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Association Between Sex Steroid Hormones and Hematocrit in a Nationally Representative Sample of Men

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Abstract

Low or high hematocrit levels are associated with increased morbidity and mortality, mediated via anemia or thromboembolic events, respectively. It is therefore important to identify factors that influence hematocrit. Although androgens are known to stimulate hematopoietic cells, it is unknown whether circulating sex steroid hormones affect hematocrit. The association between serum sex steroid hormone concentrations and hematocrit in men aged ≥20 years was evaluated in a cross-sectional study of 1273 men in the Third National Health and Nutrition Examination Survey (1988–1991). Outcomes were low (<10th percentile), high (>90th percentile), and mean hematocrit. Men with low free testosterone levels had a lower hematocrit than men with normal free testosterone levels ($P = .03$), although no relationship was found between total testosterone level and hematocrit. The relationship between sex hormone-binding globulin (SHBG) and hematocrit was complex, with both low ($P < .001$) and high ($P = .01$) SHBG levels associated with lower hematocrit in men aged ≥20 years and only high ($P = .01$) SHBG levels in men aged ≥50 years. The odds ratio (OR) of high vs normal hematocrit increased as total estradiol (OR, 2.84; P trend = .04) and free estradiol (OR, 2.23; P trend = .09) levels increased. In this nationally representative study of men, sex steroid hormone levels, particularly low free testosterone and high SHBG levels, were associated with lower hematocrit, and high total and free estradiol levels were associated with high hematocrit. Thus, changes in sex hormone levels with aging may contribute to the increased prevalence of anemia and thromboembolic stroke in men as they age.

Keywords

Testosterone; estradiol; sex hormone-binding globulin; NHANES III

Both low and high levels of hematocrit have been observed to be associated with adverse health outcomes. Specifically, anemia, defined as low hemoglobin (<13 g/dL), is associated with an increased risk of falls and fractures, cognitive impairment, mortality, and decreased physical ability (Penninx, 2007). Anemic men older than 85 years had more than twice the

risk of death than men without anemia (Izaks et al, 1999). In the Third National Health and Nutrition Examination Study (NHANES III), a nationally representative sample of Americans, anemia was present in 11% of men older than age 65 years (Guralnik et al, 2004). Among hospitalized older patients, the prevalence of anemia is even higher (24% to 40%) (Joosten et al, 1992; Smieja et al, 1996). High hematocrit was associated with an increased risk of death from cardiovascular disease in both the Honolulu Heart Program (Carter et al, 1983) and Framingham Heart Study (Gagnon et al, 1994). In addition, in disease states with elevated red cell mass, as in polycythemia vera, the prevalence of thrombosis ranges from 12% to 39% (Elliott and Tefferi, 2005).

It is unknown why anemia is so common in elderly men. Changes in sex steroid hormone levels with age may alter hematocrit and could contribute to this finding. It is well documented that with increasing age, serum testosterone concentrations decline in men and the prevalence of clinically low testosterone levels increases (Harman et al, 2001). There is some evidence that suggests that androgens raise hematocrit. For example, hemoglobin levels rise in boys during puberty (Garn et al, 1981) and with pharmacological doses of androgens in patients with hypogonadism (Tenover, 1992; Sih et al, 1997; Saad et al, 2007), whereas hemoglobin levels decline with chemical or surgical castration (Weber et al, 1991; Fonseca et al, 1998). Additionally, previous research has shown that men older than 65 years with low testosterone levels have a higher risk of anemia (Ferrucci et al, 2006). However, these studies have focused on select populations (eg, pubescent, hypogonadal, castrated, and elderly men), effectively assessing the association among men with very high or low levels of testosterone. Estrogen levels also decline with age in men, although not to the same extent as testosterone levels (Orwoll et al, 2006). There is no known mechanism by which estradiol directly increases hematocrit; however, estradiol may blunt the effects of hypoxia-induced erythropoietin expression (Mukundan et al, 2002). In addition, men have higher age-matched hemoglobin concentrations than women at particular altitudes; this effect is seen after puberty but is not evident at postmenopausal ages (Leon-Velarde et al, 2000).

We hypothesized that sex steroid hormone levels in men, in both diseased and healthy populations, are associated with hematocrit levels, leading to alterations in risk of clinical and subclinical disease, respectively (Figure). In this study, we evaluated the association of serum levels of testosterone, estradiol, and their main binding globulin, sex hormone-binding globulin (SHBG) with hematocrit across the full male adult age range using data from a national population-based study.

Materials and Methods

Study Population

NHANES III, a cross-sectional study of the US population aged 2 months, was conducted between 1988 and 1994 by the National Center for Health Statistics. NHANES III used a multistage, stratified, clustered probability sample with over-sampling of Mexican Americans, non-Hispanic African Americans, and older Americans to ensure an adequate sample size for generating prevalence estimates for these groups. In total, 33 944 people participated, of which 14 781 were male. The protocols for the conduct of NHANES III were approved by the institutional review board of the National Center for Health Statistics, US Centers for Disease Control and Prevention. Informed consent was obtained from all participants. The assay of these stored serum specimens for sex steroid hormones was approved by institutional review boards at the Johns Hopkins Bloomberg School of Public Health and the National Center for Health Statistics, US Centers for Disease Control and Prevention.

NHANES III was conducted in 2 phases (1988–1991 and 1991–1994). Participants were randomly assigned to morning or afternoon examination sessions. Unbiased national estimates of health and nutrition characteristics can be generated when using either phase and the morning or afternoon sessions. For our analysis, 2205 men aged 20 years who attended the morning examination session of the first phase were eligible for inclusion. We selected the morning session to decrease the variance due to diurnal sex hormone production. The NHANES III repository held serum from 1470 of these men. We excluded men with a self-reported history of cancer ($n = 40$); missing testosterone, estradiol, or SHBG concentrations ($n = 21$); missing data on hematocrit ($n = 26$); and missing data on percent body fat, physical activity, smoking status, or number of cigarettes smoked per day ($n = 110$), leaving a final study population of 1273 men.

Measurement of Hematocrit

Detailed documentation of the laboratory methods used to measure hematocrit in NHANES III has been published (Gunter, 1996). Whole blood was collected in tubes containing EDTA, and a complete blood count was performed (Gunter, 1996). Hematocrit was calculated using a Coulter S-Plus Jr electronic counter (Coulter Electronics, Hialeah, Florida) (Gunter, 1996).

Sex Steroid Hormones

Sex steroid hormone concentrations were measured in blood samples that were centrifuged, aliquoted, and subsequently stored at -70°C in Dr Nader Rifai's laboratory (Children's Hospital, Boston, Massachusetts). Competitive electrochemiluminescence immunoassays were performed on a 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, Indiana) to measure serum concentrations of testosterone, estradiol, and SHBG. Laboratory technicians were blinded to sample identifiers and participant characteristics. The lowest detection limits of the assay were testosterone, 20 ng/dL; estradiol, 5 pg/mL; and SHBG, 3 nmol/L. Coefficients of variation for quality control specimens were testosterone, 5.9% and 5.8% at 2.5 and 5.5 $\mu\text{g/L}$, respectively; estradiol, 6.5% and 6.7% at 102.7 and 474.1 $\mu\text{g/L}$, respectively; and SHBG, 5.3% and 5.9% at 5.3 and 16.6 nmol/L, respectively. In a separate quality control sample run for this study, the interassay coefficient of variation was 2.5% for an estradiol concentration of 39.4 pg/mL, which is in the range of typical male estradiol concentrations. Serum hormone concentrations detected in the men in NHANES III were generally within the range of reference values used for men (testosterone, 194–833 ng/dL; estradiol, 50 pg/mL [Beers et al, 2006]; and SHBG, 13–71 nmol/L [Fauci et al, 2008]). Serum total testosterone, total estradiol, SHBG, and albumin concentrations were used to estimate free testosterone and free estradiol levels with mass action equations (Vermeulen et al, 1999; Rinaldi et al, 2002).

Assessment of Covariates

Covariates considered in the analysis were those known to influence either hormone concentrations or hematocrit. Participants in NHANES III provided information on age, race/ethnicity, smoking status, number of cigarettes smoked per day, and physical activity. A standardized method was used to code and classify each type of physical activity by rate of energy expenditure (Ainsworth et al, 1993; Rohrmann et al, 2005). Weekly frequency of moderate and vigorous walking, jogging, or running; biking; swimming; aerobics; dancing; calisthenics; gardening; and lifting weights was measured. Other physical activities were considered to be at the moderate level if they met age-specific cutoffs of the metabolic equivalent (MET) of the activity when compared with rest: 3 METs for ages 20 to 39 years; 2.5 METs for ages 40 to 64 years; 2.0 METs for ages 65 to 79 years, and 1.26 METs for ages 79 years. Levels of moderate physical activities were categorized as follows: 0, 0 to 4.7, and 4.8 times/week. Additionally, those who were able to walk 1 mile

without stopping, irrespective of whether the intent was exercise, were categorized as being physically active (>0 times/week). Percent body fat was calculated from bioelectric impedance, height, and weight measurements using previously published formulas (Plan and operation of the Third National Health and Nutrition Examination Survey, 1994; Chumlea et al, 2002). A trained examiner measured height and weight. Bioelectrical impedance was estimated using a 1990B Bio-Resistance body composition analyzer (Valhalla Scientific, San Diego, California).

Statistical Analysis

Statistical analyses were performed using SUDAAN (Research Triangle Park, North Carolina) as implemented in SAS version 9.1 (Cary, North Carolina) software. In each analysis, we applied sampling weights. Those in the highest 10th percentile of hematocrit (>47.7%) were categorized as having high hematocrit, those in the lowest 10th percentile of hematocrit (<41.0%) were categorized as having low hematocrit, and those with hematocrit between 41.0% and 47.6% were categorized as having normal hematocrit. Select participant characteristics were compared among those with low, normal, and high hematocrits. Both crude and age-adjusted means and proportions were calculated.

Total testosterone, total estradiol, SHBG, free testosterone, and free estradiol levels were categorized into tertiles based on the distributions among all men included in the analysis. Multivariable logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals of low hematocrit compared with normal hematocrit and high hematocrit compared with normal hematocrit by tertile of hormone concentrations, with the lowest hormone tertile as the reference group. The models were adjusted for age, race/ethnicity, smoking status (current, former, never) and number of cigarettes smoked per day by current smokers, physical activity, percent body fat, and other hormone levels (tertiles of total estradiol, total testosterone, and SHBG levels were simultaneously included in a model, free testosterone was adjusted for tertiles of total estradiol, and free estradiol was adjusted for tertiles of total testosterone).

The mean hematocrit levels of men with low and high concentrations of testosterone, estradiol, SHBG, free testosterone, and free estradiol were compared with the mean hematocrit levels of men with normal concentrations of these hormones. Cut points for low hormone concentrations were based on either clinical cut points or the 10th percentile of the distribution: total testosterone, <250 ng/dL (Greenspan, 1994); total estradiol, <20 pg/mL (Greenspan, 1994); SHBG, <13 nmol/L (Bukowski et al, 2000); free testosterone, <5 ng/dL (Greenspan, 1994); and free estradiol, <0.59 pg/mL (10th percentile). The cut points for high hormone concentrations were defined as 90th percentile as follows: total testosterone, 800 ng/dL; total estradiol, 50.0 pg/mL; SHBG, 66 nmol/L; free testosterone, 160 ng/dL; and free estradiol, 1.37 pg/mL. Multivariable linear regression was used to estimate mean hematocrit concentrations, adjusted for age, race/ethnicity, percent body fat, current smoking status and number of cigarettes smoked per day by current smokers, and frequency of physical activity and mutually adjusted for other hormones. A subanalysis was carried out, restricting the analysis to men aged 50 years because these men were more likely to have lower testosterone, estradiol, and hematocrit levels.

We repeated the analysis excluding men with chronic kidney disease (CKD) because this condition is a common cause of anemia and then further stratified by the presence or absence of major chronic diseases to assess whether prevalent disease explained the association between hormones and hematocrit (ie, reverse causation) based on our hypothesis in the Figure. We considered prevalent chronic disease to be a history of diabetes, emphysema, chronic bronchitis, stroke, myocardial infarction, or congestive heart failure.

Results

Selected characteristics of this study population are shown in Table 1. After age adjustment, the mean hematocrits in those with low, normal, and high levels were 39.3%, 44.3%, and 48.9%, respectively. The mean age was 41.5 years. Men with low hematocrits were significantly older (51.3 years) than those with normal hematocrits (40.5 years), and men with high hematocrits were significantly younger (39.4 years) than those with normal hematocrits ($P < .05$). After adjustment for age, men with low hematocrits were more likely to be non-Hispanic African American and less likely to be non-Hispanic white or Mexican American than those with normal hematocrits ($P < .05$). There was no difference in percent body fat by hematocrit category. Men with high hematocrits were more likely to be current smokers, in agreement with prior analyses (Whitehead et al, 1995). After age adjustment, those with high hematocrits were less likely to be physically active than those with normal hematocrits ($P < .05$), consistent with previous findings (Wannamethee et al, 2002).

Table 2 presents ORs of low (<41%) and high hematocrits (≥47.7%) across tertiles of total and free estradiol, total and free testosterone, and SHBG levels after multivariable adjustment. Men with concentrations of total estradiol in the highest tertile had almost 3 times the odds of high hematocrit (OR, 2.84; 95% confidence intervals, 1.05, 7.66; $P_{\text{trend}} = .04$) than men in the lowest tertile. The odds of high hematocrit also increased with increasing tertiles of free estradiol level ($P_{\text{trend}} = .09$). Although not statistically significant, there was a suggestion that men in the highest tertiles of total and free testosterone and total estradiol levels had decreased odds of low hematocrit (Table 2).

We repeated these analyses excluding men with CKD, and the results were similar (see Supplemental Table, available online at www.andrologyjournal.org). When we excluded men with CKD and then stratified by prevalent chronic disease, the associations of total ($P_{\text{trend}} = .04$) and free estradiol ($P_{\text{trend}} = .07$) levels with high hematocrit in men without prevalent chronic disease were similar to the overall findings, whereas these associations were not present in men with prevalent chronic diseases (Table 3).

Mean hematocrit did not differ in men who had low, normal, or high total testosterone concentrations (Table 4). However, men with low free testosterone concentrations had a lower hematocrit (43.6%) compared with men in the normal range of free testosterone (44.3%; $P = .03$); the finding was similar when the analysis was restricted to men aged ≥50 years (42.4% vs 43.7%, respectively; $P = .008$). Hematocrit levels were significantly lower in men with both low SHBG (hematocrit, 41.4%; $P < .001$) and high SHBG (hematocrit, 43.8%; $P = .01$) levels as compared with normal SHBG levels (hematocrit, 44.4%). For men aged ≥50 years, those with high SHBG concentrations had lower hematocrits than men with normal SHBG levels (42.7% vs 43.8%; $P = .01$) (Table 4).

Table 5 summarizes the most important findings in this manuscript.

Discussion

Both low and high hematocrit levels have detrimental health effects. Increased mortality has been documented in patients with anemia, as well as those with erythrocytosis, which may increase predilection for thrombosis through multiple mechanisms (Gagnon et al, 1994; Izaks et al, 1999; Elliott and Tefferi, 2005; Penninx, 2007). Thus, it is important to identify predictors of both high and low levels of hematocrit among men. In this nationally representative sample of men, we found that men with clinically low free testosterone levels had lower hematocrits than men with the normal range of free testosterone. We also observed that high total and free estradiol concentrations were associated with high hematocrit. In addition, both low and high SHBG levels were associated with low

hematocrit; the association between high SHBG level and low hematocrit was similar when the analysis was restricted to men aged ≥ 50 years, whereas the association between low SHBG level and hematocrit was nonsignificant. Although the observed differences in hematocrit were often small (1% to 3%), they were statistically significant, and changes of as little as 2% in hematocrit have been shown to be associated with significant increases ($\geq 20\%$) in the frequency of major ischemic heart disease events (Carter et al, 1983; Wannamethee et al, 1994).

Our finding that men with clinically low concentrations of free testosterone (<5 ng/dL) had significantly lower hematocrits than those with free testosterone in the normal range is compatible with findings in clinical studies that consistently show an association between low total testosterone level, via surgical or chemical depletion, and low hematocrit (Weber et al, 1991; Fonseca et al, 1998). Our findings are also consistent with those of Ferrucci et al (2006), who in the Tuscany InCHIANTI study of men aged ≥ 65 years, found that those with low total and bioavailable testosterone concentrations had a higher odd of anemia as assessed by hemoglobin and that men with low baseline bioavailable testosterone had an increased risk of developing anemia. In that study, men with lower total testosterone levels had 5 times the odds of anemia than those with higher total testosterone levels and those with lower free testosterone levels had 13 times the odds of anemia than those with higher free testosterone levels. The smaller OR for total testosterone levels seen by Ferrucci et al (2006) and the lack of significant effect of lower total testosterone levels in our study could be explained by the high variability of older men in SHBG and albumin levels, both of which have strong effects on the bioactive portion of total testosterone. With respect to men aged ≥ 50 years in our analysis, low free testosterone levels were also associated with a lower hematocrit. The stronger associations observed in the InCHIANTI study than in our study may be due to the older age and thus lower testosterone levels of the men. Unlike clinical studies in which pharmacological doses of exogenous testosterone were administered, resulting in an elevated hematocrit (Tenover, 1992; Sih et al, 1997; Snyder et al, 2000; Saad et al, 2007), we did not observe an increased risk of high hematocrit levels in the highest free or total testosterone tertiles. Similar to our analysis, Yeap et al (2009) explored a cross-sectional analysis of 492 men from Australia aged 30 to 94 years and found that overall, hemoglobin and SHBG levels were inversely correlated. In addition, free testosterone levels were associated with hemoglobin levels, consistent with our findings (Yeap et al, 2009). We hypothesized that androgens would be associated with hematocrit because they are known to activate hematopoietic stem cells and stimulate erythropoietin production, thereby regulating hematopoiesis (Besa, 1994). We did not have a hypothesis about the association between estradiol and hematocrit because to our knowledge, there is no direct mechanistic link between estradiol and erythropoiesis. Yet, we found that men with higher concentrations of total and free estradiol were less likely to have low hematocrits and more likely to have high hematocrits, even after adjustments for total testosterone level and percent body fat. We adjusted for testosterone, which is converted to estradiol via catalysis by aromatase in fat, to be able to determine the independent association for estradiol. Our results for estradiol are compatible with a clinical study of testosterone supplementation in hypogonadal men that found that 12 of 14 men with an elevated hematocrit also had elevated estradiol levels (Dobs et al, 1999). As previously mentioned, estradiol blunts the effects of hypoxia on erythropoietin production in women but has unclear significance in men and would not explain our findings; thus, another possibility is that these findings occurred by chance.

The relationship between SHBG and hematocrit appears to be complex. Consistent with a prior Japanese study of men aged 52 to 74 years (Kato et al, 1992), in our study, high SHBG levels were associated with lower hematocrit levels overall and among men aged ≥ 50 years. The finding that low SHBG concentrations were associated with lower hematocrit in our

overall study population is a novel finding to our knowledge. There is no known mechanism for this finding; however, the different trends seen with age could relate to the fact that SHBG starts to rise in the fourth and fifth decades in men (Feldman et al, 2002) and steroid negative feedback is known to change as men age (Winters and Wang, 2009). In addition, the association between SHBG and hematocrit could be affected by confounding disease states such as liver disease.

Based on previous analysis of the NHANES III data, anemia appears to be related to a deficiency in iron, vitamin B₁₂, and/or folate in one-third of cases, renal insufficiency in one-third, and unexplained anemia in the remaining third of patients (Guralnik et al, 2004). Although renal insufficiency is a known cause of low erythropoietin production, in multivariable-adjusted models, the odds of a glomerular filtration rate <60 mL/min/1.73 m² did not change with tertiles of hormones with the exception of high free estradiol levels having 3 times the odds of a decreased glomerular filtration rate (Yi et al, 2009). In sensitivity analyses, we excluded men with chronic kidney disease and the result was not remarkably changed (see Supplemental Table).

In healthy men, altered hematocrit may mediate the association between hormones and health outcomes; however, in men with chronic disease, the disease may alter both hematocrit and hormone levels. Thus, we stratified by the presence of major chronic disease. In men without prevalent chronic disease, the association between high estradiol levels and high hematocrit was similar to that of the main analysis; however, in the men with prevalent chronic disease, no associations were observed between any of the hormone levels and hematocrit. Thus, there was no evidence supporting our hypothesis that disease status will alter both hematocrit and hormone levels; however, we could not take into account the duration or severity of these diseases or the nature or success of the treatments for these diseases.

To our knowledge, this is the first study to examine the association between sex steroid hormones and hematocrit in a large, nationally representative sample of the US adult male population. The men in this study were aged 20 years, allowing the association between hormones and hematocrit to be evaluated in an age range wider than that in previous studies of older men. Similarly, this analysis benefited from the standardized measurement of demographic characteristics, anthropometric measures, and laboratory analytes. The large sample size and resulting power of the NHANES III analysis provided us with a unique opportunity to detect small differences even after adjustment for relevant covariates, including measures of smoking. Analyses of hemoglobin showed results similar to those for hematocrit (data not shown). However, the study was limited by insufficient power involving men with prevalent disease (Table 3) and men aged >50 years (Table 4). An important limitation of our study is that the cross-sectional design did not allow for discerning the temporality of the observed associations of sex steroid hormones and SHBG with hematocrit.

In this nationally representative study of men, sex steroid hormones, in particular total and free estradiol, free testosterone, and SHBG, appeared to influence hematocrit levels. Although causal relationships cannot be determined from our analysis, future studies should be conducted to address whether it might be beneficial to treat older men who have low circulating testosterone, estradiol, or SHBG levels to increase hematocrit levels and general well-being.

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Men without Prevalent Chronic Disease **Men with Prevalent Chronic Disease** **Figure.**

Possible explanations for the observation that changes in hormone levels may alter hematocrit, leading to a change in health outcomes.

Table 1
Selected characteristics of 1273 men in the morning session of Phase I of NHANES III overall and for those with low (<41%) and high (47.7%) hematocrit as compared with normal hematocrit (41% to 47.6%)

Characteristic ^a	Total (n = 1273)	Unadjusted Values			Age-Adjusted Values		
		Low Hematocrit (n = 187)	Normal Hematocrit (n = 964)	High Hematocrit (n = 122)	Low Hematocrit (n = 187)	Normal Hematocrit (n = 964)	High Hematocrit (n = 122)
Age, y ^b	41.5 (0.7)	51.3 (1.6)	40.5 (0.8)	39.4 (1.6)	...	...	...
Age categories, % ^b							
20–29 y	26.4 (2.4)	12.2 (3.6)	27.9 (3.1)	28.4 (6.0)	...	...	...
30–39 y	26.2 (2.4)	14.6 (3.9)	27.8 (2.7)	25.2 (5.3)	...	...	...
40–49 y	19.9 (1.5)	22.5 (4.2)	19.5 (1.8)	20.5 (6.4)	...	...	...
50–59 y	12.0 (1.1)	18.8 (2.5)	10.4 (1.3)	17.5 (4.6)	...	...	...
60–69 y	9.4 (1.3)	15.6 (4.0)	9.1 (1.2)	5.9 (1.7)	...	...	...
70–79 y	4.7 (0.6)	11.9 (2.9)	4.1 (0.6)	2.1 (1.0)	...	...	...
80 y	1.4 (0.3)	4.5 (1.5)	1.1 (0.2)	0.5 (0.3)	...	...	...
Race/ethnicity, % ^{b,d}							
Non-Hispanic white	77.8 (3.2)	73.4 (4.4)	78.5 (3.2)	76.2 (6.7)	70.5 (5.0)	79.1 (0.03)	76.8 (6.7)
Non-Hispanic African American	9.4 (1.4)	21.0 (3.3)	8.4 (1.3)	5.3 (1.5)	23.5 (4.0)	8.2 (1.2)	5.1 (1.4)
Mexican American	5.0 (0.8)	3.0 (0.8)	5.2 (0.9)	5.7 (1.2)	3.5 (1.0)	4.9 (0.9)	5.3 (1.1)
Other	7.9 (2.2)	2.6 (1.5)	7.9 (2.2)	12.7 (6.3)	2.5 (1.6)	7.9 (2.2)	12.8 (6.3)
Hematocrit, % ^{b,c,d,e}	44.3 (0.2)	39.2 (0.1)	44.4 (0.1)	48.9 (0.1)	39.3 (0.1)	44.3 (0.1)	48.9 (0.1)
Percent body fat, %	24.9 (0.3)	24.5 (0.7)	24.8 (0.3)	25.9 (0.8)	23.7 (0.8)	24.9 (0.3)	26.0 (0.8)
Smoking, % ^{b,c,e}							
Never	35.0 (2.4)	28.6 (5.3)	36.8 (2.6)	27.6 (6.9)	34.6 (5.8)	36.4 (5.8)	27.0 (6.8)
Former	31.0 (2.8)	48.1 (3.6)	30.7 (3.0)	19.5 (6.2)	38.6 (4.0)	30.3 (2.9)	17.3 (6.2)
Current	34.0 (2.3)	23.3 (4.6)	32.6 (2.5)	55.0 (6.8)	26.8 (5.5)	33.3 (2.6)	55.7 (6.7)
Cigarettes smoked per day by current smokers ^{b,d}	19.3 (1.0)	15.2 (1.5)	19.2 (1.3)	21.0 (1.1)	14.6 (1.5)	19.3 (1.2)	20.9 (0.9)
Physical activity, % ^e							
0 times/wk	8.4 (1.4)	10.4 (2.0)	7.9 (1.6)	10.2 (4.2)	8.8 (1.8)	7.7 (1.3)	12.8 (3.5)

Characteristic ^a	Total (n = 1273)	Unadjusted Values			Age-Adjusted Values		
		Low Hematocrit (n = 187)	Normal Hematocrit (n = 964)	High Hematocrit (n = 122)	Low Hematocrit (n = 187)	Normal Hematocrit (n = 964)	High Hematocrit (n = 122)
<4.8 times/wk	40.6 (2.3)	40.4 (3.7)	39.0 (2.3)	52.3 (7.9)	41.9 (3.2)	39.4 (2.4)	48.2 (3.5)
4.8 times/wk	51.1 (3.0)	49.2 (4.1)	53.1 (3.0)	37.5 (7.7)	49.3 (4.5)	52.9 (3.1)	39.0 (6.4)

Abbreviation: NHANES III, Third National Health and Nutrition Examination Survey.

^aMean or percentage (standard error).

Indicates a significant unadjusted difference between

^b_{low} and normal hematocrit and

^c_{high} and normal hematocrit ($P < .05$).

Indicates a significant age-adjusted difference between

^d_{low} and normal hematocrit and

^e_{high} and normal hematocrit ($P < .05$)

Table 2
Association^a of tertiles of hormones with clinically low (<41%) and high (47.7%) hematocrit in men in the morning session of Phase I of NHANES III

		Hematocrit					
		Low vs Normal			High vs Normal		
	Tertile	Range	OR	95% CI	OR	95% CI	
Total testosterone, ng/dL	1	<433	1.00	Reference	1.00	Reference	
	2	433–600	1.08	0.48, 2.39	1.69	0.82, 3.48	
	3	601	0.63	0.30, 1.32	1.16	0.45, 3.03	
			<i>P</i> _{trend} = .2			<i>P</i> _{trend} = 1.0	
Total estradiol, pg/mL	1	<31.5	1.00	Reference	1.00	Reference	
	2	31.5–40.7	0.78	0.35, 1.72	1.50	0.57, 3.92	
	3	40.8	0.61	0.33, 1.14	2.84	1.05, 7.66 ^b	
			<i>P</i> _{trend} = .1			<i>P</i> _{trend} = .04	
SHBG, nmol/L	1	<29.2	1.00	Reference	1.00	Reference	
	2	29.2–44.8	1.69	0.80, 3.57	0.81	0.23, 2.87	
	3	44.9	1.63	0.85, 3.13	1.31	0.29, 5.90	
			<i>P</i> _{trend} = .2			<i>P</i> _{trend} = .7	
Free testosterone, ng/dL	1	<8.4	1.00	Reference	1.00	Reference	
	2	8.4–12.0	0.52	0.24, 1.14	0.72	0.23, 2.21	
	3	12.1	0.63	0.28, 1.45	0.64	0.18, 2.26	
			<i>P</i> _{trend} = .2			<i>P</i> _{trend} = .5	
Free estradiol, pg/mL	1	<0.794	1.00	Reference	1.00	Reference	
	2	0.794–1.04	0.86	0.42, 1.80	1.11	0.46, 2.68	
	3	1.05	0.81	0.39, 1.68	2.23	0.79, 6.24	
			<i>P</i> _{trend} = .5			<i>P</i> _{trend} = .09	

Abbreviations: CI, confidence intervals; NHANES III, Third National Health and Nutrition Examination Survey; OR, odds ratio; SHBG, sex hormone-binding globulin.

^a Adjusted for age, race/ethnicity, smoking status, cigarettes smoked per day by current smokers, physical activity, percent body fat, and mutual adjustment for other hormones.

^b *P* < .05.

Table 3

Association^a of tertiles of hormones with clinically low (<41%) and high (>47.7%) hematocrit in men with (n = 182) and without (n = 996) prevalent chronic disease and who do not have chronic kidney disease in the morning session of Phase I of NHANES III

Hematocrit													
LOW Vs Normal													
	Tertile	Range	None			Prevalent Chronic Disease			High vs Normal			Prevalent Chronic Disease	
			OR	95% CI		OR	95% CI		OR	95% CI			
Total	1	<433	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference
testosterone,	2	433–600	1.37	0.52, 3.58		0.53	0.14, 1.95		1.42	0.61, 3.26		2.50	0.26, 23.62
ng/dL	3	601	0.64	0.29, 1.43		0.45	0.04, 4.82		1.01	0.35, 2.92		3.84	0.08, 183.60
				<i>P</i> trend = .1			<i>P</i> trend = .4			<i>P</i> trend = .9			<i>P</i> trend = .4
Total estradiol,	1	<31.5	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference
pg/mL	2	31.5–40.7	0.95	0.36, 2.50		0.42	0.16, 1.10		1.47	0.53, 4.03		2.87	0.52, 15.65
	3	40.8	0.78	0.37, 1.64		0.40	0.06, 2.66		3.03 ^b	1.08, 8.52		0.95	0.06, 14.53
				<i>P</i> trend = .5			<i>P</i> trend = .3			<i>P</i> trend = .04			<i>P</i> trend = .6
SHBG, nmol/L	1	<29.2	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference
	2	29.2–44.8	1.94	0.77, 4.87		3.68	0.62, 21.97		0.68	0.18, 2.60		6.56	0.33, 130.47
	3	44.9	1.65	0.70, 3.90		4.59	0.84, 25.14		1.18	0.22, 6.45		6.15	0.52, 70.75
				<i>P</i> trend = .3			<i>P</i> trend = .09			<i>P</i> trend = .9			<i>P</i> trend = .4
Free testosterone	1	<8.4	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference
ng/dL	2	8.4–12.0	0.48	0.20, 1.15		0.68	0.15, 3.09		0.53	0.16, 1.77		1.17	0.23, 5.99
	3	12.1	0.53	0.22, 1.28		2.81	0.36, 21.71		0.46	0.12, 1.74		2.21	0.17, 28.83
				<i>P</i> trend = .2			<i>P</i> trend = .4			<i>P</i> trend = .3			<i>P</i> trend = .5
Free estradiol,	1	<0.794	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference
pg/mL	2	0.794–1.04	0.79	0.28, 2.22		1.08	0.28, 4.19		1.03	0.37, 2.83		2.37	0.26, 21.27
	3	1.05	0.94	0.37, 2.34		0.50	0.11, 2.21		2.41	0.84, 6.93		1.11	0.10, 12.88
				<i>P</i> trend = .7			<i>P</i> trend = .3			<i>P</i> trend = .07			<i>P</i> trend = .9

Abbreviations: CI, confidence intervals; NHANES III, Third National Health and Nutrition Examination Survey; OR, odds ratio; SHBG, sex hormone-binding globulin.

^a Adjusted for age, race/ethnicity, smoking status, cigarettes smoked per day, physical activity, percent body fat, and mutual adjustment for other hormones. Prevalent chronic disease includes history of diabetes, emphysema, chronic bronchitis, stroke, myocardial infarction, or congestive heart failure.

$P < .05$.

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Mean hematocrit among men with low, normal, and high concentrations of hormones in the morning session of Phase I of NHANES III

Table 4

	20 Years				50 Years			
	n	Hematocrit, % (SE) ^a	P		n	Hematocrit, % (SE) ^a	P	
Total testosterone, ng/dL								
Low: <250	77	44.1 (0.46)	.5		58	43.4 (0.39)	.6	
Normal: 250–800	1065	44.3 (0.14)	Reference		440	43.6 (0.15)	Reference	
High: 801	131	44.3 (0.46)	.9		30	43.3 (0.67)	.3	
Total estradiol, pg/mL								
Low: <20.0	37	45.1 (0.40)	.06		17	44.0 (0.67)	.6	
Normal: 20.0–50.0	1080	44.3 (0.14)	Reference		454	43.6 (0.16)	Reference	
High: 50.0	156	44.7 (0.26)	.07		57	43.7 (0.48)	.9	
SHBG, nmol/L								
Low: <13	19	41.4 (0.78)	.001		3	42.4 (2.04)	.5	
Normal: 13–66	1126	44.4 (0.14)	Reference		423	43.8 (0.17)	Reference	
High: 66	128	43.8 (0.23)	.01		102	42.7 (0.32)	.01	
Free testosterone, ng/dL								
Low: <50	100	43.6 (0.34)	.03		88	42.4 (0.43)	.008	
Normal: 50–160	1053	44.3 (0.15)	Reference		434	43.7 (0.16)	Reference	
High: 161	120	44.6 (0.48)	.7		6	45.9 (1.38)	.1	
Free estradiol, pg/mL								
Low: <0.59	123	43.8 (0.28)	.07		73	43.7 (0.57)	.9	
Normal: 0.59–1.37	1041	44.3 (0.15)	Reference		419	43.6 (0.20)	Reference	
High: 1.37	132	44.7 (0.29)	.2		36	43.0 (0.55)	.3	

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; SE, standard error; SHBG, sex hormone-binding globulin.

^a Adjusted for age, race, percent body fat, smoking status, cigarettes per day, physical activity, and mutually adjustment for other hormones.

Table 5
Summary of key findings

Hormone Level	Association With Hematocrit	Significance
Low free testosterone	Lower hematocrit	$P = .03$
High free estradiol	Higher hematocrit	$P_{\text{trend}} = .09$ (not significant)
High total estradiol	Higher hematocrit	$P_{\text{trend}} = .04$
Low and high SHBG in men 20 years	Lower hematocrit	$P = .001$ and $P = .01$, respectively
High SHBG in men 50 years	Lower hematocrit	$P = .01$

Abbreviation: SHBG, sex hormone-binding globulin.