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Serum selenium and serum lipids in US adults: National Health and Nutrition Examination Survey (NHANES) 2003–2004

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Abstract

OBJECTIVE—High selenium has been recently associated with several cardiovascular and metabolic risk factors including diabetes, blood pressure and lipid levels. We evaluated the association of serum selenium with fasting serum lipid levels in the National Health and Nutrition Examination Survey (NHANES) 2003–2004, the most recently available representative sample of the US population that measured selenium levels.

METHODS—Cross-sectional analysis of 1159 adults ≥40 years old from NHANES 2003–2004. Serum selenium was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometry. Fasting serum total-cholesterol, triglycerides, and HDL cholesterol were measured enzymatically and LDL cholesterol was calculated.

RESULTS—Mean serum selenium was 136.7 μg/L. The multivariable adjusted average differences (95% confidence interval) comparing the highest (≥147 μg/L) to the lowest (<124 μg/L) selenium quartiles were 18.9 (9.9, 28.0) mg/dL for total cholesterol, 12.7 (3.3, 22.2) mg/dL for LDL cholesterol, 3.9 (0.4, 7.5) mg/dL for HDL cholesterol, and 11.5 (−7.6, 30.7) mg/dL for triglycerides. In spline regression models, total and LDL cholesterol levels increased progressively with increasing selenium concentrations. HDL cholesterol increased with selenium but reached a plateau above 120 μg/L of serum selenium (20th percentile). The triglyceride-selenium relationship was U-shaped.

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CONCLUSION—In US adults, high serum selenium concentrations were associated with increased serum concentrations of total and LDL cholesterol. Selenium was associated with increasing HDL cholesterol only at low selenium levels. Given increasing trends in dietary selenium intake and supplementation, the causal mechanisms underlying these associations need to be fully characterized.

Keywords

Selenium; Serum Lipids; NHANES

INTRODUCTION

Selenium is involved in several important biological pathways, particularly in the defense system against oxidative stress. Because of this potential to protect against oxidative stress, high expectations were raised for selenium as a preventive factor for several chronic diseases including cancer, cardiovascular disease (CVD), and type 2 diabetes, conditions associated with oxidative stress [1]. However, recent epidemiological evidence has raised concerns about the safety and health effects of selenium intake above the Recommended Dietary Allowance (55 μg/d) 2. In the US, a country in which virtually all the population has selenium intake above 55 μg/d 2, increasing selenium levels have been associated with higher prevalence of diabetes and hypertension 3–5. Furthermore, selenium supplementation in clinical trials has failed to reduce the risk of cardiovascular events and may increase the risk of diabetes [6–8].

In the US Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, high serum selenium concentrations were positively associated with serum total, LDL, and HDL cholesterol and with serum triglycerides [9]. Widespread increases in use of selenium-containing supplements and of lipid lowering medications since the early 1990s have likely changed the distribution of both selenium and lipids. However, there is no recent data on these associations. The objective of this study was to evaluate the association of serum selenium with the concentrations of serum lipid fractions using recently available NHANES data collected in 2003–2004.

MATERIALS AND METHODS

The National Center for Health Statistics conducts periodic NHANES surveys using a complex multistage sampling design to obtain a representative sample of the civilian non-institutionalized US population. We used data from NHANES 2003–2004 [10], the most recent release with selenium data available in adults. Participants aged ≥40 years (N = 3,299) were eligible for selenium measurement according to NHANES protocol. Among them, 1,302 participated in the morning examination and had a fasting blood sample. We excluded participants with missing serum selenium levels (N = 29), dietary intakes (N = 50), body mass index (N = 22), education level (N=2), cotinine levels (N = 3), and lipid levels (N = 3). We also excluded 34 participants with triglycerides > 400 mg/dL as LDL cholesterol could not be calculated in this group. The final sample size was 1,159.

Serum selenium

Collection materials were screened for potential selenium contamination. Serum selenium was measured at the Trace Elements Laboratory at the Wadsworth Center of the New York State Department of Health using inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS). The between-assay coefficients of variation for quality control pooled samples analyzed throughout the duration of the survey ranged from 2.5 to 2.9% [10].

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Serum lipids

Fasting serum total cholesterol and triglycerides were measured enzymatically. HDL-Cholesterol was measured directly in serum after rendering apolipoprotein-B-containing lipoproteins non-reactive with a blocking agent. LDL-cholesterol levels were calculated using the Friedewald formula [10].

Other variables

Information on sex, age, race-ethnicity, education, menopausal status, smoking and use of vitamin / mineral supplements was based on self-report. Body mass index was calculated by dividing measured weight in kilograms by measured height in meters squared. Serum cotinine was measured by isotope-dilution high-performance liquid chromatography / atmospheric pressure chemical ionization tandem mass spectrometry [10].

Statistical methods

Participants were divided in quartiles of serum selenium concentration based on the weighted population distribution. Adjusted mean differences in serum lipids and total to HDL cholesterol ratio, comparing each quartile of serum selenium to the lowest quartile, were calculated using multivariable linear regression. We used 2 models with progressive degrees of adjustment. Model 1 was adjusted for sex, age, race / ethnicity and education. Model 2 was further adjusted for body mass index, smoking, cotinine, menopausal status, cholesterol, total fat, saturated fatty acids, and selenium intakes, and use of vitamin / mineral supplements. Since ignoring lipid lowering treatment may result in biased estimates of the association between selenium and serum lipids, we conducted an additional analysis using censored linear regression (Model 3) to correct for the effect of lipid lowering medication [11]. This technique was used as a sensitivity analysis to rule out potential biases induced if lipid lowering medication use was induced by increased selenium levels. Since there is no implementation of censored regression that for complex survey data, we weighted censored regression analyses using NHANES 2003–2004 survey weights to obtain unbiased point estimates, but did not correct the 95% confidence intervals to account for the complex survey design. Tests for linear trend were calculated by including serum selenium as a continuous variable in the models. To further explore the shape of the relationship between serum selenium and serum lipids, we used restricted quadratic splines with knots at the 5th, 50th and 95th percentiles of the serum selenium distribution. We also evaluated the interactions between serum selenium and sex, age, race / ethnicity, education, body mass index, smoking status, use of vitamin / mineral supplements, or lipid lowering treatment. Statistical analyses were performed using weights specific for the fasting morning sample in the survey package in the R Statistical Software (version 2.6.1, R Foundation for Statistical Computing, Vienna, Austria) to account for the complex sampling design and weights. Censored regression models were estimated using the cnreg command in Stata Statistical Software (Release 9.2, StataCorp LP, College Station, TX) weighted for NHANES survey weights.

RESULTS

The mean (standard deviation) serum selenium concentration in the study population was 136.7 (18.9) μg/L. Mean total, LDL, HDL cholesterol, and triglyceride concentrations were 204.8 (38.8), 121.3 (34.8), 55.2 (16.3), and 141.8 (72.6) mg/dL, respectively, and mean total to HDL cholesterol ratio was 3.98 (1.23). Men had higher mean serum selenium levels than women (139.0 vs. 134.7 μg/L). Non-Hispanic Blacks had lower mean serum selenium (128.4 μg/L) than Non-Hispanic Whites (137.5 μg/L) or Mexican Americans (141.3 μg/L). Serum selenium concentrations were positively associated with age, with dietary selenium intake, and with the use of vitamin / mineral supplements, and inversely associated with body mass index and current smoking (Table 1).

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The multivariable adjusted average differences (95% CI) comparing the highest to the lowest quartiles of serum selenium were 18.9 (9.9, 28.0) mg/dL for total cholesterol, 12.7 (3.3, 22.2) mg/dL for LDL cholesterol, 3.9 (0.4, 7.5) mg/dL for HDL cholesterol, 11.5 (−7.6, 30.7) mg/dL for triglycerides, and 0.10 (−0.27, 0.46) for total to HDL cholesterol ratio (Table 2, Model 2). The linear trend tests were statistically significant for all lipid fractions, except for triglycerides. Similar results were observed in censored linear regression models that controlled for the effect of lipid lowering medications (Table 2, Model 3).

In spline regression models, all lipid fractions were associated with serum selenium levels (Figure 1). Total and LDL cholesterol levels increased with increasing selenium concentrations up to 160 μg/L. HDL cholesterol levels increased with selenium but reached a plateau above 120 μg/L of serum selenium (20th percentile). The triglyceride-selenium relationship was U-shaped. The multivariable adjusted average differences (95% CI) in the spline models comparing the 90th to the 10th percentiles of serum selenium (160 and 115 μg/L, respectively) were 22.3 (14.4, 30.1) mg/dL for total cholesterol, 14.2 (5.6, 22.9) mg/dL for LDL cholesterol, 3.8 (1.1, 6.5) mg/dL for HDL cholesterol, and 21.4 (2.2, 40.5) for triglycerides.

When the associations of selenium and lipids were evaluated by subgroups of study participants, the interactions did not show any consistent pattern and they were not statistically significant except for the interaction of selenium with sex on HDL cholesterol ($p = 0.03$), and the interaction of selenium with race on triglycerides ($p = 0.02$), which showed higher triglycerides at high selenium levels among Mexican Americans. Similar results were obtained when participants with self-reported coronary heart disease, stroke or cancer were excluded or when participants with triglycerides above 400 mg/dL were not excluded.

DISCUSSION

Findings from the present study corroborate growing evidence suggesting that high selenium exposure is associated with increased serum lipid levels. In the present study, high serum selenium concentrations were associated with higher serum lipids in a representative survey of US adults ≥ 40 years old conducted in 2003–2004. The associations of selenium with total and LDL cholesterol levels were strong and linear. HDL cholesterol levels were also positively associated with selenium concentrations but only at the low end of the selenium distribution (up to the 20th percentile). The triglyceride-selenium relationship was U-shaped. These findings raise additional concerns about potential cardio-metabolic abnormalities associated with high-normal selenium status.

In agreement with the present study, an earlier cross-sectional analysis of serum selenium and blood lipids in the NHANES III (1988–1994), high serum selenium concentrations were associated with high total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, apolipoprotein B, and apolipoprotein A1 levels 9. In the EVA (Epidemiology of Vascular Ageing) study, conducted in France, plasma selenium was positively associated with total cholesterol and LDL-cholesterol among men, and with HDL-cholesterol and apolipoprotein A-1 among women 12. Furthermore, high-normal selenium status was associated with increased total and non-HDL cholesterol, but not with increased HDL, in the 2000–2001 UK National Diet and Nutrition Survey (NDNS), a nationally representative sample of British adults13. Interestingly, British and French adults have substantially lower mean serum selenium levels compared to US adults. Positive associations of selenium status with total cholesterol levels have also been found in other populations with optimal or suboptimal selenium status, but those studies did not provide detailed dose-response analyses 14–16. Altogether, the current epidemiological evidence consistently indicates that serum/plasma selenium is associated with blood lipids across a wide range of selenium concentrations.

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Randomized evidence on the effect of selenium supplementation on lipid metabolism is limited. In a French population, the SU.MI.VAX (Supplementation with Antioxidant Vitamins and Minerals) trial showed that long-term daily supplementation with selenium (100 μg), vitamin C (120 mg), vitamin E (30 mg) and zinc (20 mg) resulted in higher serum triglyceride levels and higher total cholesterol levels among women, and higher use of lipid lowering medication among men [17]. In a randomized trial in a rural Chinese population with low selenium intake, long-term supplementation with selenium (37.5 μg), vitamin C (250 mg) and vitamin E (100 IU) resulted in small but significant increases in total and LDL cholesterol levels, whereas HDL concentrations were not affected 18. These studies were multi-element supplementation trials and could not isolate the effect of selenium from that of other antioxidants administered. Two smaller, short-term intervention studies have examined the lipid profile effects of selenium supplementation alone, but their results were inconsistent 19 20.

Current evidence on potential mechanisms for the effect of high selenium exposure on lipid metabolism is sparse and any such discussion is highly speculative. There is, however, evidence of a connection between lipoprotein and selenium metabolism. Small amounts of serum selenium can be identified in human lipoproteins [21]. Early studies found that an intravenously administered selenium isotope was mainly attached to very low density lipoproteins and low density lipoproteins [22]. Additionally, research on animal models suggests interdependence between selenoprotein and lipoprotein metabolic pathways. For example, selenoprotein P is taken up by the brain and the testes *via* the apolipoprotein E receptor-2 23, whereas megalin, another apolipoprotein receptor, mediates its uptake by the kidney 24. In mouse knock-out models with impaired selenoprotein synthesis, liver apolipoprotein E concentrations, plasma cholesterol levels and the expression of genes involved in cholesterol biosynthesis, metabolism and transport are altered 25. A further connection between selenium and cholesterol is found in the common use of isopentenyl pyrophosphate as a substrate for the synthesis of Sec-tRNA and of isoprenoid in the mevalonate pathway [26]. The formation of selenoproteins requires the isopentenylation of Sec-tRNA with isopentenyl pyrophosphate, a substrate that is also required by farnesyl pyrophosphate synthetase in the pathway to cholesterol. Finally, recent findings from the EVA study indicate that long-term use of fibrates (but not statins) may increase plasma selenium concentrations in dyslipidemic aged patients [27], further supporting a link between selenium and lipid metabolism.

Notwithstanding the potential biological mechanisms involved, selenium is known to have a narrow therapeutic window and large inter-individual variability in the low adverse effect level (LOAEL) of dietary selenium [28]. Above the physiological range for optimal activity of antioxidant selenoproteins such as glutathione peroxidases (55 μg/day, resulting in serum or plasma concentrations of 70–90 μg/L) 29, further increases in selenium intake result in the non-specific incorporation of selenomethionine replacing methionine in albumin and other proteins. The metabolic pathways involving this extra pool of selenium are incompletely understood, and may be responsible for some of the associations between selenium and lipids.

The present study is limited by its cross-sectional design, and we were unable to determine whether lipid levels rise as a consequence of increased selenium intake or whether a common metabolic pathway or common co-exposures might explain the association between selenium status and lipid levels. Besides, selenium data were only available for subjects above 40 years of age and the observed association could be different among younger individuals. The strengths of our study are the US population representativeness of the sample and the rigorous data collection and laboratory assays. The possibility of confounding by concomitant intake of high fat and high selenium foods was addressed through adjusting for cholesterol, total fat, saturated fatty acids, and selenium intakes, although measurement error in dietary data may result in residual confounding.

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In addition to association with adverse lipid metabolism, high selenium exposure has been associated with other cardio-metabolic outcomes such as type 2 diabetes and hypertension 3–5 7. Given high selenium intake from natural sources in the US and the increasing use of selenium enriched foods, supplements and fertilizers in many countries [30], these findings call for a thorough evaluation of the risks and benefits associated with high selenium status. Indeed, in the present study mean serum selenium concentrations were 136.7 μg/L, substantially higher than mean concentrations in NHANES III (125.7 μg/L). The use of vitamin/mineral supplements has likely contributed to the increase in selenium levels over the last decade, as reflected by the high percentage of dietary supplement users in the top quartiles of serum selenium in the present study. Increasing selenium intake in individuals with a replete selenprotein status, such as the average NHANES participant, has little potential for additional health benefits but can result in toxic effects. The relationship between selenium status and atherosclerosis is more complex than its role as antioxidant and should be clarified to enlighten preventive and therapeutic uses of selenium and to help determine the optimal level of selenium intake in the general population that maximizes the antioxidant benefits but avoids potential subclinical toxic effects of selenium.

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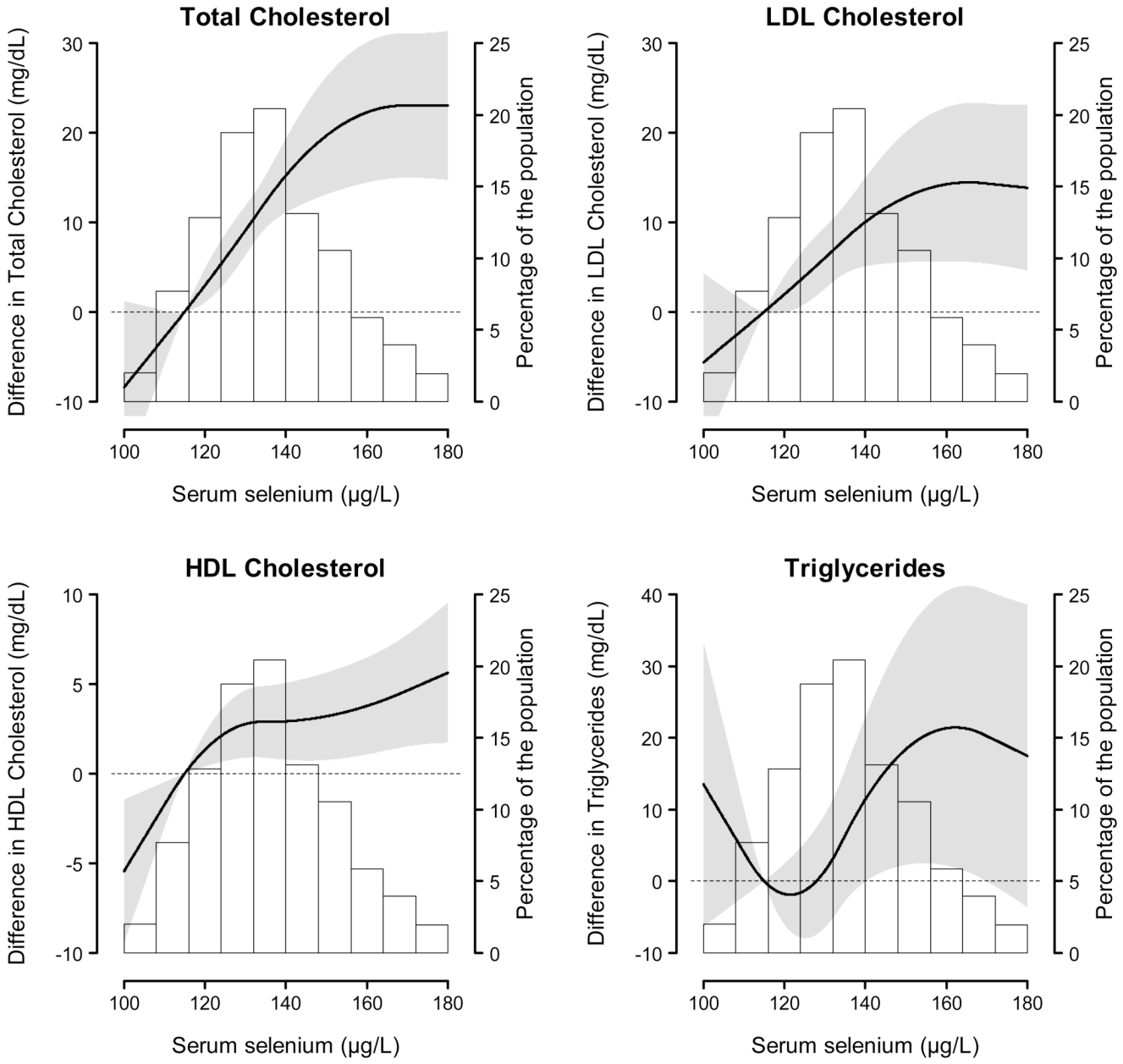

Figure 1.

Adjusted differences (95% CI) in serum lipids by serum selenium concentrations. Serum selenium was modeled as restricted quadratic splines with nodes at the 5th, 50th, and 95th percentiles. The multivariable linear regression models were adjusted for sex, age, race, education, body mass index, smoking, cotinine, postmenopausal status, cholesterol, total fat, saturated fatty acids, and selenium intakes, and use of vitamin and mineral supplements (Model 2). Lipids concentrations at the 10th percentile (115 µg/L) of the serum selenium distribution were used as reference. The histogram shows the distribution of selenium concentrations in the study population.

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Table 1

Characteristics of the study population by serum selenium quartile.

		Quartile of serum selenium (interval in μg/L)				
		1st	2nd	3rd	4th	
	Overall					p trend
		< 124	124 – 133	134 – 146	≥ 147	
N	1159	266	280	307	306	
Age (years)	56.8 (12.2)	55.8	56.8	56.8	57.5	<0.001
Gender (% female)	53.8	61.6	61.3	48.8	45.0	0.001
Race						
Non-Hispanic White (%)	78.4	75.6	75.4	78.2	83.9	0.02
Non-Hispanic Black (%)	9.7	16.4	10.6	8.3	4.2	0.001
Mexican American (%)	5.2	4.0	4.3	4.9	7.3	0.05
Other (%)	6.8	4.0	9.7	8.6	4.6	0.76
Education (% High school)	82.1	79.3	81.0	85.8	81.8	0.51
Body Mass Index (kg/m^2)	28.6 (5.9)	29.2	28.8	28.7	27.8	0.01
Current Smoker (%)	19.6	27.8	18.8	19.1	13.4	0.002
Cotinine (ng/mL)	60.5 (136.1)	78.2	58.3	54.9	52.2	0.36
Cholesterol Intake (mg/d)	282.8 (181.9)	283.4	273.0	286.7	287.4	0.89
Total Fat Intake (g/d)	80.1 (37.1)	75.8	79.6	81.9	82.6	0.50
Saturated Fat Intake (g/d)	26.1 (13.0)	24.8	25.1	27.0	27.4	0.45
Selenium Intake (μg/d)	105.3 (50.7)	94.7	104.7	106.1	114.4	0.001
Dietary Supplements (%)	65.1	49.9	61.6	71.7	75.1	0.001
Selenium (μg/L)	136.7 (18.9)	115.2	128.9	139.2	161.0	

Values are survey weighted means (standard deviation) or percentages for continuous or categorical variables, respectively.

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Table 2

Adjusted differences (95% CI) in serum lipids and total to HDL cholesterol ratio comparing the three highest quartiles to the first quartile of serum selenium.

	Quartile of serum selenium (interval in μg/L)				
	1st	2nd	3rd	4th	
	< 124	124 – 133	134 – 146	≥ 147	p trend
Total Cholesterol (mg/dL)	195.5	200.0	208.7	213.7	
Model 1	0.00	4.8	14.8	19.9	<0.001
	(Reference)	(−2.9, 12.5)	(8.5, 21.1)	(10.7, 29.2)	
Model 2	0.00	4.7	13.2	18.9	<0.001
	(Reference)	(−3.9, 13.3)	(7.1, 19.3)	(9.9, 28.0)	
Model 3	0.00	5.4	12.9	17.8	<0.001
	(Reference)	(−1.5, 12.3)	(5.9, 19.8)	(10.6, 24.9)	
LDL Cholesterol (mg/dL)	115.2	118.7	123.5	126.7	
Model 1	0.00	4.3	9.3	12.3	0.006
	(Reference)	(−4.2, 12.8)	(3.5, 15.0)	(3.1, 21.5)	
Model 2	0.00	4.7	8.8	12.7	0.004
	(Reference)	(−4.1, 13.5)	(2.8, 14.8)	(3.3, 22.2)	
Model 3	0.00	4.7	8.0	10.9	0.001
	(Reference)	(−1.6, 11.0)	(1.7, 14.3)	(4.4, 17.4)	
HDL Cholesterol (mg/dL)	53.1	55.3	55.6	56.5	
Model 1	0.00	2.2	4.0	5.6	0.001
	(Reference)	(−1.9, 6.4)	(−0.2, 8.1)	(1.5, 9.8)	
Model 2	0.00	1.8	3.2	3.9	0.006
	(Reference)	(−1.7, 5.2)	(−0.4, 6.9)	(0.4, 7.5)	
Model 3	0.00	2.4	3.8	3.5	0.001
	(Reference)	(−0.3, 5.1)	(1.0, 6.5)	(0.7, 6.3)	
Triglycerides (mg/dL)	135.5	129.8	148.1	152.2	
Model 1	0.00	−8.5	7.9	10.0	0.24
	(Reference)	(−21.9, 4.9)	(−5.4, 21.3)	(−12.6, 32.5)	
Model 2	0.00	−8.7	6.1	11.5	0.15

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	Quartile of serum selenium (interval in μg/L)				
	1st	**2nd**	**3rd**	**4th**	
	< 124	**124 – 133**	**134 – 146**	**≥ 147**	**p trend**
	(Reference)	(−24.6, 7.3)	(−8.7, 20.9)	(−7.6, 30.7)	
Model 3	0.00	−7.3	5.8	11.5	0.02
	(Reference)	(−20.7, 6.0)	(−7.6, 19.2)	(−2.3, 25.3)	
Total to HDL cholesterol ratio	3.94	3.86	4.02	4.07	
Model 1	0.00	−0.07	0.01	0.02	0.92
	(Reference)	(−0.37, 0.23)	(−0.26, 0.28)	(−0.40, 0.43)	
Model 2	0.00	−0.05	0.02	0.10	0.53
	(Reference)	(−0.30, 0.21)	(−0.23, 0.28)	(−0.27, 0.46)	
Model 3	0.00	−0.06	−0.01	0.06	0.47
	(Reference)	(−0.28, 0.15)	(−0.23, 0.21)	(−0.17, 0.28)	

The first line of each part of the table shows the unadjusted (survey-weighted) averages of serum lipids. Models 1 and 2 used multiple linear regression models with survey weights, strata, and clusters to account for complex survey design. Model 3 used censored regression with survey weights only.

Model 1. Adjusted for sex, age, race and education (high school or higher vs. less than high school).

Model 2. Further adjusted for body mass index, smoking category (never, former, current), cotinine levels, postmenopausal status (yes/no), cholesterol, total fat, saturated fatty acids, and selenium intakes, and use of vitamin and mineral supplements (yes/no).

Model 3. Censored linear regression to correct for the effect of lipid lowering medication, adjusted for the same variables as Model 2.