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Evidence for Geographical and Racial Variation in Serum Sex Steroid Levels in Older Men

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Background: Despite considerable racial and geographical differences in human phenotypes and in the incidence of diseases that may be associated with sex steroid action, there are few data concerning variation in sex steroid levels among populations. We designed an international study to determine the degree to which geography and race influence sex steroid levels in older men.

Methods: Using mass spectrometry, concentrations of serum androgens, estrogens, and sex steroid precursors/metabolites were measured in 5003 older men from five countries. SHBG levels were assessed using radioimmunoassay.

Results: There was substantial geographical variation in the levels of sex steroids, precursors, and metabolites, as well as SHBG. For instance, Asian men in Hong Kong and Japan, but not in the United States, had levels of total testosterone approximately 20% higher than in other groups. Even greater variation was present in levels of estradiol, SHBG, and dihydrotestosterone. Group differences in body mass index did not explain most geographical differences. In addition, body mass index-independent racial differences were present; Black men had higher levels of estrogens (estradiol, estrone), and Asian men had lower levels of glucuronidated androgen metabolites.

Conclusions: On a global scale, there are important geographical and racial differences in the concentrations of serum sex steroids and SHBG in older men. (*J Clin Endocrinol Metab* 95: 0000–0000, 2010)

Sex steroids have pleiotropic actions in men. In addition to their effects on reproductive tissues, they influence numerous biological systems including those that determine body composition, immunological function, glucose and lipid metabolism, and cardiovascular health. Aging is well known to result in a decline in sex hormone levels, and those changes have been linked to disorders such as frailty, muscle and skin atrophy, fat accumulation, osteoporosis, and prostate disease, as well as sexual and cognitive dysfunction.

Abbreviations: ADT, Androsterone; ADT-G, ADT-glucuronide; CI, confidence interval; CV, coefficient of variation; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; DHT, dihydrotestosterone; 3α-diol-3G, androstane-3α,17β-diol-3-glucuronide; 3α-diol-17G, androstane-3α,17β-diol-17-glucuronide; 4-dione, androstenedione.

Racial and geographical differences exist in some human phenotypes that are influenced by sex steroids (*e.g.* lean mass, bone density) and in the incidence of age-related disorders that are linked to sex steroid actions. For instance, the risk of developing prostate cancer is higher in Black men, whereas Asian men living in the Far East have rates considerably lower than those living in Western countries (1, 2). These differences have stimulated interest in whether serum sex steroid concentrations or metabolism are affected by race and geography. Although some comparisons have suggested that there are racial differences in sex hormone levels (3–5), those findings are not consistent and are difficult to interpret because of small study sizes and the use of some sex steroid assay methods (RIA) with questionable specificity in lower concentration ranges. There are fewer studies of geographical variation, but some indicate that there may be environmental factors that affect sex hormone physiology (6, 7).

To examine racial and geographic differences in sex hormone levels, we assembled a large international cohort of older men and measured the serum levels of the most biologically active estrogens and androgens as well as their precursors and metabolites.

Subjects and Methods

Study populations

We evaluated 5003 ambulatory, community-dwelling men at least 65 yr of age from five countries (Japan, Hong Kong, Sweden, Tobago, and the United States). All were participants in ongoing observational studies that used similar enrollment criteria and evaluation methods (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Men in the United States, Sweden, and Hong Kong were participants in the Osteoporotic Fractures in Men Study (MrOS). Details of the U.S. MrOS cohort have been described (8). Self-defined racial/ethnic ancestry (Caucasian, Black, or Asian) was ascertained through questionnaire; fasting morning serum was collected. A random sample of MrOS Caucasian men and all Black and Asian men with sufficient stored serum were included. Samples were collected between 0800 and 1200 h, and serum was prepared and frozen for 6–7 yr in 1.0-ml cryovials at −80 C until assay. MrOS participants in Sweden (9) were Caucasian; all participants with sufficient morning, fasting serum were included. After phlebotomy, serum was prepared and stored for 2–4 yr in 0.5-ml microtubes at −70 C until assay. The MrOS Study in Hong Kong included Chinese men (10). All participants with sufficient stored serum from a morning, fasting blood draw were included. Serum was prepared and stored for 4–5 yr at −20 to −85 C in 0.6-ml microtubes. Vials were briefly thawed and refrozen once before assay.

In Tobago, the parent study was the Tobago Prostate Cancer Survey (11), a study of men of West African descent. A random sample of 500 participants at least 65 yr old was included. Fasting morning serum was obtained. After phlebotomy, serum was prepared and stored for 0.5–2.5 yr in 2.0-ml tubes at −80 C until assay.

In Japan, the parent study was the Research on Osteoarthritis and Osteoporosis Against Disability (ROAD) Study. Japanese participants were recruited from resident registration lists in two communities in the Wakayama District: a mountainous region in Hidakagawa and a coastal region in Taiji (12). Samples from all 367 men who were at least 65 yr old were analyzed; serum was collected between 0900 and 1500 h and stored for 1–2 yr in 2.0-ml vials at −80 C until assay.

The Institutional Review Board at each study center approved the protocol, and written informed consent was obtained from all participants.

Laboratory methods

The steroids measured are depicted in Fig. 1. All hormone assays were performed at the Centre de Recherché du CHUL (University of Laval, Quebec, Canada) using gas chromatography/liquid chromatography/mass spectrometry (13). Serum was stored at −80 C until assay. Standard samples of several concentrations were included in all assay runs to ensure precision and accuracy. Moreover, blinded aliquots of a single serum pool included in all assay runs showed no longitudinal trend in any measurement. Ranges of detection for each steroid and mean coefficients of variation (CV) for pooled serum aliquots are in Supplemental Table 2.

SHBG assays for Japan, the United States, and Tobago samples were performed at the Oregon Clinical and Translational Research Institute (Diagnostic Products Corp., Los Angeles, CA; CV, 7.1%), and Hong Kong and Sweden samples at the Clinical Pharmacology Lab, Sahlgrenska University Hospital, Gothenburg (Orion Diagnostics, Espoo, Finland; CV, 10.7%). Duplicate measures of 50 serum samples in each laboratory resulted in nearly identical mean values (40.3 *vs.* 40.4 nM) and SD values (14.2 *vs.* 13.2) and a very high correlation (r = 0.98). A Bland-Altman plot showed that 48 of 50 (96%) pairs fell within the 95% confidence limits of agreement (Supplemental Fig. 1). In addition, we tested a term for "laboratory" in the adjusted SHBG models and found that the term was not statistically significant (P = 0.25) and did not alter our estimates of mean SHBG levels across country or race. For these reasons, we assume any small differences in assay performance between the labs are not influential. Free fractions of testosterone and estradiol were calculated as described by Sodergard *et al.* (14). These calculated values appear to accurately reflect directly measured results (15–18).

Statistical methods

Men who reported the use of androgen or antiandrogen therapy had been orchidectomized or had testosterone or dihydrotestosterone (DHT) below the limit of detection (Supplemental Table 2) were excluded. Seasonal variation was not present in any steroid, and adjustment for season did not reduce group differences. Square root or natural log transformations were made to produce normally distributed variables. Age-adjusted least-squares means and 95% confidence intervals (CIs) were calculated for each group, and a P for ANOVA was presented. Age-group and BMI-group interactions were tested for each analyte; when significant (P < 0.10), the interaction term was retained to allow age and BMI adjustments to be group-specific. Means and CIs were back-transformed to facilitate the presentation of results in the original units of measure. Evaluation of patterns in mean concentrations across groups led to *post hoc* tests of differ-
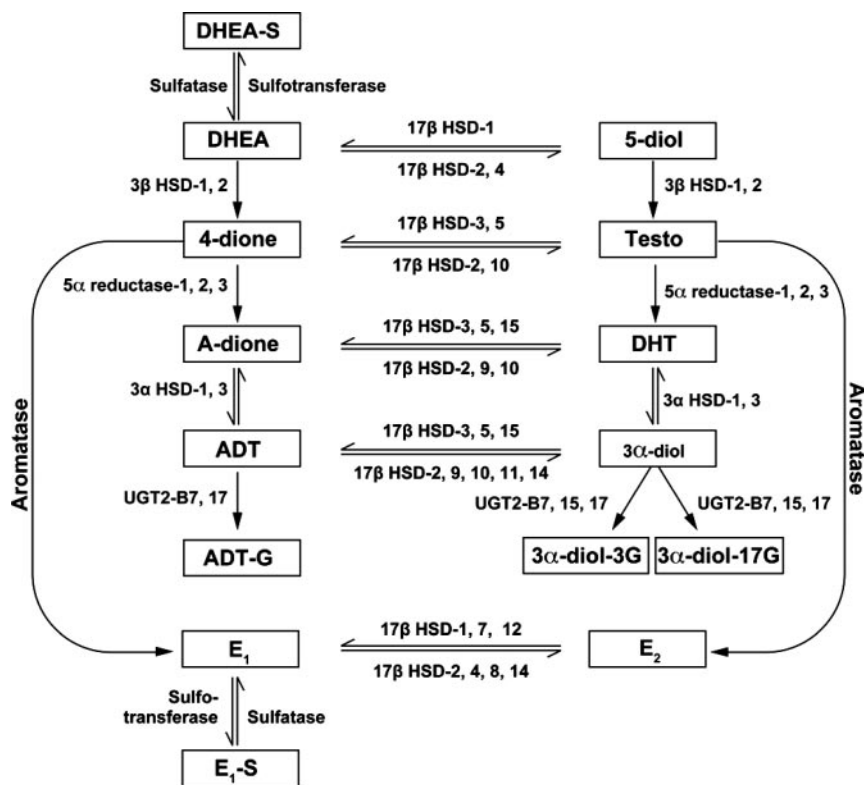
FIG. 1. Measured steroids and their metabolic relationships. 5-diol, Androst-5-ene-3β,17β-diol; A-dione, androstanedione; E2, estradiol; E1, estrone; E1-S, estrone sulfate; HSD, hydroxysteroid dehydrogenase. [Adapted from Refs. 41–43.]

ences after collapse of groups with similar means. Spearman correlations among untransformed sex steroid variables are shown in Supplemental Table 3.

For racial comparisons, we used three major groups (Caucasian, Black, and Asian). Country means were weighted equally within racial group to account for heterogeneity of sample sizes across countries. All analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC).

Results

The mean ages of the participants in the seven geographical/racial groups were very similar, but there were differences in indices of body size (Table 1).

Geographical variation in sex steroid and SHBG concentrations

Androgen and estrogen levels varied among populations (Table 1). For example, whereas age-adjusted mean total testosterone levels were similar in men from Sweden, Tobago, and the United States, they were higher (16%; $P < 0.0001$) in men living in Hong Kong and Japan (Fig. 2A); Asian men living in the United States had levels similar to other U.S. residents. As a result of geographical heterogeneity, the proportion of men with total testosterone levels suggestive of hypogonadism (<230 ng/dl) (19) differed between populations (*e.g.* 5–6% in U.S. Caucasian and Swedish men;

3% in Hong Kong and Japanese men) (Fig. 3). There was also geographical variation in DHT concentrations, but the interpopulation pattern was distinct from that of testosterone. When compared with men in the United States and Sweden, age-adjusted levels were higher (33%; $P < 0.0001$) in Tobago and in Asia (Fig. 2B). Total estradiol levels were higher in men from Hong Kong and Tobago (22%) and among Black men in the United States (20%) (Fig. 2C) (Table 1). Free estradiol showed a similar pattern. We recently identified a level of free estradiol (0.3 pg/ml) below which fractures (including hip fracture) are more likely in older Caucasian men (20). The proportion of men with levels below that threshold varied considerably between cohorts (4 to 28%) (Fig. 3).

Major geographical variation was also present in sex steroid precursors and metabolites (Table 1). For example, the age-adjusted mean dehydroepiandrosterone (DHEA) level was 44% higher, and the mean DHEA sulfate (DHEA-S) level was 20% higher in Sweden than in U.S. Caucasians. The concentrations of androgen metabolites varied across groups, primarily because androgen glucuronide levels were lower in Asian men (see *Racial variation*).

Whereas SHBG levels were similar in most groups, they were slightly lower (12%) in Swedish men and markedly higher (47%) in Japanese (Fig. 2D). As a result, mean free testosterone levels were significantly lower in Japanese (Fig. 2E). Mean free estradiol levels were higher in Hong Kong, U.S. Black, and Tobagonian men, but were lower in Japanese (Fig. 2F).

Adjustment for BMI somewhat altered the population differences in serum concentrations of steroids and SHBG, but significant heterogeneity generally remained or was enhanced (Supplemental Table 4). For instance, BMI adjustment had little effect on the cohort differences in SHBG, total estradiol, free estradiol, or free testosterone levels. On the other hand, total testosterone levels were similar among populations after BMI adjustment (Fig. 2G).

Racial variation

In addition to the effects of geography, two consistent racial patterns were found. First, Black men (from the United

TABLE 1. Cohort characteristics (mean ± SD) and age-adjusted mean (95% CI) sex steroid concentrations

	Sweden	U.S. White	U.S. Asian	Hong Kong	Japan	Tobago	U.S. Black	P^a
n	1874	427	156	1479	364	482	221	
Age (yr)	75 ± 3	74 ± 6	73 ± 5	72 ± 5	74 ± 6	72 ± 6	72 ± 5	
BMI (kg/m²)	26 ± 4	27 ± 4	25 ± 3	23 ± 3	23 ± 3	27 ± 4	28 ± 4	
SHBG (nmol/liter)	42.95 (42.1–43.38)	47.47 (45.6–49.4)	47.47 (44.7–50.91)	48.42 (47.47–49.40)	72.97 (70.11–75.94)	51.42 (49.9–53.52)	50.40 (47.94–52.98)	<0.0001
Precursors								
DHEA-S (μg/ml)[b]	0.67 (0.66–0.71)	0.55 (0.52–0.59)	0.76 (0.69–0.83)	0.85 (0.83–0.88)	0.81 (0.76–0.86)	0.94 (0.88–1.00)	0.58 (0.52–0.62)	0.003
DHEA (ng/ml)[b]	1.90 (1.88–1.96)	1.21 (1.14–1.3)	1.51 (1.37–1.66)	1.72 (1.66–1.77)	1.35 (1.25–1.44)	1.39 (1.32–1.46)	1.35 (1.23–1.46)	<0.0001
4-dione (ng/ml)	0.82 (0.8–0.82)	0.68 (0.65–0.7)	0.68 (0.65–0.73)	0.72 (0.7–0.72)	0.68 (0.65–0.7)	0.63 (0.6–0.65)	0.72 (0.68–0.75)	<0.0001
5-diol (ng/ml)[b]	0.59 (0.58–0.61)	0.50 (0.48–0.53)	0.53 (0.48–0.58)	0.62 (0.59–0.64)	0.71 (0.67–0.74)	0.58 (0.55–0.61)	0.58 (0.53–0.62)	<0.0001
Androgens								
Testosterone (ng/ml)	4.54 (4.45–4.62)	4.54 (4.37–4.71)	4.41 (4.12–4.67)	5.29 (5.15–5.38)	5.20 (4.97–5.38)	4.54 (4.37–4.67)	4.71 (4.45–4.93)	<0.0001
Free T (ng/ml)	9.52 (9.37–9.66)	9.14 (8.86–9.42)	8.82 (8.35–9.29)	10.49 (10.34–10.65)	8.17 (7.86–8.47)	8.76 (8.49–9.03)	9.06 (8.67–9.46)	<0.0001
DHT (ng/ml)	0.36 (0.36–0.37)	0.36 (0.34–0.37)	0.34 (0.31–0.36)	0.45 (0.44–0.46)	0.52 (0.49–0.53)	0.46 (0.45–0.49)	0.38 (0.36–0.41)	<0.0001
Estrogens								
E1 (pg/ml)[b]	35.28 (34.57–36)	30.36 (29.27–31.58)	29.38 (27.46–31.25)	33.41 (32.72–34.11)	25.00 (23.81–26.21)	42.51 (41.22–43.82)	39.82 (37.82–41.73)	0.0002
E1-S (ng/ml)[b]	0.48 (0.45–0.49)	0.51 (0.48–0.54)	0.55 (0.51–0.62)	0.57 (0.55–0.58)	0.45 (0.42–0.48)	0.7 (0.67–0.73)	0.48 (0.43–0.52)	0.07
E2 (pg/ml)[b]	20.7 (20.29–21.12)	20.09 (19.49–20.91)	18.73 (17.64–19.89)	22.87 (22.2–23.34)	18.17 (17.46–18.92)	24.53 (23.57–25.28)	23.10 (21.98–24.53)	0.05
Free E2 (pg/ml)[b]	0.52 (0.51–0.54)	0.49 (0.48–0.51)	0.46 (0.43–0.49)	0.55 (0.54–0.57)	0.38 (0.36–0.39)	0.58 (0.55–0.60)	0.55 (0.52–0.57)	0.02
Metabolites								
ADT (ng/ml)	0.17 (0.17–0.19)	0.16 (0.15–0.16)	0.17 (0.16–0.19)	0.21 (0.21–0.22)	0.16 (0.16–0.17)	0.17 (0.17–0.19)	0.16 (0.15–0.17)	<0.0001
ADT-G (ng/ml)	28.37 (27.79–29.27)	24.28 (22.81–25.58)	19.09 (17.54–20.98)	22.10 (21.42–22.57)	17.36 (16.29–18.49)	28.37 (26.94–29.88)	27.22 (25.31–29.27)	<0.0001
3α-Diol-3G (ng/ml)	1.29 (1.27–1.34)	1.27 (1.18–1.34)	0.86 (0.75–0.95)	0.82 (0.79–0.86)	0.58 (0.54–0.65)	1.23 (1.16–1.29)	1.16 (1.08–1.27)	<0.0001
3α-Diol-17G (ng/ml)	2.46 (2.39–2.53)	2.60 (2.46–2.74)	1.86 (1.66–2.06)	1.92 (1.83–1.97)	1.25 (1.14–1.36)	2.42 (2.32–2.56)	2.56 (2.35–2.78)	<0.0001

T, Testosterone; 5-diol, androst-5-ene-3β,17β-diol; E1, estrone; E1-S, estrone sulfate; E2, estradiol.

[a] *P* for ANOVA.

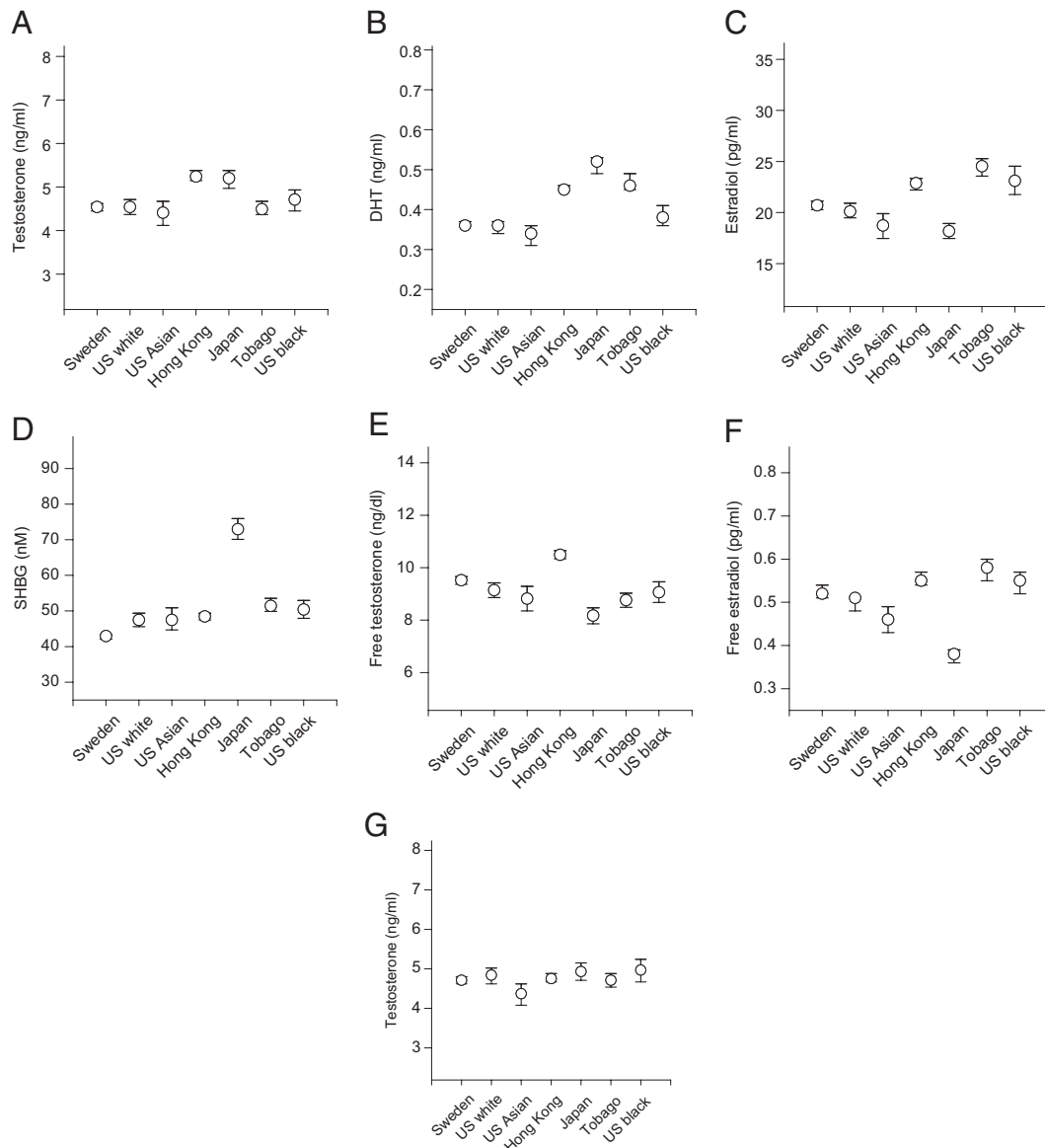[b] Model includes age × group interaction to allow age adjustment to be group-specific.

FIG. 2. Age-adjusted (A–F) and age- and BMI-adjusted (G) means (±95% CI) for selected steroids.

States and Tobago) had higher estrogen levels than Caucasians or Asians. Total and free estradiol levels were 10–16% higher and estrone levels 27–39% higher in Black men after age and BMI adjustments (Table 2). Moreover, in Blacks the ratios of total estradiol:total testosterone and estrone:androstenedione (4-dione) were increased compared with other groups (Table 2). Second, after age and BMI adjustments, Asian men (from the United States, Hong Kong, and Japan) had lower serum levels of glucuronidated androgen metabolites [androsterone-glucuronide (ADT-G), androstane-$3\alpha,17\beta$-diol-3-glucuronide (3α-diol-3G), and androstane-$3\alpha,17\beta$-diol-17-glucuronide (3α-diol-17G)] than did Blacks and Caucasians, and the ratios of these compounds to their precursors [DHT and androsterone (ADT)] were lower in Asian men (Table 2). Racial patterns in other compounds were not apparent.

Discussion

In this large, international study of older men, we found major variation between groups in the concentrations of sex steroids, in their precursors and metabolites, and in SHBG. Differences between populations transcend racial distinctions and thus strongly suggest that there are important geographical and environmental influences on sex steroid metabolism. However, in part, the variation was also the consequence of two fundamental racial differences in steroid metabolism-increased estrogen production by aromatase in Blacks and reduced androgen glucuronidation in Asians. As a result of overall population variation, there is considerable discrepancy between groups in the proportion of men who would be identified as hypogonadal or who would be considered at higher risk of fracture.
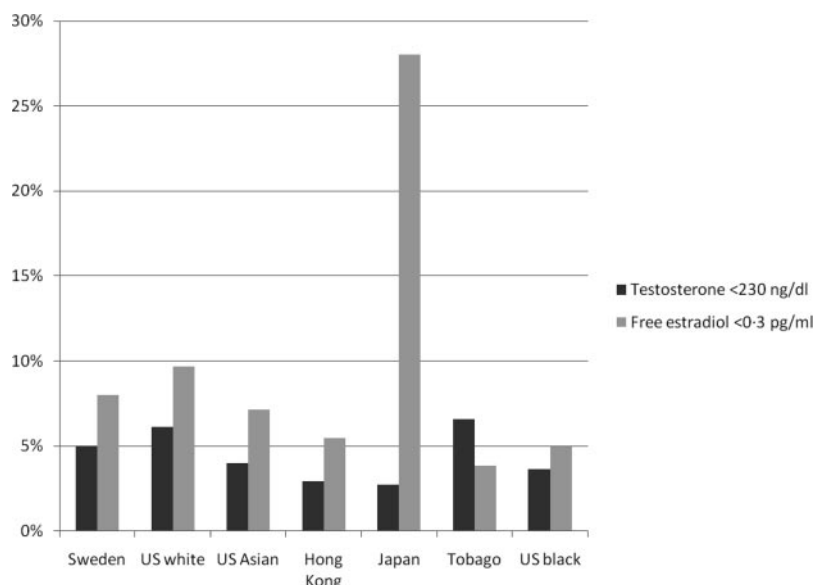
FIG. 3. Prevalence (±95% CI) of low total testosterone (<2.30 ng/ml) and low free estradiol (<0.3 pg/ml) in the cohorts studied.

We describe evidence for global variation in steroid levels. The cohorts examined were sufficiently large and geographically diverse to provide strong evidence of an effect of locale. For instance, mean levels of total testosterone varied by 18%, free testosterone by 25%, and DHT by 42% (Table 1). There are few previous evaluations of geographical differences in sex steroid levels, possibly because the assembly of sufficiently large populations and the use of uniform experimental methods are challenging. Finally, there is controversy about the assessment of free testosterone and estradiol levels. Although we used commonly applied approaches for calculating free levels based on mass action equations, those methods may be influenced by geography, race, or other factors, and any such factors may in part underlie the differences we describe among populations. Although the populations are sufficiently large and the study designs sufficiently similar to strongly suggest geographical variation, that conclusion cannot be definitively drawn from these studies because our populations represent volunteers that may not be representative of the general populations in the regions studied. Certainly our results set the stage for more targeted studies with representative cohorts.

SHBG concentrations are a major determinant of sex steroid levels and action, and we also demonstrate geographical variation in SHBG concentrations. SHBG is considered to be important in human sex steroid physiology for several reasons, including its binding of steroids in the extracellular space. SHBG has strong binding affinity for testosterone and DHT and lesser affinity for other steroids (*e.g.* estradiol), but does not bind to steroids that lack the 17β-hydroxy group (*e.g.* 4-dione, estrone). Hence, SHBG may have various effects on sex steroid actions via these binding actions. Moreover, SHBG may have direct tissue effects via specific molecular mechanisms (21), and in large population studies SHBG concentrations are independently

TABLE 2. Age- and BMI-adjusted mean (95% CI) levels for selected steroids and ratios

	White	Asian	Black	White-Asian	White-Black	Asian-Black
				P values for pairwise comparisons		
DHT (pg/ml)[a,b]	0.38 (0.37, 0.39)	0.39 (0.39, 0.40)	0.46 (0.44, 0.48)	0.03	<0.0001	<0.0001
DHT:T[a]	0.29 (0.29, 0.29)	0.28 (0.28, 0.29)	0.31 (0.31, 0.31)	<0.0001	<0.0001	<0.0001
E1 (pg/ml)	32.15 (31.58–32.83)	29.38 (28.84–29.81)	40.70 (39.44–41.86)	<0.0001	<0.0001	<0.0001
E2 (pg/ml)[a]	20.09 (19.69–20.49)	20.09 (19.69–20.49)	23.34 (22.42–24.29)	0.73	<0.0001	<0.0001
Free E2 (pg/ml)	0.49 (0.48–0.51)	0.48 (0.48–0.49)	0.54 (0.52–0.55)	0.03	<0.0001	<0.0001
E2:T	1.40 (1.38–1.41)	1.41 (1.40–1.42)	1.49 (1.46–1.51)	0.10	<0.0001	<0.0001
Free E2:free T	0.045 (0.043–0.046)	0.047 (0.046–0.048)	0.057 (0.055–0.060)	0.04	<0.0001	<0.0001
E1:4-dione[b]	10.58 (10.44–10.72)	11.11 (10.99–11.23)	13.01 (12.76–13.26)	<0.0001	<0.0001	<0.0001
ADT-G (ng/ml)[a]	26.11 (25.31–26.94)	19.91 (19.29–20.33)	27.79 (26.39–29.27)	<0.0001	0.06	<0.0001
3α-diol-3G (ng/ml)[a]	1.27 (1.23–1.32)	0.80 (0.77–0.82)	1.18 (1.12–1.25)	<0.0001	0.04	<0.0001
3α-diol-17G (ng/ml)[a]	2.39 (2.32–2.49)	1.86 (1.8–1.92)	2.39 (2.25–2.53)	<0.0001	0.93	<0.0001
3α-diol-3G:DHT	1.41 (1.37–1.44)	1.00 (0.97–1.03)	1.23 (1.17–1.29)	<0.0001	<0.0001	<0.0001
3α-diol-17G:DHT[a]	2.05 (2.01–2.09)	1.77 (1.73–1.80)	1.89 (1.82–1.96)	<0.0001	0.0005	0.001
ADT-G:ADT[a]	26.85 (25.87–27.83)	22.75 (21.87–23.64)	27.35 (25.55–29.15)	<0.0001	0.67	<0.0001

E1, Estrone; E2, estradiol; T, testosterone.

[a] BMI × group interaction included in model to allow BMI adjustment to be group-specific.

[b] Age × group interaction included in model to allow age adjustment to be group-specific.

associated with important outcomes (20–22). Levels were considerably higher in two rural areas of Japan. Similar results have been reported in Japanese women (22, 23). The significance of these findings is unclear, but high levels of SHBG in the Japanese were reflected in differences in testosterone and estradiol concentrations that could lead to alterations in androgenic and estrogenic action. Like sex steroids, SHBG may be affected by a wide variety of genetic as well as environmental factors including diet (7, 24, 25). Finally, there is controversy about the assessment of free sex steroid levels (15, 26). Although we used commonly applied approaches for calculating free levels based on mass action equations, those methods may be influenced by geography, race, or other factors, and any such factors may in part underlie the differences we describe among populations.

The causation of differences among our populations is not yet clear. Ecological influences including diet, environmental chemicals, climate, physical activity, smoking, and social status (24, 25, 27, 28) have been linked to effects on sex steroid physiology and could contribute to international variation. In addition, differences in the prevalence of reproductive disorders could contribute to our results. There were obvious differences in body mass index among the groups, and body composition is well known to influence sex steroid levels and physiology (29, 30). In fact, adjustment for body mass index in our analyses altered the population differences, but in large part they persisted, suggesting that body mass index is at best a partial explanation for group variations.

International variation in sex steroid levels could have obvious implications for the diagnosis and treatment of hypogonadism. Our results show that use of a conventional criterion for age-related androgen insufficiency (<230 ng/dl) (19) would yield noteworthy population differences in the prevalence of hypogonadism that would in turn result in differences in the number of men considered for replacement therapy. In addition, population differences in sex steroid levels may be similarly relevant to the international epidemiology of common conditions that affect older men, including inflammation, prostate disease, neoplasia, frailty, and osteoporosis. For instance, serum estradiol levels are useful in estimating fracture risk in older men (20, 31), at least in Caucasians, and we show that there appears to be substantial racial and geographical variation in the proportion of men considered at higher risk using this criterion. Variation in estrogen levels and evidence of increased aromatase activity have been linked to the risk of cardiovascular disease in older men and women (32). Finally, geographical and racial variation in sex steroid levels in older men may herald comparable variation in women, and if present during growth population variation could lead to developmental differences in sex steroid-dependent human phenotypes such as reproductive function, body composition, bone structure, and hair distribution.

Racial, presumably genetic, influences on sex steroid metabolism have long been sought. Some studies suggest the presence of higher estradiol levels in both Black men (33) (in a representative population in the United States) and women (34) but involved few participants and generally employed RIA methods that have limitations. Moreover, most comparisons involve subjects limited to one geographic area (28). Our findings considerably extend those reports and provide a global perspective. We demonstrate not only that Black men in the United States and Tobago have higher mean estradiol levels than populations of Caucasians and Asians but also provide evidence (higher estrone levels and reduced precursor/product ratios) that implicates increased aromatase activity as the likely explanation. These results may have important health implications. For instance, femoral cortical thickness and trabecular bone density are greater in older Black men (35), and Black men have lower hip fracture rates (36, 37), findings that are consistent with higher estrogen levels. In our study, considerably fewer Black men had free estradiol levels below a threshold level associated with increased fracture risk (20, 31).

We also show that androgen metabolism in Asian men is distinct. The levels of glucuronidated androgen metabolites (but not ADT) were clearly reduced in Asian men, as were the ratios of these compounds to their precursors, indicating that glucuronidation is likely affected. In support of these large population results, we previously reported that a proportion of Asians have a deletion in the uridine diphosphate-glucuronosyltransferase UGT2B17, consistent with lower rates of androgen glucuronidation. We and others have also shown that polymorphisms or copy number variation in the major enzymes responsible for glucuronidation of androgens (UGT2B15, UGT2B17, and UGT2B7) appear to have an impact on levels of glucuronidated androgens (38, 39), suggesting that these genes are interesting candidates to explain racial differences in glucuronidated androgen levels. Of potential physiological importance, serum androgen glucuronide levels may be more strongly related to total androgen activity than are measures of individual androgens. Of practical concern, a reduction in testosterone glucuronidation with high serum and low urine testosterone levels in Asians can result in misinterpretations of common monitors for androgen use in athletes (40). Other studies have explored Asian-Caucasian differences in reproductive function (27) but have been small and rarely involved disparate geographies.

The study has considerable strengths. It represents a unique international collaboration that brings together

well-characterized cohorts that were recruited and evaluated using similar methods. Large numbers of study participants provided adequate power to identify group differences, and we measured a large number of sex steroids, including potent androgens and estrogens as well as their precursors and metabolites. Importantly, all steroid measures were performed in a single laboratory employing rigorous quality control procedures, and the methods used avoid limitations of previous approaches. On the other hand, as mentioned above, the cohorts were recruited using very comparable strategies, and they are similar in many relevant respects, but they may not be completely representative of their broader populations. Our analyses are cross-sectional, and although the effects of sex steroids in older men are of considerable interest, we did not assess variation in women and younger people. The apparent racial differences we describe appear robust, but we classified race in broad racial categories and did not formally examine genetic admixture or racial subgroups. Moreover, whereas our results provide a new recognition of possible racial and geographical variation in sex steroid metabolism, we have not determined the mechanisms responsible. Finally, some variation may have been introduced by the approaches used for sample handling. For instance, whereas we attempted to standardize the methods for sample collection and storage, there were some minor differences that might have contributed to variation.

In summary, in a large, international study of older men we found evidence for substantial racial and geographical differences in the levels of major circulating androgens and estrogens, in their precursors and metabolites, and in SHBG. Such variation could result in diversity in important health outcomes, for instance in the proportion of older men with hypogonadism and in the risk of fracture attributable to estrogen deficiency. Understanding the causes of potential differences could yield new insights into racial and environmental influences on sex steroid regulation.

Acknowledgments

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