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Association of Serum Cholesterol and Cholesterol-Lowering Drug Use with Serum Sex Steroid Hormones in Men in NHANES III

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Abstract

Purpose—Low cholesterol levels and statin drugs may protect against prostate cancer with a worse prognosis. Their protective mechanism is unknown, but has been hypothesized to be related to cholesterol's role as a sex steroid hormone precursor. We evaluated whether serum testosterone and estradiol differ by cholesterol or cholesterol-lowering drug use.

Materials and Methods—Testosterone and estradiol were measured for 1,457 male participants in the Third National Health and Nutrition Examination Survey (NHANES III). We estimated multivariable-adjusted geometric mean hormone concentration by quintiles of cholesterol concentration and by cholesterol-lowering drugs use.

Results—Across quintiles of cholesterol, testosterone level did not differ (mean, 95% confidence interval (CI); Q1: 5.18, 4.90–5.47, Q5: 5.09, 4.80–5.40 ng/mL; *p-trend*=0.64), whereas estradiol levels were lower (Q1: 38.6, 36.9–40.3; Q5: 33.1, 31.8–34.5 pg/mL; *p-trend*<0.0001). Neither testosterone (no: 5.11, 4.96–5.27, yes: 5.19, 4.71–5.72 ng/mL, *p*=0.79) nor estradiol (no: 35.9, 34.8–37.1; yes: 34.1, 29.5–39.4 pg/mL; *p*=0.43) differed by cholesterol-lowering drugs use.

Conclusion—Testosterone did not differ by cholesterol or cholesterol-lowering drug use. Estradiol was lower in men with higher cholesterol, but did not differ by cholesterol-lowering drug use. Our results suggest that the lower risk of advanced prostate cancer among statin users is not readily explained by a cholesterol-mediated effect of statins on sex hormone levels.

Introduction

Low cholesterol and statin drugs,a class of cholesterol-lowering drugs, are hypothesized to protect against prostate cancer [1,2]. Several biologic mechanisms have been proposed by which they might reduce prostate cancer risk, although the mechanism remains unknown

[1]. Given the role of testosterone and its metabolite estradiol in prostate carcinogenesis [3], it has been hypothesized that reductions in circulating testosterone or estradiol via inhibition of cholesterol synthesis, their precursor, might inhibit prostate cancer development and growth [4].

Most clinical studies that compared hormone concentrations in men before and after statin therapy reported no change in testosterone concentration [5–12], although a few studies reported a small, non-significant decrease in testosterone concentration [13–15], and one found an increase in testosterone concentration [16]. While these studies do not support an important effect of statins on testosterone synthesis, most were small; only four [10,13,14,17] included more than 25 men and all had fewer than 200 men.

Most of the observational studies reported no difference in testosterone concentration between statin users and nonusers [4] and no association between circulating cholesterol and testosterone concentrations [18–32]. Three other studies found a positive association between cholesterol and testosterone [33–35], and two found an inverse association [36,37]. Many of the observational studies did not adjust for important potential confounders such as age [19–23,26,29,30,33,34,36]. Additionally, most of the observational studies only reported correlation coefficients or regression coefficients for a single continuous term in linear regression models. These methods assume a linear association between cholesterol and sex steroid hormone concentrations and might not detect non-linear associations.

Thus, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), a large, nationally representative study of the US population to investigate whether having a lower cholesterol concentration or use of a cholesterol-lowering drug is associated with lower testosterone and estradiol concentrations in men. Because Phase I of NHANES III was conducted when statin drugs were new to the market, too few men were using this class of drug to evaluate separately whether testosterone concentration differed between statin users and nonusers and between users and nonusers of other cholesterol-lowering drugs. Other cholesterol-lowering drugs are less effective at lowering cholesterol than statin drugs [38].

Materials and Methods

Study Population

NHANES III is a cross-sectional study conducted by the National Center for Health Statistics. The study is nationally representative of the U.S. civilian, non-institutionalized population. To calculate estimates more precisely in certain subgroups of the population, Mexican-Americans, non-Hispanic blacks, and the elderly were over-sampled. The study was conducted in two phases (1988–1991 and 1991–1994); unbiased national estimates can be obtained from either Phase 1 or Phase 2 separately or from both combined. For each phase, participants were randomly assigned to be examined either in the morning or in the afternoon. A total of 33,944 people were interviewed in NHANES III, 30,818 of whom gave blood samples and underwent physical examinations. Sex steroid hormone concentrations were assayed for 1,637 males ages 12 and older who participated in the morning examination of Phase 1 of NHANES III and for whom stored serum was still available in the repository. We measured hormones only for those participants who were examined in the morning to reduce diurnal variation in hormone levels. We excluded men <20 years of age (10.2%), men who had ever been diagnosed with prostate cancer (0.7%), men for whom percent body fat or waist circumference was not available (8.6%), and men for whom a total cholesterol measurement was not available (0.1%). After these exclusions, 1,457 men remained in the analytic sample. All protocols for the implementation of NHANES III were approved by the Institutional Review Board of the National Center for Health Statistics,

Centers for Disease Control and Prevention; informed consent was obtained for all participants. The Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health and the National Center for Health Statistics, Centers for Disease Control and Prevention approved the assay of stored serum specimens for the Hormone Demonstration Program.

Serum Sex Steroid Hormone and Cholesterol Measurements

Participants who were assigned to the morning examination session had blood drawn after fasting overnight. Concentrations of total testosterone, total estradiol (the major estrogen in men, which is produced from testosterone), and sex hormone binding globulin (SHBG) (their major carrier in circulation) were measured using a competitive electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis IN) in Dr. Rifai's laboratory at Children's Hospital Boston. Laboratory personnel were blinded to the participants' characteristics and samples were arranged in random order for testing. The lowest detection limits were 0.02 ng/mL for testosterone, 5 pg/mL for estradiol, and 3 nmol/L for SHBG. The coefficients of variation for embedded quality control samples were: testosterone 5.9% and 5.8% at 2.5 and 5.5 ng/mL; estradiol 6.5% and 6.7% at 102.7 and 474.1 pg/mL; and SHBG 5.3% and 5.9% at 5.3 and 16.6 nmol/L. Serum concentrations of testosterone and estradiol detected in this population were consistent with what are considered normal values for adult US men (testosterone, 1.94 – 8.33 ng/mL; estradiol, ≤ 50 pg/mL) [39]. Free testosterone and free estradiol were estimated from total testosterone and total estradiol, respectively, SHBG, and albumin concentrations using mass action equations [40,41]. Serum total cholesterol concentration was measured enzymatically previously in NHANES III [42].

Cholesterol-Lowering Drug Use and Covariate Assessment

During an in-person interview, participants were asked, "Have you ever been told by a doctor or other health professional that your blood cholesterol level was high?" If participants answered "yes" then they were asked, "Because of your high cholesterol, have you ever been told by a doctor or other health professional to take prescribed medicine?" If participants answered "yes", they were then asked, "To lower your blood cholesterol, are you now following this advice to take prescribed medicine?" We categorized participants who answered "yes" as taking cholesterol-lowering drugs' in this analysis. During a separate part of the interview, participants were also asked whether they were taking any prescription medications. If they answered yes, they were asked to provide the containers so that the interviewer could record the names of the prescriptions. Using this information, which was available for 25 of the 41 participants who were categorized as using a cholesterol-lowering drug, we determined that 44% of cholesterol-lowering drug users were using a statin. When we excluded from the group of men not taking cholesterol-lowering drugs those men who were told by their doctor that they had high cholesterol and then answered that they were not told to take prescribed medicine to lower their cholesterol or said that they did not follow the advice to take a prescribed medication to lower their cholesterol the results did not change (i.e., the geometric means changed by <2%), so we present our results without this exclusion.

In-person interviews were conducted to gather information on physical activity, cigarette smoking, and alcohol intake. Waist circumference, height, and weight were measured by trained NHANES personnel. Percent body fat was calculated from bioelectrical impedance analysis, measured height and weight, and age as described previously [43].

Statistical Analysis

All analyses were conducted using SUDAAN v 9.0 software (Research Triangle Park, NC) as implemented in SAS v 9.2 (Cary, NC). In all analyses we used the Phase I morning sampling weights and accounted for the NHANES complex survey design using methods recommended by NCHS [44]. We calculated the age-adjusted means or percentages of characteristics of the men by categories of cholesterol-lowering drug use and serum cholesterol by adjusting for the age distribution of the US population according to the 2000 Census. We calculated adjusted geometric mean concentrations of total and free testosterone and total and free estradiol and their 95% confidence intervals (CI) by quintile of serum cholesterol concentration (<169, 169-<192, 192-<212, 212-<236, ≥236 mg/dL) and by cholesterol-lowering drug use using linear regression. Hormone concentrations were not normally distributed, so we transformed them using the natural logarithm. We also calculated geometric mean hormone concentrations by deciles and clinical cutpoints of total cholesterol. The inferences were similar using each of these cutpoints, so we report the results by quintiles of cholesterol. Two multivariable models were run, one adjusting for age (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), and one further adjusting for factors that have been associated with hormone concentrations in previous NHANES III analyses: percent body fat (quintiles: <21, 21-<25, 25-<27, 27-<31, ≥31%), waist circumference (quintiles: <81.2, 81.2-<89.2, 89.2-<96.1, 96.1-<104.5, ≥104.5 cm), moderate or vigorous physical activity including walking for a mile without stopping (quintiles of times/week: <0.5, 0.5-< 2, 2-<6.5, 6.5-<10, ≥10), cigarette smoking (never, current, former), and alcohol intake (non-drinker, <1 drink/week, 1 drink/week-<1 drink/day, ≥1 drink/day). The results did not differ when we parameterized age as a restricted cubic spline with knots at the 5^{th}, 50^{th}, and 95^{th} percentiles or when we adjusted for serum cotinine, an indicator of active and passive exposure to cigarette smoke. We excluded men who used cholesterol-lowering drugs in a subanalysis for serum cholesterol. To limit the potential influence of co-morbidities on the results, we excluded men with significant comorbidities (cancer, myocardial infarction, stroke, angina, or diabetes) in subanalyses for serum cholesterol and for cholesterol-lowering drug use.

We stratified by age (20–39, 40–59, ≥60 years) to determine whether the results were consistent between younger men, who tend to have low cholesterol and high testosterone levels, and older men, who tend to have high cholesterol and low testosterone levels. When we examined the association between cholesterol-lowering drugs and hormones stratified by age, we restricted to men ≥40 years (40–59, ≥60 years) because use of cholesterol-lowering drugs in younger men was not common (N=3). We also stratified by percent body fat (tertiles) and waist circumference (tertiles). Statistical interaction was assessed by entering into the model main effects terms and a cross-product term for the stratification variable and either serum cholesterol or cholesterol-lowering drug use, the coefficient for which was evaluated using the Wald test.

Finally, we calculated multivariable-adjusted odds ratios (OR) and 95% CIs of clinically low total testosterone (≤3 ng/mL), free testosterone (≤0.07 ng/mL), and total estradiol (<20 pg/mL) comparing each clinical cutpoint of total cholesterol to the lowest clinical cutpoint and cholesterol-lowering drug use to nonuse after adjustment age and race/ethnicity using logistic regression. We excluded men whose total (≤2.16 ng/mL) and free (≤0.04 ng/mL) testosterone concentrations were extremely low (n=58 and 78, respectively), possibly due to congenital hypogonadism or treatment for prostate cancer. There is no clinical definition for low free estradiol in men; thus, this was not examined.

Results

Characteristics of the study population by quintiles of serum cholesterol concentration and by use of cholesterol-lowering drugs are shown in Tables 1a and 1b. At the time their blood was drawn, men with higher serum cholesterol tended to be older (Table 1a). After adjusting for age, men with higher cholesterol had a higher percent body fat and were less physically active. Men taking cholesterol-lowering drugs tended to be older (Table 1b). After adjusting for age, men taking cholesterol-lowering drugs were more likely to be non-Hispanic white, had a higher percent body fat, were less likely to be current smokers, and were less likely to drink alcohol daily.

Serum Cholesterol

Serum total testosterone concentration appeared to decrease over quintiles of cholesterol after adjustment for age and race/ethnicity (Table 2). However, testosterone did not differ by quintiles of cholesterol after multivariable adjustment (Table 2) or after further excluding men taking cholesterol-lowering drugs (n=41) (Table 2). None of the covariates individually explained the change in association after multivariable adjustment. Although men with major co-morbidities (n=243) had lower testosterone than men without major co-morbidities, the cholesterol-testosterone association was the same in men with major co-morbidities (multivariable-adjusted geometric mean, 95%: lowest quintile of total cholesterol 5.00, 4.33–5.77 ng/mL; highest quintile of total cholesterol 4.84, 3.89–6.03 ng/mL, *p-trend*=0.70) as for overall. As for total testosterone, there was no association between free testosterone and quintiles of cholesterol after multivariable adjustment (geometric mean, 95% CI: lowest quintile of total cholesterol 0.103, 0.098–0.107 ng/mL; highest quintile of total cholesterol 0.097, 0.091–0.104 ng/mL; *p-trend*=0.33). The association between cholesterol and total testosterone or free testosterone did not vary by age (*p-interaction*=0.13, 0.18*)*, percent body fat (*p-interaction*=0.75, 0.41), or waist circumference (*p-interaction*=0.65, 0.72). There was no association between clinical cutpoints of total cholesterol and clinically low testosterone (≥240 vs <200 mg/dL: age and race/ethnicity-adjusted OR=0.84, 95% CI 0.34–2.03; *p-trend*=0.89) or clinically low free testosterone (≥240 vs <200 mg/dL: age and race/ethnicity-adjusted OR=1.04, 95% CI 0.54–2.01; *p-trend*=0.92).

Total estradiol concentration was statistically significantly inversely associated with total cholesterol after adjustment for age and race/ethnicity; this association remained after multivariable adjustment (Table 2), after excluding men with major co-morbidities (data not shown), and after excluding men taking cholesterol-lowering drugs (Table 2). As for total estradiol, total cholesterol was inversely associated with free estradiol after multivariable adjustment (geometric mean, 95% CI: lowest quintile of total cholesterol 0.98, 0.93–1.05 pg/mL; highest quintile of total cholesterol 0.83, 0.79–0.87 pg/mL; *p-trend<0.0001*). The association between cholesterol and total estradiol or free estradiol did not vary by age (*p-interaction*=0.09, 0.32*)*, percent body fat (*p-interaction*=0.89, 0.80), or waist circumference (*p-interaction*=0.26, 0.18). Men with higher total cholesterol were more likely to have clinically low estradiol, but the result was not statistically significant (≥ 240 vs <200 mg/dL: age/race adjusted OR=2.91, 95% CI 0.61–13.90; *p-trend*=0.20).

Cholesterol-Lowering Drug Use

There was no association between use of cholesterol-lowering drugs and total testosterone, total estradiol concentration (Table 2), free testosterone (multivariable-adjusted geometric mean, 95% CI: no 0.102, 0.099–0.105 ng/mL; yes 0.111, 0.099–0.125 ng/mL; *p*=0.17), or free estradiol (no 0.92, 0.88–0.95 ng/mL; yes 0.89, 0.76–1.05 pg/mL; *p*=0.75). The association between cholesterol-lowering drugs and either testosterone or free testosterone

did not differ by age (both *p-interaction*>0.15). Total and free estradiol levels did not differ between users and nonusers of these drugs in men 60+ years old, but levels were lower in users (total estradiol 30.6 pg/mL, free estradiol 0.80 pg/mL) than nonusers (total estradiol 35.3, free estradiol 0.90 pg/mL) in men 40–59 years old (both *p-interaction*=0.02). The association between use of cholesterol-lowering medications and total and free hormones did not differ by percent body fat or waist circumference (all *p-interaction*>0.15).

Cholesterol-lowering drug use was not associated with clinically low testosterone (OR=0.93, 95% CI 0.38–2.28; *p*=0.88), clinically low free testosterone (OR=0.91, 95% CI 0.35–2.33; *p*=0.84), or clinically low estradiol (OR=1.93, 95% CI 0.42–8.76; *p*=0.38); this latter result is based on only 2 men with clinically low estradiol among cholesterol-lowering drug users.

Discussion

To our knowledge, this is the first report on the association of serum cholesterol and cholesterol-lowering drug use with serum sex steroid hormone concentrations in a nationally representative sample of US men. After taking into account modifiable factors associated with testosterone, we found no evidence that serum cholesterol or use of a cholesterol-lowering drug, 44% of which was a statin, was associated with levels of total or free testosterone or with prevalence of clinically low testosterone. The results for serum cholesterol did not change when men with major co-morbidities or men taking cholesterol-lowering drugs were excluded from the analysis. Our findings support those from the majority of previous studies on serum cholesterol, cholesterol-lowering drugs, and circulating testosterone concentration [5–12,17–32,45–47].

We also observed a statistically significant inverse association between serum cholesterol and total and free estradiol concentrations. However, this association was in the opposite direction we would have expected if cholesterol-lowering were causing a deficit of the precursor molecule for testosterone and, thus, estradiol synthesis. An alternative explanation for this observation is that men with higher cholesterol have more comorbidities and men with comorbidities such as diabetes [48] tend to have lower testosterone, thus possibly leading to lower estradiol production. However, when we excluded men with comorbidities the results were unchanged. Although two previous studies have observed an inverse association between total cholesterol and estradiol concentrations [21,23], the majority of previous studies have found no association [18–20,22,24,[26],28–30,35,36] and a few reported a positive association [25,32,37] between total cholesterol and estradiol in men. All of the studies that examined estradiol concentration before and after statin therapy found no change [7,12,17,45]. Our results in older men are consistent with these other studies, although we did observe in younger men that users of cholesterol-lowering drugs had lower total and free estradiol levels.

Several studies have observed an inverse association between statin use and advanced and/or high-grade prostate cancer [49–54], but the mechanisms by which statins may exert a protective effect remain unclear. Our data suggest that it is unlikely that the degree of cholesterol-lowering by a statin would reduce serum testosterone and thus, prostate cancer risk; cholesterol is present in approximately a 300,000 times higher concentration in circulation than testosterone in men, making it unlikely that even the 17–35% serum cholesterol reduction achieved with statin therapy [55] would substantially influence testosterone production.

However, we cannot rule out the possibility that there may be an association with testosterone at extremely low concentrations of cholesterol, which was not evaluable using these data as most (53%) of the population had a cholesterol concentration above the cut

point for borderline high cholesterol (>200 mg/dL). However, we observed no association between serum cholesterol and testosterone concentrations even when we categorized serum cholesterol into deciles. The weighted mean cholesterol level among men in the lowest decile was 139 mg/dL, which is approximately 1.5 standard deviations lower than the estimated mean total cholesterol concentration of 203.6 mg/dL using the entire male NHANES III population over 20 years old.

Another possibility is that circulating cholesterol and testosterone concentrations may not reflect cholesterol and testosterone concentrations in the prostate. Thus, we cannot rule out the possibility of an association between intraprostatic cholesterol and testosterone concentrations.

Although we observed no association between the use of cholesterol-lowering drugs and serum testosterone concentration, only 44% of cholesterol-lowering drug users in our analytic cohort were using a statin (based on the 25 of the 41 cholesterol-lowering drug users for whom specific prescription information was available). Other classes of cholesterol-lowering drugs are not as effective at lowering cholesterol as statin drugs [38]. Thus, it is possible that had we been able to evaluate statin users separately, we may have observed an association. However, it seems likely that were there a profound association between cholesterol-lowering drug use and circulating testosterone concentration, we would have observed some difference in our analysis. Despite the fact that our sample size for evaluating the associations with cholesterol-lowering drug use was rather small (n=41), we had 80% power at $\alpha = 0.05$ to detect a difference of at least $+/- 0.4$ standard deviations in sex steroid hormone concentration between users and non-users of cholesterol-lowering drugs. However, we cannot rule out a subtle association between cholesterol-lowering drug use and sex steroid hormone concentrations. Our results are consistent with most clinical studies that have evaluated circulating testosterone concentration in patients before and after statin use, which have not observed any change after statin treatment [5–12].

Our study has several strengths including the use of nationally representative data. We were able to adjust for many potential confounding factors, conduct restricted analyses, and examine potential interactions. We estimated mean hormone concentrations by categories of cholesterol, which allowed us to detect non-linear associations. However, because NHANES III is a cross-sectional study, we were unable to examine the longitudinal association of change in use of cholesterol-lowering drugs or circulating cholesterol concentration with change in circulating hormone concentrations.

Conclusion

Overall, these data provide no evidence for associations of serum cholesterol and cholesterol-lowering drugs with circulating testosterone concentration. However, these data suggest that circulating cholesterol concentration, but not cholesterol-lowering drug use, may be inversely associated with circulating estrogen concentration in men. These findings for cholesterol help rule out the hypothesis that the mechanism by which statins protect against prostate cancer is by reducing cholesterol synthesis and thus, sex steroid hormone synthesis. Other cholesterol-dependent (e.g. Akt and sonic hedgehog signaling) and independent (eg. effects on inflammation and prenylation) mechanisms should be explored to explain the association between statin use and advanced prostate cancer.

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Table 1a

Age-Adjusted[†] Weighted Characteristics by Quintiles of Serum Total Cholesterol, Men, NHANES III 1988–1991

	Serum Total Cholesterol (mg/dL)				
	Q1 92 - <169	**Q2 169-<192**	**Q3 192-<212**	**Q4 212-<236**	**Q5 236 - 702**
N	249	246	270	265	286
Age (years)					
mean	34	39	43	45	48
Race (%)					
Non-Hispanic white	73.8	76.1	79.1	81.4	72.5
Non-Hispanic black	12.9	11.2	8.8	8.3	12.8
Mexican-American	6.2	5.3	3.7	4.4	7.4
Other race/ethnicity	7.1	7.4	8.5	5.9	7.4
Body Fat (%)					
mean	25.0	24.5	25.3	26.1	26.8
Waist Circumference (cm)					
mean	93.8	94.4	95.2	98.0	97.6
Physical Activity (times/ week)*					
mean	8.2	6.7	6.6	5.5	6.3
Cigarette Smoking (%)					
never	30.6	35.1	35.4	32.4	34.2
former	31.6	37.5	35.6	30.6	41.4
current	37.9	27.4	29.0	37.1	24.4
Alcohol Intake (%)					
non-drinker	36.3	31.7	32.4	36.5	28.9
>0-<1/week	9.2	11.4	9.3	11.1	18.0
≥1/week-<1/day	36.0	39.7	40.4	33.1	36.9
≥1/day	18.5	17.2	18.0	19.3	16.3

† Standardized to the 2000 US Census age distribution

* Includes walking for a mile without stopping

Table 1b

Age-Adjusted[†] Weighted Characteristics by Use of Cholesterol-Lowering Drugs, Men, NHANES III 1988–1991

	Current Use of Cholesterol-Lowering Drugs	
	No	**Yes**
N	1,275	41
Age (years)		
mean	42	60
Race (%)		
Non-Hispanic white	78.1	86.3
Non-Hispanic black	9.0	10.1
Mexican-American	5.0	3.6
Other race/ethnicity	7.9	0.0
Body Fat (%)		
mean	25.3	27.0
Waist Circumference (cm)		
mean	95.4	100.5
Physical Activity (times/ week)[*]		
mean	6.5	6.5
Cigarette Smoking (%)		
never	32.8	16.5
former	35.1	65.6
current	32.1	18.0
Alcohol Intake (%)		
non-drinker	32.9	17.6
>0-<1/week	11.3	4.8
≥ 1/week-<1/day	37.3	76.7
≥ 1/day	18.5	0.8

[†] Standardized to the 2000 US Census age distribution. The percentages of men in each racial/ethnic group by cholesterol-lowering drug use was not adjusted for age because of instability due to small numbers in strata of race/ethnicity and age among cholesterol-lowering drug users.

[*] Includes walking for a mile without stopping

Table 2

Geometric Mean (95% Confidence Intervals) Serum Testosterone and Estradiol Concentrations by Quintiles of Serum Total Cholesterol and by Cholesterol-lowering Drug Use, Men, NHANES III 1988–1991

	Testosterone (ng/mL)		Estradiol (pg/mL)	
	Model 1*	**Model 2†**	**Model 1***	**Model 2†**
Serum Cholesterol Concentration (mg/dL)				
All Men				
Q1: 72-<169	5.52 (5.32– 5.72)	5.25 (5.02 – 5.49)	38.6 (36.6– 40.6)	38.7 (36.9– 40.5)
Q2: 169-<192	5.18 (4.91– 5.45)	5.12 (4.89 – 5.36)	36.0 (34.2– 37.8)	36.3 (34.7– 37.9)
Q3: 192-<212	5.16 (4.79– 5.56)	5.20 (4.87 – 5.55)	36.3 (34.4– 38.4)	36.7 (34.9– 38.5)
Q4: 212–<236	4.89 (4.61– 5.20)	4.97 (4.71 – 5.23)	35.8 (33.7– 38.0)	34.9 (33.2– 36.8)
Q5: 236–702	4.87 (4.53– 5.23)	5.05 (4.76 – 5.37)	32.9 (31.2– 34.7)	33.1 (31.8– 34.5)
p-trend	*0.09*	*0.32*	*0.0003*	*<0.0001*
Excluding Cholesterol- Lowering Drugs Users				
Q1: 92<169	5.52 (5.32 – 5.73)	5.25 (5.02 – 5.49)	38.6 (36.6 – 40.6)	38.6 (36.8 – 40.5)
Q2: 169–<192	5.18 (4.91 – 5.47)	5.11 (4.88 – 5.36)	36.0 (34.2 – 37.8)	36.3 (34.7 – 37.9)
Q3: 192–<212	5.18 (4.80 – 5.60)	5.21 (4.87 – 5.58)	36.6 (34.8 – 38.5)	36.9 (35.2 – 38.6)
Q4: 212–<236	4.89 (4.60 – 5.20)	4.97 (4.71 – 5.24)	35.8 (33.7 – 37.9)	34.9 (33.2 – 36.7)
Q5: 236–702	4.86 (4.51 – 5.23)	5.03 (4.73 – 5.34)	32.9 (31.1 – 34.7)	33.1 (31.7 – 34.6)
p-trend	*0.03*	*0.43*	*0.004*	*< 0.0001*
Cholesterol-Lowering Drug Use				
No	5.12 (4.94– 5.30)	5.11 (4.97– 5.26)	35.9 (34.6– 37.3)	35.9 (34.8– 37.1)
Yes	4.91 (4.33– 5.57)	5.16 (4.67– 5.70)	32.9 (28.0– 38.6)	33.9 (29.4– 39.2)
p	*0.57*	*0.87*	*0.22*	*0.39*

*Adjusted for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other)

†Adjusted for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), percent body fat (quintiles), waist circumference (continuous), physical activity (quintiles of times/week), cigarette smoking (never, current, former), and alcohol intake (non-drinker, <1 drink/week, 1 drink/week-<1 drink/day, ≥1 drink/day)