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## Association of cigarette smoking, alcohol consumption and physical activity with sex steroid hormone levels in U.S. men

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### Abstract

**Background**—We evaluated the associations of smoking, alcohol consumption, and physical activity with sex steroid hormone concentrations among 1,275 men 20–90 years old who participated in the Third National Health and Nutrition Examination Survey (NHANES III).

**Methods**—Serum concentrations of testosterone, estradiol and sex hormone-binding globulin (SHBG) were measured. We compared geometric mean concentrations across levels of smoking, alcohol, and physical activity using multiple linear regression.

**Results**—Current smokers had higher total testosterone (5.42, 5.10 and 5.26 ng/mL in current, former and never smokers), free testosterone (0.110, 0.102 and 0.104 ng/mL), total estradiol (40.0, 34.5 and 33.5 pg/mL) and free estradiol (1.05, 0.88 pg/mL and 0.84 pg/mL) compared with former and never smokers (all  $P \leq 0.05$ ). Men who consumed  $\geq 1$  drink/day had lower SHBG than men who drank less frequently (31.5 vs. 34.8 nmol/L,  $P=0.01$ ); total ( $P$ -trend=0.08) and free testosterone ( $P$ -trend=0.06) increased with number of drinks per day. Physical activity was positively associated with total ( $P$ -trend=0.01) and free testosterone ( $P$ -trend=0.05).

**Conclusions**—In this nationally-representative sample of men, smoking, alcohol and physical activity were associated with hormones and SHBG, thus these factors should be considered as possible confounders or upstream variables in studies of hormones and men's health, including prostate cancer.

### Medical Subject Headings

hormones; men; physical activity; alcohol; smoking

## INTRODUCTION

Sex steroid hormone concentrations have been previously shown to be associated with health conditions in men, including prostate cancer [1], diabetes [2,3], low bone mineral density [4], lower urinary tract symptoms [5], impaired cognitive function [6,7] and cardiovascular disease [8–10]. In previous studies published in NHANES III, low free and bioavailable testosterone were associated with type 2 diabetes [2], low free estradiol and low free testosterone were associated with osteopenia [4], and increased androstenediol glucuronide and total estradiol were associated with lower urinary tract symptoms [5]. Additionally, men with low free testosterone, low bioavailable testosterone, and low estradiol had a higher risk of mortality, while men with low SHBG had a lower risk of mortality [11], which was consistent with some, but not all previous studies [12].

To reduce the risk of these and other hormone-associated conditions, factors that influence hormone levels, but are modifiable, need to be identified. Age [13,14] and race [13–15] are well-established, but non-modifiable, predictors of sex steroid hormone concentrations in men. Adiposity is a well-known modifiable predictor of sex steroid hormones in men [14,16–20], however, much less is known about the association of other modifiable risk factors, such as cigarette smoking, alcohol consumption and physical activity with sex steroid hormones. In some studies, current smokers had higher circulating concentrations of total testosterone, free testosterone, total estradiol and sex hormone-binding globulin (SHBG) [16,18–23], a carrier of both testosterone and estradiol in circulation. The association between alcohol consumption and sex steroid hormone concentrations has been inconsistent, with some evidence suggesting no association [16–19], and other evidence supporting increased levels of androstenediol glucuronide [16], and estradiol [17], and decreased levels of SHBG [18] with increased alcohol consumption. Few studies have addressed the association between physical activity and hormone levels, with inconsistent findings [16–19]. Additionally, endurance athletes may have lower concentrations of free and total testosterone than non-athletes [24,25]. Previous studies of cigarette smoking, alcohol consumption and physical activity with sex steroid hormones and SHBG levels in men were limited by small sample sizes [22], were restricted to older men [17], or both [20].

The objective of this study was to investigate the association of cigarette smoking, alcohol consumption and physical activity with sex steroid hormones and SHBG in a nationally-representative sample of adult men in the Third National Health and Nutrition Examination Survey (NHANES III). If these lifestyle factors are shown to be associated with sex steroid hormone concentrations among men, they should be considered as possible confounders or upstream variables (variables that are related to the outcome only via their influence on sex steroid hormones) in future studies of hormones and men's health. Because of the wealth of information collected in NHANES III, we were able to examine various measures of cigarette smoking, alcohol consumption and physical activity, and rigorously control for the possible confounding effects of known and suspected correlates of hormone levels such as demographic characteristics, percent body fat and other hormones.

## METHODS

### Study population

NHANES III was conducted between 1988 and 1994 by the National Center for Health Statistics. NHANES III was designed as a cross-sectional study using a multistage stratified, clustered probability sample of the U.S. civilian non-institutionalized population. Children, older adults, non-Hispanic blacks, and Mexican Americans were over-sampled to produce more precise estimates for these groups. Interviews were conducted with all participants and physical examinations were performed at a mobile examination center.

NHANES III was conducted in two phases (1988–1991 and 1991–1994). Unbiased national estimates can be independently produced for each phase. Within each phase, subjects were randomly assigned to participate in either the morning or afternoon/evening examination session. Morning sample participants were chosen for this hormone study to reduce variation due to diurnal production of sex hormones. Of the 2,205 men who participated in the morning session of Phase I (1988–1991), 1,470 were 20 years of age or older and had available serum samples in the repository. Men were excluded if they self-reported a history of prostate cancer (n=12), as certain treatments may alter hormone levels, or if they were confined to a wheelchair or had leg paralysis (n=57), as physical activity may be limited. Additionally, men with missing or extremely low hormone values, based on the distribution on the natural logarithmic scale (n=53) (total testosterone <1.5 ng/mL, SHBG <5.5 nmol/L, androstenediol glucuronide <1.0 ng/mL, free testosterone <0.02 ng/mL and free estradiol <0.22 pg/mL – no observations were excluded for total estradiol), and men missing information on exposures or percent body fat (n=73) were excluded, for a final study population of 1,275 men.

### Hormone measurements

Stored serum samples, which had been aliquotted and stored at  $-70^{\circ}\text{C}$  since the time of the survey, were assayed for sex steroid hormones at the Children's Hospital Boston, MA. Testosterone, estradiol, and SHBG concentrations were measured by competitive electrochemiluminescence immunoassays on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN) in 2005. Androstenediol glucuronide, an indicator of the conversion of testosterone to dihydrotestosterone, was measured by an enzyme immunoassay (Diagnostic Systems Laboratories, Webster, TX). Laboratory technicians were blinded to participant characteristics. The detection limits of the assays were: testosterone 0.02 ng/mL, estradiol 5 pg/mL, androstenediol glucuronide 0.33 ng/mL, and SHBG 3 nmol/L. The coefficients of variation for quality control specimens were as follows: testosterone 5.9% and 5.8% at 2.5 and 5.5 ng/mL; estradiol 2.5%, 6.5% and 6.7% at 39.4, 102.7 and 474.1 pg/mL; androstenediol glucuronide 9.5% and 5.0% at 2.9 and 10.1 ng/mL; and SHBG 5.3% and 5.9% at 5.3 and 16.6 nmol/L. Free testosterone was estimated from total testosterone, SHBG, and albumin and free estradiol was estimated from total estradiol, SHBG and albumin using mass action equations [26,27].

### Exposure measurements

Information on age, race/ethnicity, cigarette smoking, alcohol consumption and physical activity was collected during the interview. Participants were classified as never, former and current smokers based on self-reported smoking habits; participants were asked if they had smoked more than 100 cigarettes in their lifetime and if they were current smokers. Serum cotinine, a metabolite of nicotine, was analyzed using high performance liquid chromatography/atmospheric-pressure ionization tandem mass spectrometry [28]. Participants were categorized as either unexposed to tobacco smoke (cotinine below the limit of detection of <0.035 ng/mL), as passively exposed only (0.35 to 9.99 ng/mL), or as actively exposed ( $\geq 10$  ng/mL) [29]. Additionally, current smokers were categorized into groups based on cigarettes smoked per day, pack-years smoked and serum cotinine concentrations.

Frequency of alcohol consumption was measured by a food frequency questionnaire. Participants reported the number of times in the past month that they drank beer, wine and hard liquor. Frequency of alcohol consumption was calculated as the sum of monthly beer, wine, and hard liquor intake. We categorized the frequency of total alcohol consumption or consumption of types of beverages as 0, <1/month, 1–3/month, 1–6/week,  $\geq 1$ /day. Alcohol consumption (in grams/day) was also evaluated with a 24-hour dietary recall and

categorized into quartiles of consumption for the purposes of our analysis. Grams of alcohol consumed as evaluated by the 24-hour dietary recall and by the food frequency questionnaire were found to be correlated with each other ( $r=0.37$ ;  $p\text{-value}<0.0001$ ). Frequency of heavy episodic drinking was assessed during the alcohol and drug assessment component of the examination by asking participants how many times in the past year they had consumed at least five alcoholic drinks in one day.

A standardized scheme [30] was utilized to code and classify each reported physical activity by rate of energy expenditure. Moderate physical activities included walking, jogging or running, biking, swimming, aerobics, dancing, calisthenics, gardening and lifting weights. Other physical activities were considered to be moderate if they met age-specific cut-offs of the metabolic equivalent (METs) of the activity when compared with being at rest:  $\geq 3.0$  METs for ages 20–39 years;  $\geq 2.5$  METs for ages 40–64 years;  $\geq 2.0$  METs for ages 65–79 years and  $\geq 1.26$  METs for men age 80 years or older. Jogging or running was considered to be a vigorous physical activity for all men. Swimming and aerobics were also classified as vigorous for men 40 years or older. Biking, dancing, gardening and calisthenics were also classified as vigorous for men 65 years or older. For men 80 years and older, walking and lifting weights were also classified as vigorous. Activities at the following age-specific METs were also considered to be vigorous:  $\geq 7.2$  METs for ages 20–39 years,  $\geq 6.0$  METs for ages 40–64 years,  $\geq 4.8$  METs for ages 65–79 years and  $\geq 3.0$  METs for age 80 years and older [31]. Weekly total physical activity (both moderate and vigorous physical activity) and weekly vigorous physical activity were categorized into quartiles.

Percent body fat was included as a covariate in our analysis. A trained examiner measured height, weight and bioelectrical impedance analysis (BIA) resistance. BIA measurement of resistance was assessed using the Valhalla 1990B Bio-Resistance Body Composition Analyzer (Valhalla Scientific, Sand Diego, CA, USA) [32]. We calculated percent body fat from the BIA data using previously published formulas [33].

### Statistical Analysis

All statistical analyses were performed using SUDAAN 9.0 (Research Triangle Park, NC) as implemented in SAS v.9.1 (Cary, NC) software. In all analyses, we applied the Phase I morning sampling weights to account for the complex NHANES sampling design, including unequal probabilities of selection, over-sampling, and non-response [34]. Hormones and SHBG were transformed using the natural logarithm to normalize their right-skewed distributions. Geometric means and their 95% confidence intervals (CIs) were calculated from multivariable linear regression models adjusted for total testosterone, total estradiol, SHBG, androstanediol glucuronide, free testosterone and free estradiol by exposure category. All models included terms for adjustment for age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other race/ethnicity), percent body fat (continuous), mutual adjustment for other exposures of interest (smoking status (never, former, current), alcohol consumption measured by food frequency questionnaire (0 drinks/month, <1 drink/month, 1–3 drinks/month, 1–6 drinks/week and  $\geq 1$  drink/day) and total physical activity (quartiles of weekly total activity), as well as mutual adjustment for the other hormones in quartiles (total testosterone, total estradiol and SHBG adjusted for each other; free testosterone adjusted for total estradiol; free estradiol adjusted for total testosterone). Estradiol and testosterone compete to bind with SHBG, and estradiol, testosterone and SHBG are significantly correlated with each other [1,35]. In our study, the correlation coefficients were:  $r=0.45$  ( $p<0.0001$ ) for total testosterone and total estradiol,  $r=0.36$  ( $p<0.0001$ ) for total testosterone and SHBG and  $r=0.07$  ( $p=0.05$ ) for total estradiol and SHBG. Therefore, as we have done in our other publications [2,4,15], we mutually adjusted for other hormones in the analyses to be able to identify independent associations. We use percent body fat instead of body mass index to be consistent with our previous

analyses in NHANES III. Percent body fat is a measure of adiposity, whereas body mass index combined both fat and lean mass and varies by race/ethnicity and age. Tests for trend were conducted for all measures of alcohol consumption and physical activity, and for cigarettes smoked per day, pack-years smoked and categories of serum cotinine among current smokers. We additionally examined associations stratified by age (at or above and below the median age of 44 years), and tested for interactions by age by including a cross-product term in a separate model. Tests for heterogeneity were calculated with multivariable linear regression for smoking status and active, passive or no smoke exposure measured by cotinine. All tests were two-sided with  $\alpha=0.05$ .

## RESULTS

The weighted mean age was 41.5 years (Table 1). The study population consisted of 78.9% non-Hispanic white, 9.1% non-Hispanic black, 5.0% Mexican-American, and 7.1% men of other race/ethnicities. The geometric mean hormone concentrations were 5.27 ng/mL for total testosterone, 0.106 ng/mL for free testosterone, 36.0 pg/mL for total estradiol, 0.919 pg/mL for free estradiol, 34.4 nmol/L for SHBG, and 12.0 ng/mL for androstanediol glucuronide.

In the multivariable-adjusted model, current smokers had higher concentrations of total testosterone (the geometric means were 5.42, 5.10 and 5.26 ng/mL in current, former and never smokers, respectively), free testosterone (0.110, 0.102 and 0.104 ng/mL), total estradiol (40.0, 34.5 and 33.5 pg/mL) and free estradiol (1.05, 0.878 and 0.844 pg/mL) than former and never smokers (all  $P\leq 0.05$ ) (table 2). Former smokers appeared to have lower concentrations of both total and free testosterone than never smokers, although the differences were not statistically significant ( $P=0.3$  and  $0.6$ , respectively). Concentrations of androstanediol glucuronide ( $P=0.2$ ) and SHBG ( $P=0.7$ ) did not differ by smoking status. However, a significant interaction was observed between age and smoking status and androstanediol glucuronide ( $P$ -interaction=0.01), such that older men ( $\geq 44$  years) who were current smokers (never: 11.6 ng/mL; former: 10.5 ng/mL; current: 9.1 ng/mL) had lower androstanediol glucuronide than never smokers ( $P=0.06$ ) (younger men  $<44$  years: never: 12.7 ng/mL; former: 13.7 ng/mL; current: 13.2 ng/mL). Men currently actively exposed to tobacco smoke, as measured by cotinine, also had higher concentrations of testosterone, free testosterone, estradiol, and free estradiol compared with men unexposed (i.e., neither active, nor passive exposure) to tobacco smoke. Men passively exposed to cigarette smoke also had greater total testosterone (5.21 compared with 4.90 ng/mL,  $P=0.03$ ) and free testosterone (0.104 compared with 0.096 ng/mL,  $P=0.005$ ) concentrations than those unexposed to tobacco smoke. Compared with never smokers, men unexposed to cigarette smoke based on cotinine concentration had lower concentrations of total and free testosterone. This difference is likely due to the never smoker category consisting of men with both no exposure and passive exposure to tobacco smoke. Among current smokers, no dose-response relationship was seen between cigarettes smoked per day, pack-years smoked or serum cotinine and concentrations of total testosterone, SHBG, androstanediol glucuronide or free testosterone (all  $P$ -trend $>0.4$ ). However, higher daily number of cigarettes smoked, pack-years smoked and serum cotinine were all associated with greater concentrations of total estradiol and free estradiol (all  $P$ -trend $\leq 0.06$ ; table 2).

In a sub-analysis, we re-defined current smokers as those who were self-reported current smokers and were active smokers based on cotinine concentration; never smokers were redefined as self-reported never smoker and had cotinine concentration in the no exposure range. Using these definitions, total testosterone (5.42 vs. 4.95 ng/mL;  $P=0.04$ ), free testosterone (0.110 vs. 0.096 ng/mL;  $P=0.009$ ), total estradiol (40.0 vs. 33.8 pg/mL;  $P<0.001$ ) and free estradiol (1.05 vs. 0.84 pg/mL;  $P=0.001$ ) concentrations were higher in

current smokers than in never smokers, findings that were consistent with those seen when defining smoking status based on self-report only or based on cotinine only.

In the multivariable model, men with usual intake of at least one drink per day had lower concentrations of SHBG than men who consumed 0 to 6 drinks/week (31.5 vs. 34.8 nmol/L,  $P=0.01$ ) (table 3); the inverse trend was statistically significant ( $P$ -trend=0.01). The frequency of alcohol consumption was positively associated with total testosterone ( $P$ -trend= 0.08) and free testosterone ( $P$ -trend=0.06), although these associations were not statistically significant. An interaction ( $P$ -interaction=0.06) was observed between age and the frequency of alcohol consumption with total and free testosterone. Both total ( $P$ -trend=0.06) and free ( $P$ -trend=0.05) testosterone increased with an increasing number of drinks consumed per day among younger (<44 years), but not older men ( $P$ -trend=0.4 and  $P$ -trend=0.3, respectively). No consistent patterns were seen between the amount of alcohol consumed, as measured by the 24-hour dietary recall, or the frequency of heavy episodic drinking and any of the hormones or SHBG. Additionally, no associations were observed between specific types of alcohol (beer, wine and liquor) and serum hormone and SHBG concentrations (data not shown).

In the multivariable model, men in the highest category of frequency of physical activity had higher concentrations of both total (5.42 vs. 5.05 ng/mL;  $P=0.003$ ) and free testosterone (0.109 vs. 0.098 ng/mL;  $P=0.005$ ) and lower concentrations of both total (35.2 vs. 38.1 pg/mL;  $P=0.009$ ) and free estradiol (0.88 vs. 0.95 pg/mL;  $P=0.09$ ) than those who reported no physical activity, although the trends in concentrations across activity levels were not statistically significant (table 4). Age was found to modify the association between physical activity and both total and free estradiol ( $P$ -interaction=0.004), such that total and free estradiol concentrations decreased with increasing frequency of physical activity among younger men (<44 years;  $P$ -trend=0.03 and  $P$ -trend=0.03, respectively), but not older men ( $\geq 44$  years;  $P$ -trend=0.7 and  $P$ -trend=0.5, respectively). In contrast, men who engaged in vigorous physical activity at least four times a week had higher concentrations of total estradiol than men who engaged in no physical activity (37.3 vs. 35.5 pg/mL;  $P=0.09$ ). No associations were seen between total or vigorous physical activity and androstanediol glucuronide or SHBG.

## DISCUSSION

In this large, representative sample of U.S. men, current cigarette smokers had higher concentrations of total testosterone, total estradiol, free testosterone and free estradiol compared with never smokers, current drinkers had lower concentrations of SHBG and possibly higher testosterone and free testosterone levels compared with non-drinkers, men who engaged frequently in physical activity had higher concentrations of total and free testosterone compared with sedentary men, and men who engaged in vigorous physical activity had higher concentrations of total estradiol compared with sedentary men.

### Cigarette smoking

Our study is consistent with previous research reporting that male current smokers had higher concentrations of both total and free testosterone than never smokers [16,18,19,22]. Former smokers did not have higher total and free testosterone levels than never smokers, suggesting that the association between cigarette smoke and hormones is reversible following smoking cessation. We did not observe a dose-response relationship between the number of cigarettes smoked and concentrations of total testosterone or free testosterone, which was consistent with some previous findings [16,20], but not others [17,21,23]. The biological mechanisms for a possible direct relationship between smoking and testosterone remain unclear. Smoking may alter testosterone secretion from the Leydig cells [21].

Although some studies in animal models support this theory, testosterone levels were found to decrease when rats were exposed to cigarette smoke [36], in contrast to the higher testosterone levels among smokers in our study. Another potential mechanism is that cigarette smoke and nicotine may act as aromatase inhibitors [37,38], reducing the conversion of testosterone to estradiol, thus increasing testosterone concentrations. This inhibition of aromatase by cigarette smoke might be a possible explanation for the association that we observed between passive smoke and hormone levels as well as active smoking. Men passively exposed to cigarette smoke had elevated mean total and free testosterone concentrations, approaching levels observed among active smokers.

However, not consistent with the aromatase explanation, we observed that total and free estradiol concentrations were higher in current smokers than in never smokers, with a positive dose-response relationship seen with increasing number of cigarettes smoked per day and number of pack-years smoked. Similar associations were observed in the Rancho Bernardo Study in California [23] and the Tromso study in Norway [21]. Other studies, however, found no association between smoking and estradiol levels in men [17,18,22], perhaps due to lack of adjustment for age [17,22] and other important covariates [22]. The higher estradiol concentrations observed among smoking compared with never smoking men in this study are also disparate with studies of women, which have found women smokers have significantly lower estrogen than non-smokers [39].

Previous studies have reported higher SHBG concentrations among current smokers [16,18,19,22], while we observed no association. The association seen in previous studies may be due to confounding by testosterone and estradiol, which were adjusted for in our study, but not in previous research [16,18,19,21,22]. Consistent with this explanation for the SHBG findings in other studies, in our study population, in analyses unadjusted for testosterone and estradiol, current smokers were observed to have significantly greater concentrations of SHBG than former and never smokers (the geometric means of SHBG were 37.0, 33.5 and 33.1 nmol/L in current, former and never smokers, respectively;  $P \leq 0.005$ ).

### Alcohol consumption

Our results, based on either the food frequency questionnaire or the 24-hour dietary recall, are consistent with previous studies that reported no or a positive association between alcohol consumption habits and total and free testosterone concentrations [16–20,40]. In contrast, one study found lower concentrations of testosterone in male alcoholics, and proposed that alcohol abuse may damage the Leydig cells or impair the hypothalamic-pituitary-gonadal axis [41]. These effects may only be seen among those with chronic exposure to high levels of alcohol, while the men in our study had relatively low levels of alcohol consumption. Men who consumed more than one alcoholic drink per day had significantly lower levels of SHBG than those who consumed no alcohol, despite previous studies reporting no association [19,40]. The difference in findings for alcohol and SHBG in our study and other studies may be due to lack of adjustment for cigarette smoking or total testosterone in previous studies [19,40]. The biological explanation for the association of alcohol drinking with SHBG is unknown. Interestingly, studies of men with alcoholic cirrhosis of the liver have increased SHBG concentrations when compared with those with normal liver function [42]. However, the increase in SHBG seen in our study occurred at a low level of alcohol consumption, thus it is unlikely that it is due to liver damage. Our results were similar when grams of alcohol per day were calculated from the food frequency questionnaire when compared with the 24-hour dietary recall, with the exception of SHBG, which was inversely associated with increasing amount of alcohol consumed ( $p$ -trend=0.07) based on the food frequency questionnaire, but not associated based on the dietary recall.

## Physical activity

Higher frequency of total physical activity was associated with higher total and free testosterone concentrations, consistent with one previous study [18], but not with two others that observed no association [16,17]. In contrast, no association was observed between vigorous physical activity and total or free testosterone in our study. Previous research has found that endurance athletes have lower mean concentrations of free and total testosterone [24,25], possibly due to alterations in the hypothalamic-pituitary-gonadal axis. This may suggest a nonlinear relationship between physical activity and testosterone, with a positive association among those with higher levels of general physical activity, no association among those with moderate levels of vigorous physical activity and an inverse association among those with extreme levels of vigorous activity. Additionally, those who reported vigorous physical activity more than four times a week had higher total estradiol concentrations than those who reported less frequent vigorous physical activity. These results are contrary to the intuition that those who engage in vigorous physical activity tend to have lower body fat, and thus should have lower estradiol production by adipocytes given the same testosterone level.

Several aspects of this study merit further discussion. The cross-sectional design of NHANES III precluded us from drawing conclusions regarding the temporality of the observed associations. For example, it is possible that higher testosterone concentrations could lead to greater muscle mass, thus increasing an individual's ability to exercise more frequently, rather than physical activity influencing testosterone concentrations directly. Reliance on self-report for many of the lifestyle factors may have led to misclassification. Additionally, there may have been confounding by unrecognized factors associated with smoking, alcohol, and physical activity and with hormone concentrations. The large sample size and the generalizability of these results to the adult United States male population are major strengths of this analysis. From an epidemiologic perspective, we were able to control for confounders that have not been previously measured or considered in other studies. We found mutual adjustment for other hormones to be of particular importance. In the absence of adjustment for testosterone and estradiol, current smokers had higher SHBG concentrations than never smokers, and we found a significant positive trend between frequency of physical activity and SHBG concentration. In contrast, after adjustment for testosterone and estradiol, no associations were seen between smoking status or physical activity and SHBG.

In conclusion, modifiable behaviors such as cigarette smoking, alcohol consumption and physical activity may be associated with concentrations of sex steroid hormones among adult men. The findings of this study suggest that future epidemiologic studies that examine the associations between sex steroid hormones and disease risk should carefully consider the role that cigarette smoking, alcohol consumption and physical activity may play, either as potentially confounding factors or factors upstream of hormone concentrations. Although previous studies were of men with either extreme behaviors (such as alcoholics) or clinically low levels of sex steroid hormones, the biological mechanisms possibly underlying the associations of smoking, alcohol drinking, and physical activity and hormones among men in the general population remain unclear. Future studies should work toward elucidating the biological mechanisms between these factors and sex steroid hormones among adult men in the general population with hormone levels within the normal range.

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**Table 1**

Selected Characteristics and Hormone Concentrations of 1,275 Adult Men Who Participated in the Third National Health and Nutrition Examination Survey (NHANES III)

Subject characteristics	Unweighted sample size	Mean or percentage (SE) <sup>*</sup>
Age, y	1,275	41.5 (0.7)
Race-ethnicity, %		
Non-Hispanic White	595	78.9 (3.0)
Non-Hispanic Black	304	9.1 (1.4)
Mexican-American	327	5.0 (0.8)
Other	49	7.1 (2.1)
Percent body fat, %	1,275	24.8 (0.3)
Smoking, %		
Never	438	34.3 (2.3)
Former	423	31.2 (2.9)
Current	414	34.4 (2.3)
Mean serum cotinine, (ng/mL)	1,266	101.5 (6.2)
Alcohol consumption, %		
0 drinks/month	466	30.8 (2.7)
<1 drink/month	225	16.9 (1.5)
1 to 3 drinks/month	178	15.5 (1.5)
1 to 6 drinks/week	252	24.6 (2.0)
≥ 1 drink/day	154	12.2 (1.9)
Frequency of physical activity, %		
0 times/week	165	7.93 (1.3)
0.1 to 2.9 times/week	390	29.6 (2.0)
3.0 to 7.9 times/week	361	29.9 (1.3)
≥ 8.0 times/week	359	32.6 (3.0)
Total testosterone (ng/mL) <sup>†</sup>	1,275	5.27 (0.09)
Free testosterone (ng/mL) <sup>†, a</sup>	1,275	0.106 (0.002)
Total estradiol (pg/mL) <sup>†</sup>	1,275	36.0 (0.7)
Free estradiol (pg/mL) <sup>†, a</sup>	1,275	0.919 (0.02)
SHBG (nmol/L) <sup>†</sup>	1,275	34.4 (0.7)
Androstenediol glucuronide (ng/mL) <sup>†</sup>	1,275	12.0 (0.3)

SE: standard error

<sup>\*</sup> sampling weights were applied

<sup>†</sup> geometric mean

<sup>#</sup> includes walking for at least one mile without stopping

<sup>a</sup> estimated using the mass action equation [26,27]

Table 2

Adjusted Geometric Mean Hormone and Sex Hormone-Binding Globulin (SHBG) Concentrations and 95% Confidence Intervals by Measures of Cigarette Smoking in a Nationally-Representative Sample of Adult Men in NHANES III

	Total Testosterone (ng/mL)	Total Estradiol (pg/mL)	SHBG (nmol/L)	Androstenediol glucuronide (ng/mL)	Free Testosterone (ng/mL)	Free Estradiol (pg/mL)
	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
<b>Smoking status (n=1275)</b>						
Never	5.26 (5.16, 5.36)	33.5 (31.5, 35.5)	33.8 (31.9, 35.8)	12.2 (11.5, 12.9)	0.104 (0.102, 0.106)	0.84 (0.80, 0.90)
Former*	5.10 (4.91, 5.31)	34.5 (33.1, 35.8)	34.8 (33.5, 36.2)	12.4 (11.7, 13.2)	0.102 (0.096, 0.108)	0.88 (0.86, 0.90)
Current*	5.42 (5.31, 5.53)	40.0 (39.3, 40.8)	34.8 (33.5, 36.2)	11.5 (10.6, 12.4)	0.110 (0.108, 0.112)	1.05 (1.01, 1.09)
<i>p</i> -heterogeneity	0.05	<0.001	0.7	0.2	0.007	<0.001
<b>Cotinine (ng/mL) (n=1269)</b>						
No exposure	4.90 (4.62, 5.20)	34.5 (31.3, 38.0)	34.1 (30.9, 37.6)	13.7 (12.0, 15.8)	0.096 (0.091, 0.102)	0.85 (0.74, 0.98)
Passive	5.26 (5.16, 5.36)	34.1 (32.8, 35.5)	33.8 (33.1, 34.5)	12.1 (11.6, 12.5)	0.104 (0.102, 0.106)	0.86 (0.83, 0.90)
Active	5.37 (5.26, 5.47)	39.3 (37.7, 40.8)	35.2 (33.8, 36.6)	11.7 (10.8, 12.7)	0.108 (0.105, 0.110)	1.01 (0.97, 1.05)
<i>p</i> -heterogeneity	0.04	<0.001	0.2	0.08	0.01	<0.001
<b>Current smokers only</b>						
<b>Cigarettes per day (n=414)</b>						
<1	4.95 (4.58, 5.36)	40.0 (37.0, 43.3)	38.9 (34.6, 43.7)	9.21 (7.28, 11.7)	0.099 (0.088, 0.112)	1.00 (0.91, 1.10)
1 to 9.9	5.75 (5.43, 6.10)	35.9 (33.2, 38.8)	35.5 (33.5, 37.7)	14.4 (11.4, 18.3)	0.115 (0.109, 0.122)	0.90 (0.81, 1.01)
10 to 19.9	5.26 (4.96, 5.58)	39.7 (38.1, 41.2)	34.5 (31.3, 38.0)	11.3 (9.43, 13.4)	0.105 (0.097, 0.114)	1.04 (0.96, 1.12)
20 to 29.9	5.53 (5.32, 5.75)	40.9 (39.3, 42.5)	34.1 (32.2, 36.2)	11.1 (9.71, 12.8)	0.112 (0.106, 0.119)	1.08 (1.03, 1.14)
30+	5.47 (5.26, 5.69)	42.1 (39.7, 44.7)	34.1 (31.6, 36.9)	11.1 (9.52, 13.0)	0.111 (0.107, 0.115)	1.12 (1.06, 1.18)
<i>p</i> -trend	0.99	0.02	0.4	0.8	0.8	0.002
<b>Pack-years (n=404)</b>						
<3	5.26 (5.06, 5.47)	39.7 (37.4, 42.1)	37.3 (34.5, 40.4)	13.6 (11.9, 15.6)	0.104 (0.098, 0.111)	0.99 (0.92, 1.07)
3 to 9.9	5.42 (5.11, 5.75)	39.7 (38.1, 41.2)	33.5 (31.5, 35.5)	12.6 (11.2, 14.1)	0.111 (0.104, 0.118)	1.04 (0.98, 1.10)
10 to 23.9	5.47 (5.26, 5.69)	39.7 (38.1, 41.2)	34.8 (32.2, 37.7)	10.8 (9.42, 12.4)	0.113 (0.107, 0.120)	1.04 (0.98, 1.10)
24+	5.47 (5.26, 5.69)	41.7 (40.1, 43.4)	34.1 (32.2, 36.2)	10.3 (8.28, 12.8)	0.110 (0.105, 0.114)	1.09 (1.03, 1.16)
<i>p</i> -trend	0.81	0.001	0.48	0.33	0.73	<0.001
<b>Cotinine (ng/mL) (n=414)</b>						

	Total Testosterone (ng/mL)	Total Estradiol (pg/mL)	SHBG (nmol/L)	Androstenediol glucuronide (ng/mL)	Free Testosterone (ng/mL)	Free Estradiol (pg/mL)
	<b>Geometric mean (95% CI)</b>	<b>Geometric mean (95% CI)</b>	<b>Geometric mean (95% CI)</b>	<b>Geometric mean (95% CI)</b>	<b>Geometric mean (95% CI)</b>	<b>Geometric mean (95% CI)</b>
<127.0	5.42 (5.21, 5.64)	37.0 (34.9, 39.2)	34.1 (31.6, 36.9)	11.9 (10.6, 13.4)	0.109 (0.102, 0.115)	0.96 (0.89, 1.04)
127.0–229.6	5.31 (5.11, 5.52)	40.9 (39.3, 42.5)	33.8 (31.9, 35.8)	10.8 (9.06, 12.9)	0.109 (0.102, 0.115)	1.09 (1.03, 1.16)
229.6–320.3	5.31 (5.11, 5.52)	41.7 (40.1, 43.4)	36.2 (34.2, 38.4)	10.4 (8.70, 12.4)	0.108 (0.103, 0.112)	1.07 (1.03, 1.12)
320.3+	5.70 (5.37, 6.04)	41.3 (38.9, 43.8)	35.2 (33.2, 37.3)	12.9 (11.3, 14.8)	0.115 (0.109, 0.122)	1.07 (1.01, 1.14)
<i>p-trend</i>	0.32	0.04	0.56	0.22	0.36	0.07

Analyses were adjusted for age, race/ethnicity, percent body fat, alcohol intake, total physical activity, and mutually adjusted for other hormones (testosterone, estradiol and SHBG adjusted for each other; free testosterone adjusted for total estradiol and free estradiol adjusted for total testosterone).

\* Current smokers included 1 man unexposed to cigarette smoke, 28 passively exposed and 384 actively exposed. Former smokers included 35 men unexposed to cigarette smoke, 324 passively exposed and 61 actively exposed. Never smokers included 30 men unexposed to cigarette smoke, 370 passively exposed and 33 actively exposed.

**Table 3**  
Adjusted Geometric Mean Hormone and Sex Hormone Binding Globulin (SHBG) Concentrations and 95% Confidence Intervals by Measures of Alcohol Consumption in a Nationally-Representative Sample of Adult Men in NHANES III

	Total Testosterone (ng/mL)	Total Estradiol (pg/mL)	SHBG (nmol/L)	Androstenediol glucuronide (ng/mL)	Free Testosterone (ng/mL)	Free Estradiol (pg/mL)
	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
<b>Usual alcohol intake (drinks)<sup>*</sup> (n=1,236)</b>						
0	5.16 (4.96, 5.36)	37.0 (35.6, 38.4)	35.5 (34.2, 36.9)	11.8 (10.5, 13.3)	0.102 (0.098, 0.106)	0.92 (0.87, 0.98)
<1/month	5.26 (5.06, 5.47)	35.5 (34.2, 36.9)	34.8 (33.5, 36.2)	11.7 (11.0, 12.4)	0.105 (0.101, 0.110)	0.90 (0.87, 0.94)
1 to 3/month	5.26 (5.06, 5.47)	34.5 (33.1, 35.8)	33.8 (31.2, 36.5)	12.2 (11.3, 13.2)	0.106 (0.102, 0.111)	0.89 (0.85, 0.92)
1 to 6/week	5.37 (5.26, 5.47)	35.9 (34.5, 37.3)	34.5 (32.5, 36.6)	12.2 (11.3, 13.2)	0.108 (0.103, 0.112)	0.92 (0.87, 0.98)
≥1/day	5.42 (5.11, 5.74)	36.2 (34.2, 38.4)	31.5 (29.1, 34.1)	12.4 (10.6, 14.5)	0.110 (0.103, 0.116)	0.96 (0.91, 1.02)
<i>p-trend</i>	0.08	0.99	0.01	0.52	0.06	0.21
<b>Alcohol (grams/day)<sup>†</sup> (n=1,275)</b>						
0	5.21 (5.11, 5.31)	35.9 (34.5, 37.3)	34.8 (34.1, 35.5)	11.8 (11.2, 12.5)	0.104 (0.102, 0.106)	0.91 (0.88, 0.95)
0.1 to 13.9	5.31 (5.11, 5.52)	35.2 (33.2, 37.3)	34.1 (30.9, 37.6)	11.1 (10.1, 12.3)	0.106 (0.100, 0.113)	0.90 (0.83, 0.97)
14.0 to 33.9	5.26 (5.06, 5.47)	36.6 (35.2, 38.1)	34.8 (32.8, 36.9)	12.6 (10.7, 14.7)	0.104 (0.100, 0.109)	0.92 (0.87, 0.98)
34 to 57.9	5.37 (4.96, 5.80)	36.2 (33.5, 39.2)	32.1 (28.9, 35.1)	13.5 (12.5, 14.6)	0.108 (0.099, 0.116)	0.96 (0.88, 1.03)
58+	5.53 (5.21, 5.86)	36.2 (32.9, 40.0)	34.8 (31.0, 39.2)	12.6 (10.3, 15.3)	0.112 (0.101, 0.123)	0.93 (0.85, 1.03)
<i>p-trend</i>	0.13	0.79	0.71	0.22	0.17	0.63
<b>Heavy episodic drinking (times/year) (n=789)</b>						
0	5.58 (5.37, 5.81)	35.2 (33.2, 37.3)	33.8 (32.5, 35.1)	13.3 (12.3, 14.4)	0.114 (0.110, 0.119)	0.91 (0.86, 0.97)
1 to 5	5.47 (5.26, 5.69)	35.2 (33.2, 37.3)	34.8 (32.8, 36.9)	12.8 (11.4, 14.4)	0.111 (0.107, 0.115)	0.89 (0.85, 0.92)
6 to 47	5.47 (5.37, 5.58)	36.2 (34.8, 37.7)	33.5 (31.5, 35.5)	11.6 (10.3, 13.0)	0.112 (0.108, 0.116)	0.93 (0.86, 1.01)
48 to 103	5.26 (4.86, 5.69)	37.3 (34.5, 40.4)	33.5 (30.3, 36.9)	11.6 (10.1, 13.3)	0.106 (0.098, 0.115)	0.96 (0.89, 1.04)
104+	5.53 (5.32, 5.75)	36.2 (34.8, 37.7)	32.8 (30.3, 35.5)	12.4 (10.4, 14.8)	0.112 (0.107, 0.120)	0.94 (0.89, 1.00)
<i>p-trend</i>	0.19	0.20	0.72	0.22	0.21	0.09

Analyses were adjusted for age, race/ethnicity, percent body fat, smoking status, total physical activity, and mutually adjusted for other hormones testosterone, estradiol and SHBG adjusted for each other; free testosterone adjusted for total estradiol and free estradiol adjusted for total testosterone.

<sup>\*</sup> Data from food frequency questionnaire

<sup>†</sup> Data from 24-hour dietary recall

Table 4

Adjusted Geometric Mean Hormone and Sex Hormone-Binding Globulin (SHBG) Concentrations and 95% Confidence Intervals by Total and Vigorous Physical Activity in a Nationally-Representative Sample of Adult Men in NHANES III

	Total Testosterone (ng/mL)	Total Estradiol (pg/mL)	SHBG (nmol/L)	Androstenediol glucuronide (ng/mL)	Free Testosterone (ng/mL)	Free Estradiol (pg/mL)
	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
<b>Total physical activity (times/week) (n=1,275)</b>						
0	5.05 (4.86, 5.26)	38.1 (35.9, 40.4)	37.0 (34.2, 40.0)	13.0 (11.1, 15.1)	0.098 (0.094, 0.102)	0.95 (0.88, 1.03)
0.1 to 2.9	5.21 (5.11, 5.31)	35.5 (34.2, 36.9)	34.1 (32.2, 36.2)	11.6 (10.3, 13.0)	0.104 (0.102, 0.106)	0.92 (0.89, 0.96)
3.0 to 7.9	5.21 (5.01, 5.42)	36.2 (34.8, 37.7)	33.8 (32.5, 35.1)	11.8 (11.2, 12.5)	0.103 (0.099, 0.107)	0.93 (0.90, 0.97)
≥8.0	5.42 (5.21, 5.64)	35.2 (33.8, 36.6)	35.5 (33.5, 37.7)	12.3 (11.4, 13.3)	0.109 (0.104, 0.113)	0.88 (0.83, 0.93)
<i>p-trend</i>	0.01	0.11	0.49	0.54	0.05	0.11
<b>Vigorous physical activity (times/week) (n=1,275)</b>						
0	5.21 (5.11, 5.31)	35.5 (34.2, 36.9)	34.8 (33.5, 36.2)	11.9 (11.3, 12.7)	0.103 (0.101, 0.105)	0.90 (0.87, 0.94)
0.1 to 1.0	5.21 (4.91, 5.52)	35.9 (33.8, 38.1)	34.1 (31.6, 36.9)	12.2 (10.8, 13.7)	0.104 (0.098, 0.111)	0.93 (0.88, 0.99)
1.1 to 4.0	5.47 (5.37, 5.58)	35.9 (34.5, 37.3)	33.5 (32.2, 34.8)	12.1 (10.7, 13.6)	0.110 (0.108, 0.112)	0.92 (0.87, 0.98)
>4	5.26 (4.96, 5.58)	37.3 (36.6, 38.1)	37.0 (34.2, 40.0)	11.7 (10.4, 13.2)	0.104 (0.096, 0.113)	0.92 (0.89, 0.96)
<i>p-trend</i>	0.40	0.11	0.34	0.75	0.68	0.46

Analyses were adjusted for age, race/ethnicity, percent body fat, smoking status, alcohol intake and mutually adjusted for other hormones testosterone, estradiol and SHBG adjusted for each other; free testosterone adjusted for total estradiol and free estradiol adjusted for total testosterone.