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Racial variation in sex steroid hormone concentration in black and white men: a meta-analysis

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SUMMARY

Sex steroid hormones are associated with chronic diseases and mortality with risk associations that differ between racial and ethnic groups. However, it is currently unclear whether sex steroid hormone levels differ between black and white men. The aim of this study was to assess racial variation in circulating testosterone, free testosterone, sex hormone-binding globulin (SHBG) and estradiol levels in men. We searched PubMed for articles comparing circulating hormones in black and white men. A meta-analysis was performed using weighted mean differences (WMD) to compare hormones levels between black and white men. Fifteen eligible studies were identified; three did not report adjusted means. After age adjustment, free testosterone levels were significantly higher in black than in white men (WMD = 4.07 pg/mL, 95% CI 1.26, 6.88). Depending on the free testosterone concentration in white men, this WMD translates into a racial difference ranging from 2.5 to 4.9%. Total testosterone (WMD = 0.10 ng/mL, 95% CI −0.02, 0.22), estradiol (WMD = 0.67 pg/mL, 95% CI −0.04, 1.38) and SHBG (WMD = −0.45 nmol/L, 95% CI −1.75, 0.85) concentrations did not differ comparing blacks with whites. After adjustment for age, black men have a modestly but significantly 2.5 to 4.9% higher free testosterone level than white men. Based on previous studies on effects of sex steroid hormones on risk of chronic

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diseases or mortality, this modest difference is unlikely to explain racial differences in disease risk.

Keywords

meta-analysis; racial variation; sex steroid hormones; SHBG

INTRODUCTION

Sex steroid hormones influence the development of primary and secondary sex characteristics as well as many other biological processes during the lifetime of a man. Circulating levels of steroid hormones change as men age; testosterone concentrations decrease (Orwoll *et al.*, 2006), whereas estradiol levels increase (Jasuja *et al.*, 2013). Abnormally low hormone levels of testosterone and/or high concentrations of estradiol are associated with a number of chronic diseases, such as diabetes mellitus (Ding *et al.*, 2006) and cardiovascular disease (Ruige *et al.*, 2010). Androgens influence the development and growth of prostate cancer, however, the long postulated association between steroid hormone concentrations and risk of prostate cancer is less than clear (Ross *et al.*, 1986; Ellis & Nyborg, 1992; Kehinde *et al.*, 2006; Roddam *et al.*, 2008; Muller *et al.*, 2012). The incidence and prevalence of several chronic diseases vary between different racial and ethnic groups, for example, Hispanics and blacks having a higher prevalence of diabetes (National Center for Health Statistics, 2012), blacks having a higher incidence of prostate cancer (Siegel *et al.*, 2013) and mortality from cardiovascular disease (National Center for Health Statistics, 2012), and whites having a higher incidence of osteoporosis (Looker *et al.*, 2012). Racial variation in circulating levels of sex hormones might, in part, explain these health disparities. However, the results on racial variation in circulating steroid hormone levels in previous studies were not consistent (Ross *et al.*, 1986; Ellis & Nyborg, 1992; Wright *et al.*, 1995; Kehinde *et al.*, 2006).

To explore possible explanations of racial variation in diseases, knowledge about racial variation in circulating sex steroid hormones is essential. To the best of our knowledge, no meta-analysis has been conducted to date to determine racial variation in circulating levels of different sex steroid hormones between black and white men.

METHODS

Study identification and selection

Articles were searched in the PubMed database through May 2013 with keywords in combination as listed below: steroid hormones, testosterone, free testosterone, sex hormone-binding globulin (SHBG), racial, race and ethnicities. We did not include ‘estradiol’ in our original search strategy as our starting point was differences in testosterone concentration. However, adding ‘estradiol’ to our search terms added one more publication of potential importance to our analysis (Abd Elmageed *et al.*, 2013), which was ineligible because the authors did not provide means and standard deviations or confidence intervals. Also, the reference lists of already known articles were examined for other eligible studies based on

the above-mentioned key words. All studies provided with a title and abstract were screened by two independent reviewers (A.R., S.R.) to select reports for full textual review. Disagreement between them was resolved by consensus. Studies were included:

- If the included participants were men.
- If they reported at least one of the following hormones: testosterone, free testosterone, estradiol, SHBG. We selected these hormones for the following reasons: (i) testosterone is the major male androgen, (ii) free testosterone is a measure of bioavailable testosterone, (iii) estradiol is the major oestrogen in men and (iv) SHBG is the major carrier of testosterone and estradiol in the peripheral circulation.
- If they reported on differences in circulating levels of the above-mentioned hormones and SHGB in male healthy study participants. Thus, studies including on men with prostate cancer or other diseases that may affect hormone levels (such as benign prostatic hyperplasia or other cancers) were excluded (e.g. Mohler *et al.*, 2004).
- If races/ethnicities included in the study were referred to as ‘black’, ‘African-American’, ‘Non-Hispanic black’, ‘white’, ‘non-Hispanic white’ or ‘Caucasian’. We did not include men of Hispanic or Asian origin.
- If data have (partly) been published twice, only data of the first publication were used. This refers to two publications: (i) Nyante *et al.* (2012) shows hormone data that were previously published by Rohrmann *et al.* (2007). We used the data published by Rohrmann *et al.* (2007). (ii) We used the information published by Orwoll *et al.* (2006); the 2010 publication (Orwoll *et al.*, 2010) is at least partly based on the same study cohort and therefore not included in our analysis.
- If publications presented the levels of hormones in arithmetic or geometric means with corresponding standard error, standard deviation or confidence interval. Studies reporting only medians were excluded (Asbell *et al.*, 2000; Litman *et al.*, 2006; Tsai *et al.*, 2006) as recommended by the Cochrane Collaboration (Higgins & Green, 2011).
- If the study was published in English.
- Case reports, editorials and reviews were excluded.

Data extraction

For each included study, data were extracted with regard to: year of publication, race (blacks and whites), number of participants, sex of participants (only men included), sex steroid hormones levels presented either in geometric means or in arithmetic means (testosterone, free testosterone, estradiol, SHBG), age of participants (≥18 years), country of study and whether the reported mean concentrations were adjusted for potential confounding factors (unadjusted, age-adjusted or multivariable-adjusted results). Data were extracted from tables and text.

Where geometric means were presented in studies (5 of 15), they were transformed into arithmetic means using large sample approximation. In a further step, all units were converted into the same units; total testosterone in ng/mL, free testosterone and estradiol in pg/mL and SHBG in nmol/L. For the results of Rohrmann *et al.* (2007), the difference in total and free testosterone levels, which was not significant when comparing the geometric mean, became statistically significant after transformation in arithmetic means. For two studies (Wu *et al.*, 1995; Gapstur *et al.*, 2002), the authors were contacted for more information. If necessary, the standard deviations were approximated for the different adjustment levels using the standard deviation from the unadjusted level (Ellis & Nyborg, 1992) and multivariable-adjusted level (Wu *et al.*, 1995) respectively.

Different information was available from the 15 studies concerning hormone types measured and the extent to which the means were adjusted for potential confounders, thus we report unadjusted-, age- and multivariable-adjusted results in this meta-analysis.

Statistical analyses

The results of the included studies were presented measuring the absolute difference in means between hormone levels in black and white men. This method, called weighted mean difference (WMD), is used to compare continuous variables with the same units accounting for sample size (Higgins & Green, 2011). Thus, results of WMD represent the absolute difference in the given units of hormones and SHBG. Standard deviations (SD), which are needed to calculate mean difference, were obtained from tables or calculated from standard errors and confidence intervals (Higgins *et al.*, 2008; Higgins & Green, 2011). For the test of heterogeneity of the WMD across the studies, the I^2 statistic was used. The I^2 statistic describes the percentage of total variation across studies that is caused by heterogeneity and thus, is an appropriate tool to assess inconsistency across studies (Higgins *et al.*, 2003). Two subgroups were used for sensitivity analysis; firstly, only studies that could be used in all three models (unadjusted, age and multivariable adjustment) were included in the analysis for testosterone and secondly, only studies with young men were included. We computed the per cent difference in hormone concentrations between black and white men by dividing the WMD from the meta-analysis by the hormone concentration in white men and multiplying by 100. To get a possible range in the per cent difference, we compute this figure for the study with the lowest and the highest hormone concentration in white men. The meta-analysis was done using STATA version 11 (Stata Corporation, College Station, TX, USA).

RESULTS

Through the electronic database search (PubMed), a total of 4933 studies were identified for potential inclusion (Fig. 1). After a full text review of 103 studies, 14 studies were included (Ross *et al.*, 1986; Ellis & Nyborg, 1992; Wright *et al.*, 1995; Wu *et al.*, 1995; Eastham *et al.*, 1998; Platz *et al.*, 2000; Ukkola *et al.*, 2001; Winters *et al.*, 2001; Gapstur *et al.*, 2002; Cheng *et al.*, 2005; Hoffman *et al.*, 2005; Orwoll *et al.*, 2006; Rohrmann *et al.*, 2007; Nyante *et al.*, 2012) and a search of references led to one further study to include (Ettinger *et al.*, 1997). Overall 15 studies, all conducted in US populations, were identified (Fig. 1). Table 1 shows the characteristics of the study populations included in these reports. From

Table 1, it is evident that the type of adjustment made in these different studies is very diverse, such that not all of them included, for example, body mass index (BMI) in their analysis. Some studies described potential confounders (Table 1), but did not provide multivariable-adjusted mean levels of sex steroid hormones (Ross *et al.*, 1986; Ellis & Nyborg, 1992; Wright *et al.*, 1995; Eastham *et al.*, 1998; Ukkola *et al.*, 2001; Winters *et al.*, 2001; Hoffman *et al.*, 2005). Therefore, Table 1 shows whether the studies reported unadjusted, age-adjusted or multivariable-adjusted hormone and SHBG concentrations. A funnel plot was conducted giving a hint of publication bias in the unadjusted models (data not shown).

Black men had significantly higher unadjusted (WMD = 0.27 ng/mL, 95% CI 0.16–0.39), and multivariable-adjusted (WMD = 0.27 ng/mL, 95% CI 0.15–0.38) total testosterone levels than white men (Table 2), but age-adjusted concentrations did not differ (WMD = 0.10 ng/mL, 95% CI −0.02 to 0.22, Fig. 1a). However, the variation in WMD attributable to heterogeneity in the results across the studies was high with 60% (unadjusted), 55% (age adjusted) and 60% (multivariable adjusted). As the meta-analyses using age-adjusted and multivariable-adjusted results included different subsets of studies, we performed sensitivity analyses for total testosterone with studies that each reported unadjusted, age- and multivariable-adjusted results (Ellis & Nyborg, 1992; Gapstur *et al.*, 2002; Orwoll *et al.*, 2006; Rohrmann *et al.*, 2007). In this subset of studies, similar, although not identical inferences were found as for overall: black men had higher testosterone levels than white men (unadjusted: WMD = 0.19 ng/mL, 95% CI 0.06–0.31; age-adjusted WMD = 0.19 ng/mL, 95% CI 0.06–0.33; multivariable-adjusted WMD = 0.24 ng/mL, 95% CI 0.10–0.37). Restricting to this subset of studies, variation in the WMD attributable to heterogeneity was lower with 35% for the unadjusted results and 49% for the age-adjusted results. A second sensitivity analysis with only younger men in the studies (Ross *et al.*, 1986; Wright *et al.*, 1995; Ettinger *et al.*, 1997; Winters *et al.*, 2001; Gapstur *et al.*, 2002) showed similar unadjusted and multivariable-adjusted compared results to all men (data not shown).

In contrast to total testosterone, we observed statistically significantly higher unadjusted (WMD = 4.77 pg/mL, 95% CI 1.89–7.66; Table 2), age-adjusted (WMD = 4.07 pg/mL, 95% CI 1.26–6.88; Fig. 2B) and multivariable-adjusted (WMD = 5.99 pg/ mL, 95% CI 2.91–8.42; Table 2) free testosterone concentration in black than in white men. Using the lowest (Orwoll *et al.*, 2006) and highest (Gapstur *et al.*, 2002) free testosterone concentrations in white men in the studies included in our analysis, these sizes of differences would equate to black men having a 3.0–5.8% (unadjusted), 2.5–4.9% (age-adjusted) and 3.5–6.8% (multivariable-adjusted) higher free testosterone levels than white men.

Unadjusted and multivariable-adjusted estradiol concentrations were significantly higher in black than in white men (Table 2); age-adjusted estradiol concentrations did not differ (Fig. 2C). SHBG concentration did not statistically significantly differ between black and white men (Table 2; Fig. 2d), although the variation in the WMD caused by heterogeneity was high (83, 90 and 89%, respectively).

DISCUSSION

The aim of this study was to evaluate whether sex steroid hormone levels differ in adult black and white men. We did this using different approaches to take into account factors that affect circulating hormone concentrations. Adjusting only for age, we did not observe statistically significant differences in total testosterone concentrations between black and white men, but free testosterone levels were significantly although modestly higher in blacks than in whites. In the multivariable-adjusted models, total testosterone was also significantly higher in black than white men, but the magnitude of the racial difference was very heterogeneous between the studies, as were the factors adjusted for (see Tables 1 and 2). To evaluate how much of the difference in results was because of a different subset of studies in the meta-analyses of the unadjusted, age-adjusted and multivariable-adjusted results, we performed sensitivity analyses including only those studies that each provided all three estimates. The results in this subset of studies were similar to those overall; however, the differences between black and white men were statistically significant, irrespective of the level of adjustment. This may be because of the smaller heterogeneity in this sample.

Only free testosterone differed between black and white men in all models. Using the actual free testosterone concentration of the studies included in our analysis and the result of our meta-analysis, we estimate that black men have a 2.5–4.9% higher free testosterone level than white men. To evaluate whether this percentage difference in free testosterone concentrations between black and white men may have implications on health, we set this figure in relation to results of a previous NHANES III analysis that examined the association between sex steroid hormone concentrations and all-cause mortality (Menke *et al.*, 2010). Given that, in this study (Menke *et al.*, 2010), we only detected modestly increased mortality when comparing the extremes of the distribution of free testosterone level, we conclude that a 2.5–4.9% difference in concentration between black and white men is unlikely to explain the all-cause mortality disparity (Cullen *et al.*, 2012). At lower free testosterone concentration, we cannot rule out that the small racial difference in concentration might account for a small racial difference in all-cause mortality. The influence of steroid hormones on the risk of chronic diseases and mortality is complex and estimates based on one measurement in adulthood very likely do not adequately reflect these associations. This is particularly true as hormone levels change over time and the changes might differ by race/ethnicity.

We presented unadjusted, age-adjusted and multivariable-adjusted differences in hormone concentrations. The unadjusted levels (or age-adjusted levels) are the concentration the men (or the men if they were the same age) actually experience and thus, could be an explanation of why men of a certain racial or ethnic group have a higher risk of a certain disease than others, irrespective of the reasons for the differences in hormone levels by race. The levels taking into account factors influencing hormone levels, such as obesity, and the prevalence of which differ by race, help us to understand whether there may be inherent differences (e.g. genetic) in hormone levels between black and white men.

A high degree of heterogeneity of the results among the studies was observed including when using the unadjusted and adjusted hormone levels. There are numerous explanations of

the observed heterogeneity in the results. In general, there may be residual confounding and the extent of confounding may differ from study to study. Concerning multivariable adjustment, the set of possible confounders adjusted for in studies varied greatly from study to study (Table 1). For example, studies took into account body weight (Ellis & Nyborg, 1992), BMI (Wu *et al.*, 1995; Orwoll *et al.*, 2006), per cent of body fat (Rohrmann *et al.*, 2007) or waist circumference (Gapstur *et al.*, 2002). Black men had a statistically significant higher estradiol level compared with white men, although the results for the age-adjusted model were only borderline statistically significant. Only three studies presented results with age (Platz *et al.*, 2000; Orwoll *et al.*, 2006; Rohrmann *et al.*, 2007) and multivariable (Orwoll *et al.*, 2006; Rohrmann *et al.*, 2007; Nyante *et al.*, 2012) adjustment for estradiol. It is well-known that circulating estradiol concentration is especially affected by differences in body fat mass as testosterone is converted into estradiol in fat tissue (Schneider *et al.*, 1979), and, thus, differences between studies might well be explained by differences in body composition between men with different ethnic background. However, all studies included in the multivariable analysis of differences in free testosterone levels included BMI or body weight and height, leading to a slightly larger WMD than only adjusting for age. Other factors taken into account in some of the studies were, for example, smoking, physical activity, alcohol consumption or health status. Thus, results of the meta-analysis should be interpreted with caution and future studies should pay special attention to possible confounders such as obesity, smoking or physical activity when addressing whether there are differences in hormone levels between blacks and whites beyond those factors for which their prevalences are known to differ by race.

In our analysis, we included studies that were published between 1986 and 2013. Factors that are associated with sex steroid hormone and SHBG concentrations, in particular the prevalences of obesity and of cigarette smoking, have changed in this time period. Between 1988–1994 (NHANES III) and 1999–2000, the age-adjusted prevalence of obesity increased from 22.9 to 30.5%. Similar increases occurred for men in all age groups and all racial/ethnic groups (Flegal *et al.*, 2002). The increase in the prevalence of obesity until 2009–2010 was also similar among racial/ethnic groups, with comparable prevalence rates among non-Hispanic black (38.8%) compared with non-Hispanic white men (36.2%) (Flegal *et al.*, 2012). In contrast to obesity, the prevalence of current smoking had decreased in US men from 30.8% in 1988–1994 to 25.6% in 2007–2008 (Huffman *et al.*, 2012). Interestingly, a lower prevalence of smoking among black adolescents has been reported, but at some point in young adulthood, the pattern is reversed with higher smoking prevalence among black than white men (Kandel *et al.*, 2011). Therefore, secular trends in the prevalence need to be considered in potential confounders for the analysis and interpretation of the results.

None of the studies included in our analyses controlled for environmental or geographic factors. Some studies found that the grade of urbanization may influence testosterone level. For example, South African men had higher testosterone levels when living in urban than in rural areas (Gray *et al.*, 2006). Also, significantly higher levels of testosterone in men living in Western industrialized societies versus men in pre-industrial societies were found (Kehinde *et al.*, 2006). However, these hormone differences are may be because of higher energy intake because men in urban areas were found to have increased BMI compared with

men in rural areas (Gray *et al.*, 2006). As discussed, some of the studies included in this meta-analysis adjusted for body fatness (see Table 1).

Few studies (Orwoll *et al.*, 2010) have examined differences in hormone levels between different subgroups of white or black populations. Little is known about steroid hormone concentrations in healthy black men outside the United States (e.g. Campbell *et al.*, 2006; Giton *et al.*, 2011; Lukas *et al.*, 2004). One small study, conducted in the United States showed similar testosterone and SHBG concentrations among middle-aged black men of different origin (Chen *et al.*, 2004).

Further limitations concern the design of the studies included in this meta-analysis. Most studies were conducted to assess racial difference in serum hormone levels; other studies instead set the primary focus on the associations between circulating hormone levels and disease outcomes such as bone density, PSA, prostate cancer and visceral adipose tissue. Recruitment of study participants was very different such that the studies did not select random/representative samples from their target population and, therefore, it might be questionable whether the results can be extrapolated back to the general population. Only two of the studies used a nationally representative sample (Rohrmann *et al.*, 2007; Nyante *et al.*, 2012). Three studies (Asbell *et al.*, 2000; Litman *et al.*, 2006; Tsai *et al.*, 2006) only reported median hormone concentrations, which cannot be used for meta-analyses. The largest one (Litman *et al.*, 2006) with 538 black and 710 white men reported no racial/ethnic differences in testosterone or SHBG concentration. Also, Asbell *et al.* (2000) observed no difference between black and white men, but in the study by Tsai *et al.* (2006), including 238 African-Americans and 412 Caucasians, total and bioavailable testosterone as well as total and bioavailable estradiol, but not SHGB concentrations, were statistically significantly higher in African-American than Caucasian men. Thus, results of our meta-analyses could have been different, if it was possible to include these three studies. Because of the explorative character of this meta-analysis, only a few quality criteria of including studies into the meta-analyses were defined in advance. Furthermore, we found a hint of a publication bias, although interpretation is difficult because of the small number of studies. There may be also other causes of asymmetry.

Differences in the methods used to measure circulating hormone concentrations, for example, sensitivity and detection limits, may also have influenced the results. Sex steroid hormones were mostly measured by chemiluminescent immunoassays or radioimmunoassay (DeVane *et al.*, 1975; Anderson *et al.*, 1976; Ross *et al.*, 1986), another study did not describe the method used (Ellis & Nyborg, 1992). None of these studies used mass spectrometry to determine circulating levels of testosterone and estradiol, which is considered to be gold standard for their determination (Huhtaniemi *et al.*, 2012). As shown in a European study, using immunoassays may lead to unreliable measurements of estradiol in men, whereas testosterone can be measured reasonably well using immunoassays (Huhtaniemi *et al.*, 2012). Free testosterone can be examined in two ways, by serum extraction followed by equilibrium dialysis (Pardridge & Mietus, 1979) or by calculation from concentrations of SHBG, testosterone and albumin and the laws of mass action (Sodergard *et al.*, 1982). Most studies used mass action equation. Whether morning samples were used for testosterone measurements is not sufficiently described. Despite these various

methodological approaches results are still comparable because of the fact that differences between black and white men were calculated within a study.

In summary, this meta-analysis supports statistically significant differences in circulating level of free testosterone, but not other steroid hormones, between black and white men when taking into account age. However, it is unlikely that small differences between black and white men as observed in this study may account for racial differences in mortality rates at least in the normal range of free testosterone concentration. There is still little evidence about determinants of racial differences in steroid hormone levels. On the one hand there are direct effects of genetics on hormone metabolism (Ahn *et al.*, 2009), but it has not been addressed in much detail how strongly this differs by race/ethnicity (Lunn *et al.*, 1999; Zeigler-Johnson *et al.*, 2004). As discussed above, lifestyle and anthropometry are determinants of circulating hormone levels and the prevalences of these factors may differ by race. To our knowledge, this is the first meta-analysis comparing steroid hormone levels between races and therefore it may contribute to further knowledge about associations of disease incidence and mortality and hormonal influence. However, given the heterogeneous study designs and sparse results existing to data, further large studies with a special attention to possible confounders are recommended to illuminate these associations in more detail and also clarify which factors most strongly affect and influence possible associations between circulating hormones and chronic diseases.

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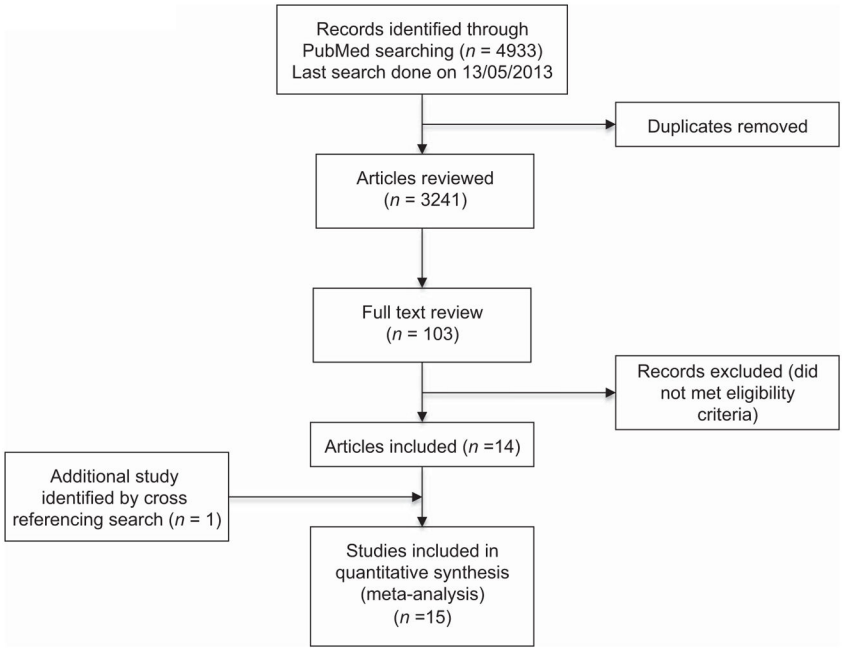

Figure 1.
Consort diagram for search strategy.

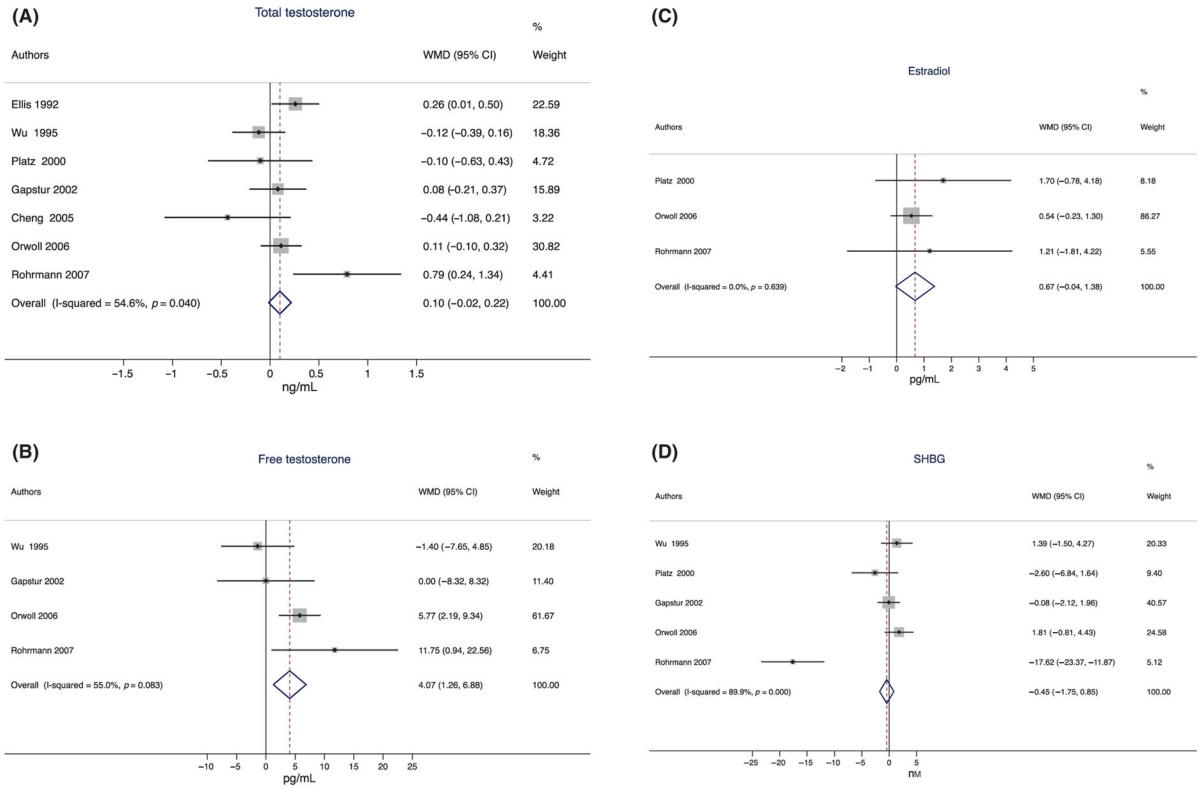

Figure 2.

Meta-analysis of age-adjusted differences between black and white men in (a) total testosterone, (b) free testosterone, (c) estradiol and (d) SHBG concentration. This figure represents the weighted mean difference (WMD) in total testosterone, free testosterone, estradiol and sex hormone-binding globuline (SHBG) concentrations between black and white men.

Table 1

Characteristics of the study population, study type and confounders

Reference	Race [a]	N	Age (mean)	Confounders examined	Study Population	Total Testosterone	Free Testosterone	Estradiol	SHBG
Cheng et al (2005)	B	129	63.3	Age	Multiethnic Cohort Study	Age-adjusted	–	–	–
	W	159	60.9						
Eastham et al (1998)	B	45	64.5	Age, serum level of PSA[b]	Prostate biopsy patients	Unadjusted	–	–	–
	W	82	64.9						
Ellis et al (1992)	B	525	38.34	Age, weight	Centers for Disease Control: male army enlistees	Unadjusted	–	–	–
	W	3564	38.37			Age-adjusted			
						Multivariable-adjusted			
Ettinger et al (1997)	B	109	30.7	None	Cohort from Kaiser Permanente in Northern California	Unadjusted	Unadjusted	–	Unadjusted
	W	114	31.3						
Gapstur et al (2002)	B	482	28.4	Age, weight, waist circumference	CARDIA male hormone study, USA	Unadjusted	Unadjusted	–	Unadjusted
	W	692	28.8			Age-adjusted	Age-adjusted		Age-adjusted
						Multivariable-adjusted	Multivariable-adjusted		Multivariable-adjusted
Hoffman et al (2005)	B	20	36.8	Age, weight, height, waist circumference, hip circumference, VAT, subcutaneous adipose tissue[b]	New York metropolitan area	Unadjusted	–	–	Unadjusted
	W	21	44						
Nyante et al. (2012)	B	183	48 [c]	Age, race/ethicity, BMI, waist circumference, smoking, alcohol	NHANES 1999–2004 [f]	Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted
	W	503							
Orwoll et al (2006)	B	236	73.2 [d]	BMI, health status, smoking, alcohol, age	Osteoporotic Fractures in Men Cohort Study (Mr. OS)	Unadjusted	Unadjusted	Unadjusted	Unadjusted
	W	2009				Age-adjusted	Age-adjusted	Age-adjusted	Age-adjusted
						Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted
Platz et al (2000)	B	43	55	Age	Health Professionals Follow-Up Study, USA	Age-adjusted	–	Age-adjusted	Age-adjusted
	W	55	54.4						
Rohrmann et al (2007)	B	363	29.5 [e]	Age, percent body fat, alcohol, smoking, physical activity, and sampling weights applied	NHANES III [f]	Age-adjusted	Age-adjusted	Age-adjusted	Age-adjusted
			56.2 [e]			Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted	Multivariable-adjusted
			73.4 [e]						
	W	674	31.8 [e]						
			55.9 [e]						
			74.4 [e]						

Reference	Race [a]	N	Age (mean)	Confounders examined	Study Population	Total Testosterone	Free Testosterone	Estradiol	SHBG
Ross et al (1986)	B	50	20.6	Health, height, weight, use of cigarettes, alcohol, licit and illicit drugs	Volunteers from 2 universities in Los Angeles	Unadjusted	Unadjusted	Unadjusted	Unadjusted
	W	50	19.9						
Ukkola et al (2001)	B	95	33.9	Age, BMI, smoking, caffeine, calories[b]	HERITAGE Family Study, multicenter cohort study, USA	Unadjusted	–	Unadjusted	Unadjusted
	W	215	36.3						
Winters et al (2001)	B	23	19.8	Age, weight, BMI, waist-to-hip ratio, fasting insulin levels[b]	Students from University of Pittsburgh recruited by advertisement	Unadjusted	Unadjusted	Unadjusted	Unadjusted
	W	23	21.5						
Wright et al (1995)	B	16	27	Age, weight, BMI[b]	General Clinical Research Center of the Medical University of South California	Unadjusted	–	Unadjusted	Unadjusted
	W	17	27						
Wu et al (1995)	B	306	69.9 [c]	Age, BMI, physical activity	Controls from a multicenter case-control study of prostate cancer: USA and Canada	Age-adjusted	Age-adjusted	–	Age-adjusted Multivariable-adjusted
	W	402				Multivariable-adjusted	Multivariable-adjusted		

[a] B = Black, W = White

[b] Confounders were assessed in the study but not used to compute adjusted hormone concentrations

[c] Total median age for all ethnic groups included in the study

[d] Total mean age for all ethnic groups included in the study

[e] Median age for different age categories (20–44 yr, 45–69 yr, 70+ yr)

[f] National Health and Nutrition Examination Survey.

Table 2

Differences in serum hormones between black and white men in a meta-analyses using unadjusted and multivariable-adjusted data (age-adjusted results are shown in Figure 2)

Type of adjustment	Analyte	Studies (n)	WMD	95% CI	I-squared (%)	p-value
Unadjusted	Total T (ng/ml)	10	0.27	0.16, 0.39	59.9	0.005
Multivariable		6	0.27	0.15, 0.38	53.6	0.056
Unadjusted	Free T (pg/ml)	5	4.77	1.89, 7.66	25.4	0.258
Multivariable		5	5.66	2.91, 8.42	38.9	0.162
Unadjusted	Estradiol (pg/ml)	5	1.26	0.62, 1.90	64.2	0.016
Multivariable		3	0.75	0.02, 1.49	91.3	<0.001
Unadjusted	SHBG (nmol/l)	8	−0.25	−1.24, 0.74	83.0	<0.001
Multivariable		5	0.36	−0.92, 1.65	88.7	<0.001

WMD = weighted mean difference.