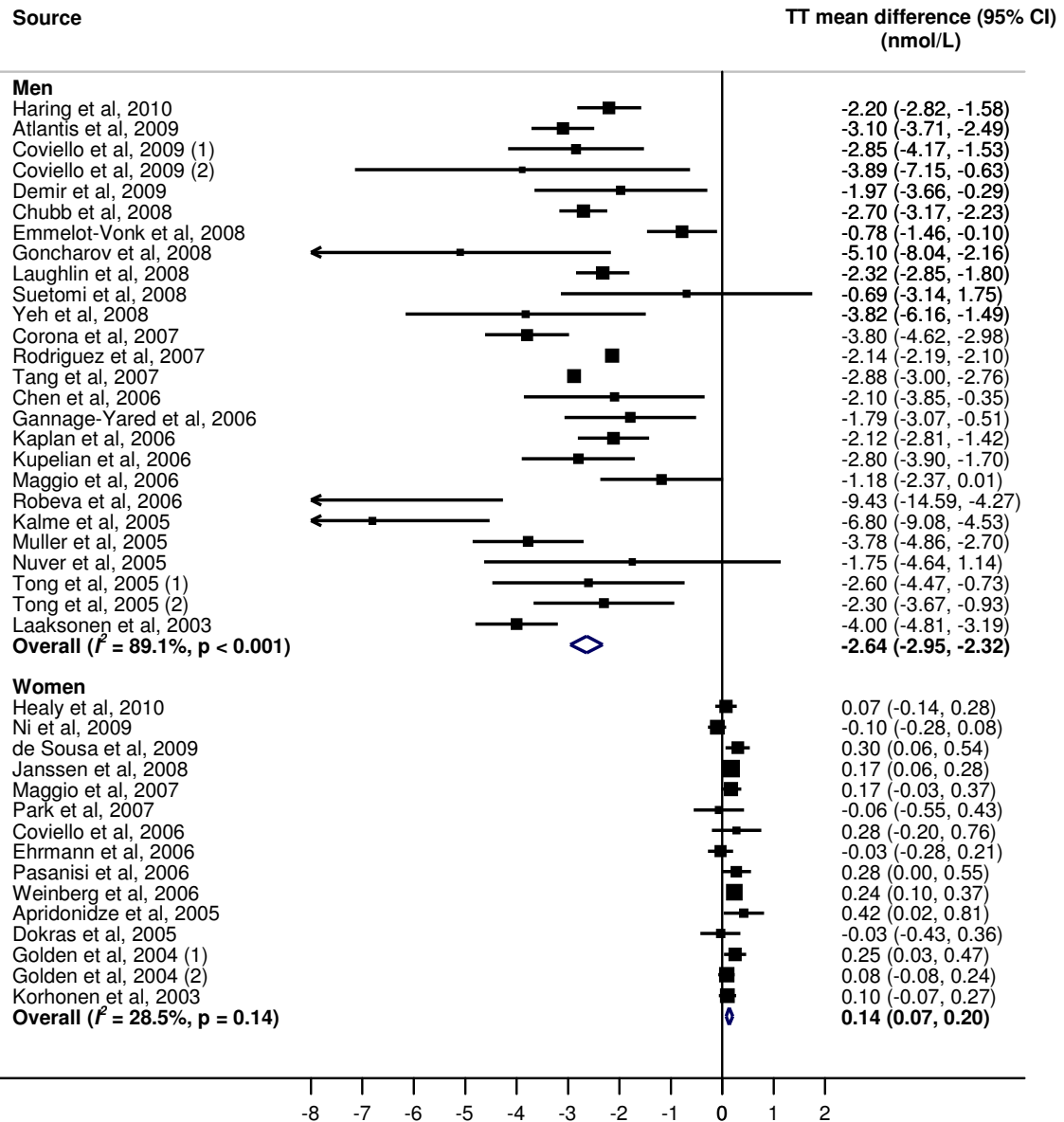


Figure 2A Random effects pooled mean difference of TT levels between subjects with and without MetS, men and women. CI, confidence interval; MetS, metabolic syndrome; TT, total testosterone. Negative values indicate lower TT levels in subjects with MetS; positive values indicate higher TT levels in subjects with MetS. Sizes of squares represent the weight of each study.

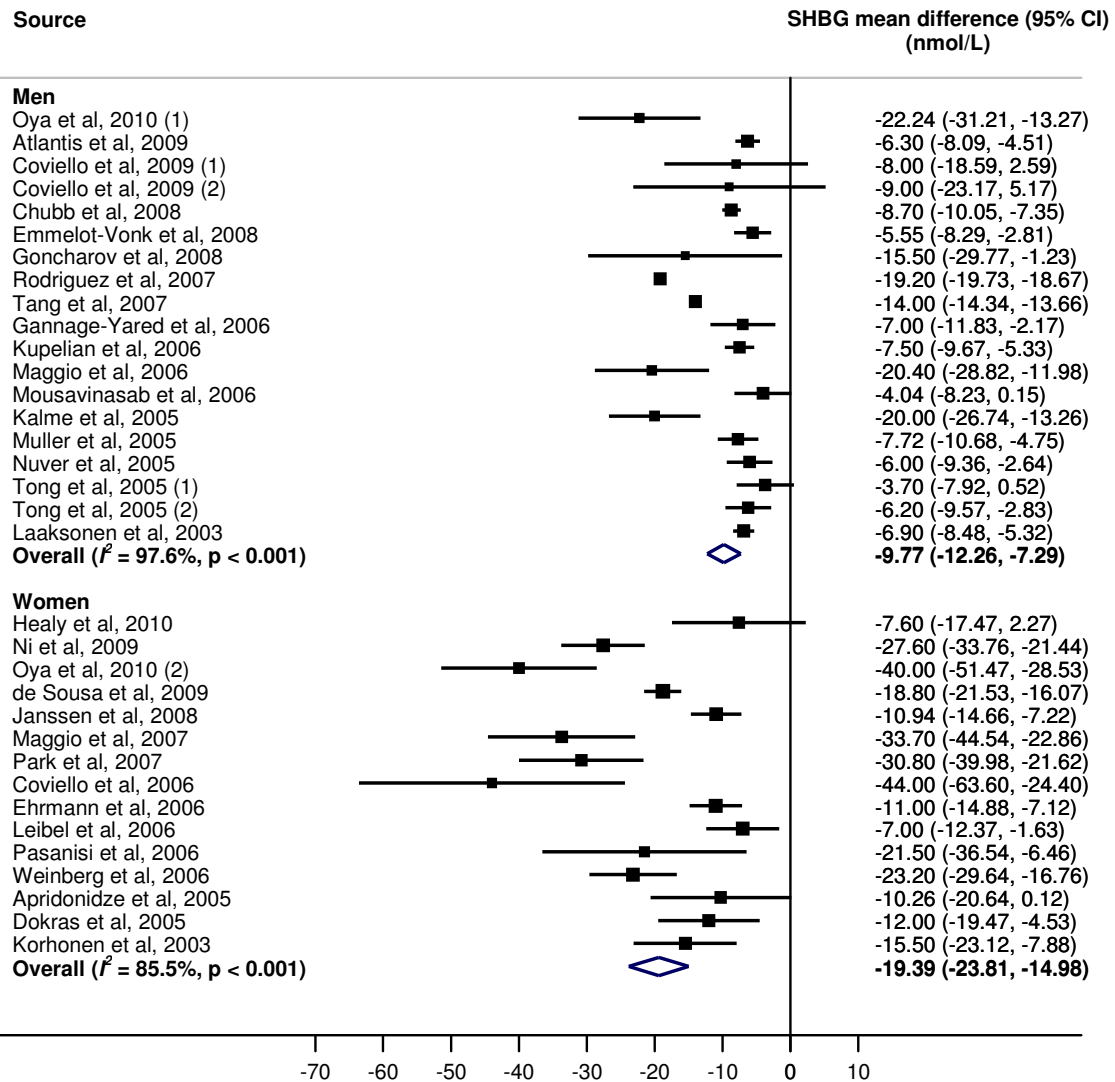


Figure 2B Random effects pooled mean difference of SHBG levels between subjects with and without MetS, men and women. CI, confidence interval; MetS, metabolic syndrome; SHBG, sex hormone-binding globulin. Negative values indicate lower SHBG levels in subjects with MetS; positive values indicate higher SHBG levels in subjects with MetS. Sizes of squares represent the weight of each study.

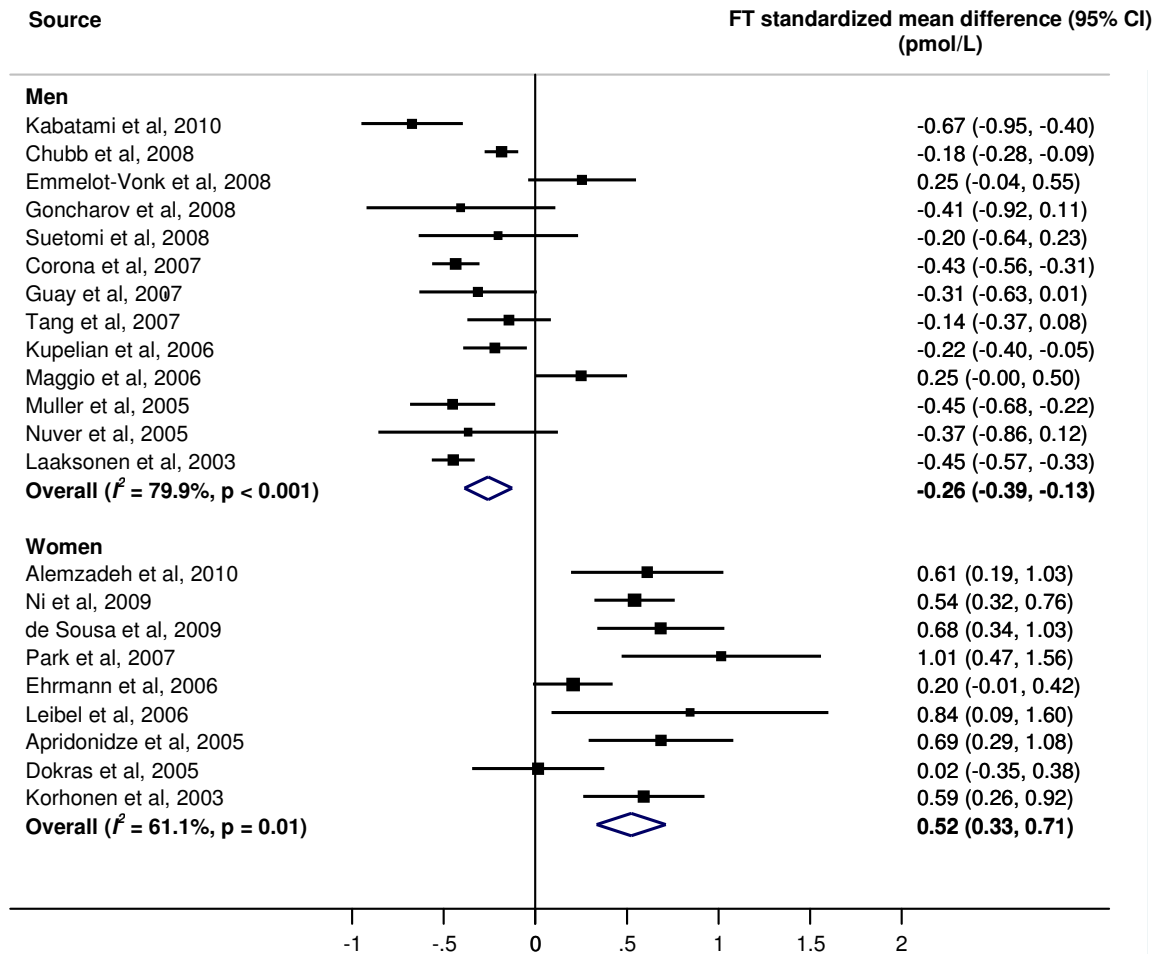


Figure 2C Random effects pooled mean difference of FT levels between subjects with and without MetS, men and women. CI, confidence interval; MetS, metabolic syndrome; FT, free testosterone. Negative values indicate lower FT levels in subjects with MetS; positive values indicate higher FT levels in subjects with MetS. Sizes of squares represent the weight of each study.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

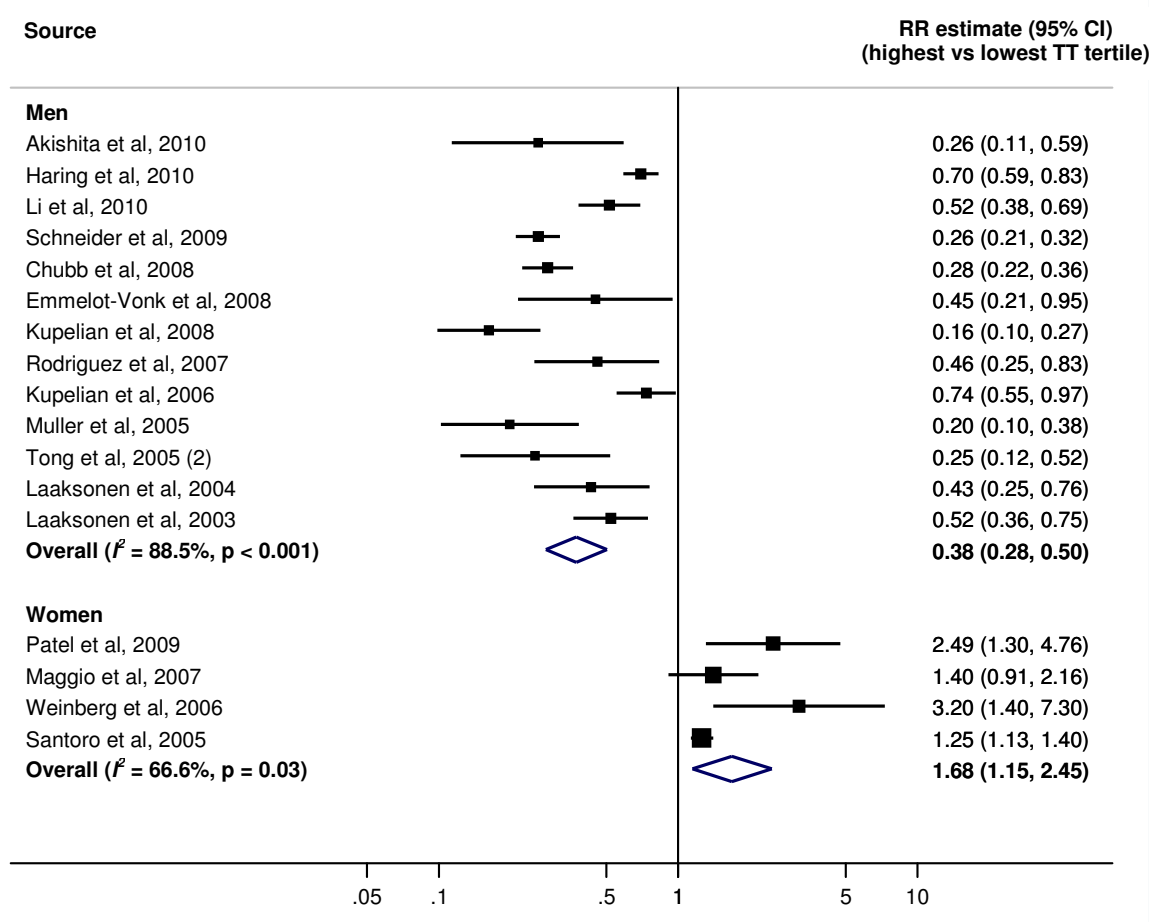


Figure 3A Random effects pooled relative risk estimate for MetS comparing highest versus lowest TT tertile, men and women. CI, confidence interval; MetS, metabolic syndrome; TT, total testosterone. Sizes of squares represent the weight of each study.

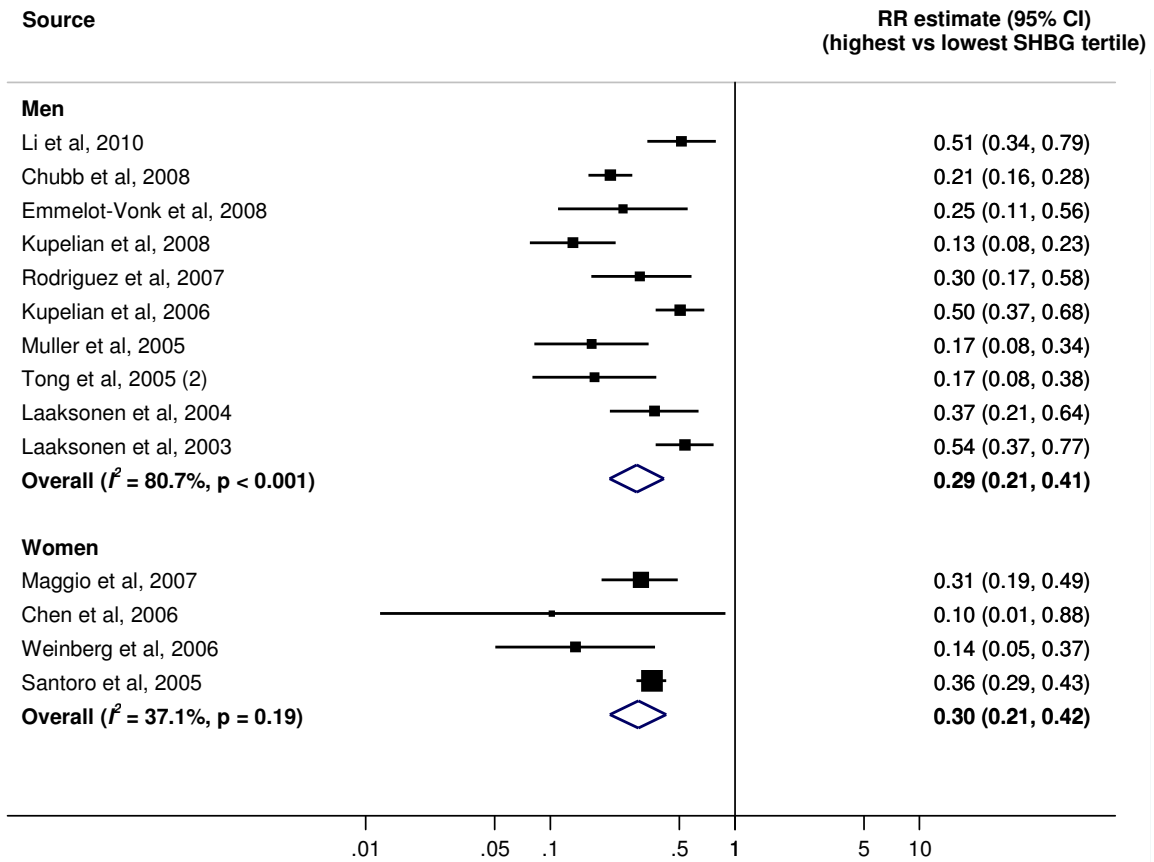


Figure 3B Random effects pooled relative risk estimate for MetS comparing highest versus lowest tertile of SHBG, men and women. CI, confidence interval; MetS, metabolic syndrome; SHBG, sex hormone-binding globulin. Sizes of squares represent the weight of each study.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

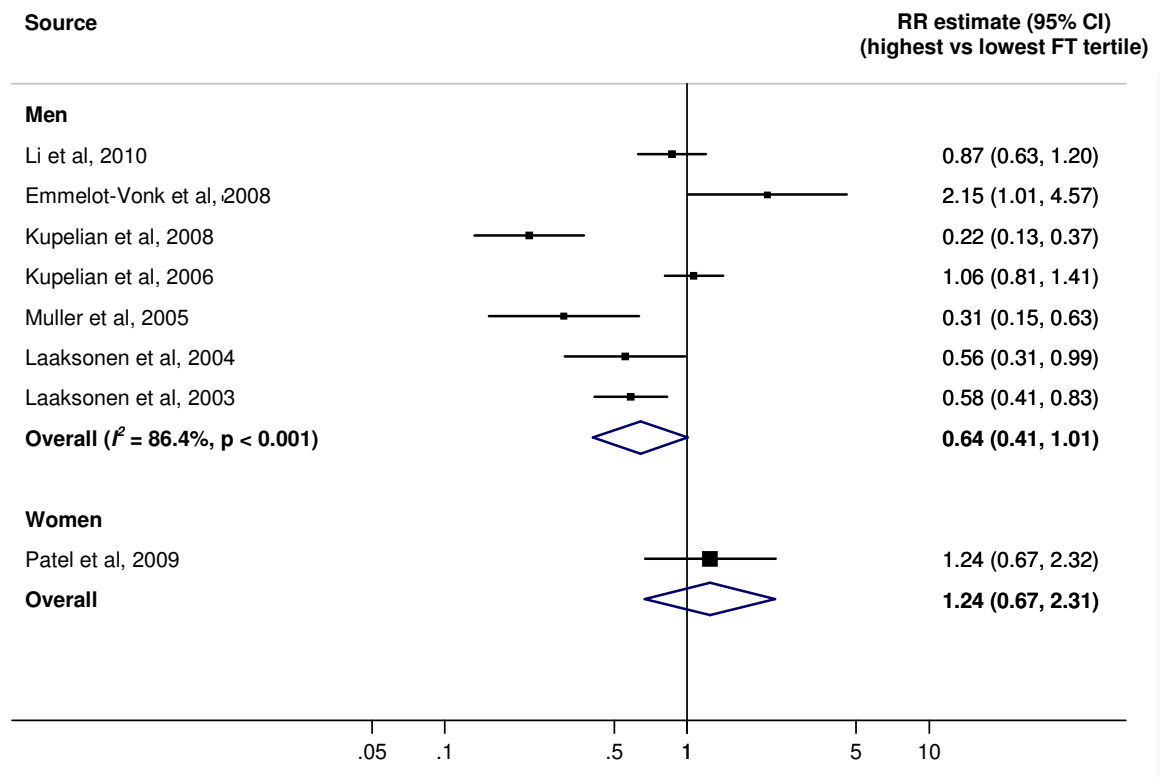


Figure 3B Random effects pooled relative risk estimate for FT comparing highest versus lowest tertile of FT, men and women. CI, confidence interval; MetS, metabolic syndrome; FT, free testosterone. Sizes of squares represent the weight of each study.