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Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein

Emily B. Levitan[a], **Nancy R. Cook**[b,c,d,e], **Meir J. Stampfer**[b,c,f,g], **Paul M. Ridker**[b,c,d,e,h], **Kathryn M. Rexrode**[b,f], **Julie E. Buring**[b,c,d,e,i], **JoAnn E. Manson**[b,c,f], and **Simin Liu**[b,c,j]

a*Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA, USA*

b*Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

c*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA*

d*Donald W. Reynolds Center for Cardiovascular Research, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

e*Leducq Center for Molecular and Genetic Epidemiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

f*Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

g*Department of Nutrition, Harvard School of Public Health, Boston, MA, USA*

h*Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

i*Department of Ambulatory Care and Prevention, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

j*Program on Genomics and Nutrition, Departments of Epidemiology and Medicine, UCLA, Los Angeles, CA, USA*

Abstract

Carbohydrate quantity and quality may influence risk of cardiovascular disease through blood lipid concentrations and inflammation. We measured dietary glycemic index (GI) and dietary glycemic load (GL) among 18,137 healthy women ≥ 45 years old without diagnosed diabetes using a food-frequency questionnaire. We assayed fasting total, HDL, and LDL cholesterol, LDL:HDL cholesterol ratio, triacylglycerols (TG), and C-reactive protein (CRP). We evaluated associations with dietary GI and GL using a cross-sectional design, adjusting for age, body mass index, lifestyle factors, and other dietary factors. Dietary GI was significantly associated with HDL and LDL cholesterol, LDL:HDL cholesterol ratio, TG, and CRP (comparing top to bottom quintile difference in HDL cholesterol = -2.6 mg/dL, LDL cholesterol = 2.2 mg/dL, LDL:HDL cholesterol ratio = 0.16, TG = 12 mg/dL, and CRP = 0.21 mg/L). Dietary GL was associated with HDL cholesterol, LDL:HDL cholesterol ratio, and TG (comparing top to bottom quintile HDL cholesterol = -4.9 mg/dL, LDL:HDL cholesterol ratio = 0.24, and TG = 13 mg/dL). Differences in blood lipids and CRP

Corresponding author: E.B. Levitan, Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Feldberg 2, Boston, MA 02215, phone: 617-667-3172, fax: 617-632-7698, email: elevitan@bidmc.harvard.edu..

between extreme quintiles of dietary GI and GL were small, but may translate into a clinically meaningful difference in cardiovascular risk.

1. Introduction

Dietary glycemic index (GI), the average propensity of carbohydrate in the diet to increase blood glucose compared to a reference food [1,2], and dietary glycemic load (GL), the product of dietary GI and carbohydrate [2], have been associated with elevated risk of coronary heart disease, stroke, and type 2 diabetes, particularly among overweight individuals [2-5]. Dietary GI and GL may increase risk of these diseases through adverse effects on blood lipids and systemic inflammation [6-9]; however, many of the studies on this topic have been relatively small. We examined the cross-sectional associations of dietary GI and dietary GL with blood lipids and C-reactive protein (CRP) in nondiabetic participants in the Women's Health Study, a large population of middle-aged and older women. Because these associations maybe stronger in overweight individuals [6,9], we tested whether the relationships varied by body mass index (BMI).

2. Participants and methods

2.1. Study participants

The Women's Health Study was a double-blind, placebo-controlled, randomized trial of vitamin E and low-dose aspirin for the primary prevention of cardiovascular disease and cancer among 39,876 women [10-12]. Female health professionals aged 45 and older with no prior diagnosis of cardiovascular disease or cancer, except nonmelanoma skin cancer, enrolled in the trial [13]. The participants were postmenopausal or did not plan to become pregnant. The women completed baseline questionnaires to provide information about demographic, behavioral, and lifestyle factors, medical history including medication use, height and weight, and use of multivitamins and other supplements.

In this analysis, we included 18,137 women who provided fasting blood samples (≥ 8 hours since last meal), were not diabetic (assessed by self-report), were not taking lipid lowering medications, and reported total energy intake between 600 and 3500 kcal per day (45% of all participants, 64% of those who provided blood samples). The institutional review board of Brigham and Women's Hospital approved the Women's Health Study, and all participants provided written informed consent.

2.2. Assessment of dietary intake

The women completed a 131-item, validated, semi-quantitative food-frequency questionnaire (FFQ) at baseline. Detailed information regarding the development of the FFQ, procedures used to calculate energy-adjusted nutrient values, and reproducibility and validity of the questionnaire in a similar population has been reported [14]. For each food a commonly used unit or portion size (e.g. 1 slice of bread, 1 cup of milk) was specified on the FFQ, and participants were asked how frequently they had consumed the food over the previous year. Nine responses were possible ranging from "never or less than once per month" to "6 or more times per day." We estimated nutrient intakes by multiplying the frequency of consumption of each food and dietary supplement by the nutrient estimated using food-composition tables from the US Department of Agriculture [15] and other sources.

The calculation of dietary GI and GL has been described previously [3]. For most foods included on the FFQ, we used published GI values which have been collected in a database by investigators at the University of Sydney [16]. Foods from the FFQ were matched to foods with reported GI values based on caloric and nutrient content, types of ingredients, and

processing. For other foods, the GI was measured using standard methods. Dietary GI was calculated using the formula dietary $GI = \sum_{foods} C \times F \times GI / \sum_{foods} C \times F$ where C represents the grams of carbohydrate in a serving of food, F the frequency of consumption of the food, and GI the glycemic index using glucose as the reference. Dietary GL was calculated as dietary $GL = \sum_{foods} C \times F \times GI / 100$ or equivalently the product of total carbohydrate and dietary GI expressed as a percentage. The nutrients, dietary GI, and dietary GL were energy-adjusted using the residuals method [14]. In a similar population of female health professionals, correlations between the FFQ and diet records were 0.66 for potatoes, 0.60 for cold breakfast cereal, and 0.71 for white bread [17]; these foods were the 3 biggest contributors to dietary GL in the Women's Health Study [9].

2.3. Blood collection and assessment of biomarkers

Participants received blood collection kits including collection tubes and a cooling pack. Participants had their blood drawn and sent the samples to the lab by overnight courier. Ninety-three percent of the blood samples were collected before the participants started study treatments. After processing, the samples were stored in liquid nitrogen until thawing for the analysis of total cholesterol (enzymatic assay, day-to-day variability 1.7 and 1.6% at concentrations of 132.8 and 280.4 mg/dL respectively) [18], HDL cholesterol (enzymatic colorimetric assay, day-to-day variability 3.3 and 1.7% at concentrations of 27.0 and 54.9 mg/dL respectively) [19], LDL cholesterol (direct assay, day-to-day variability 3.0, 2.3, and 2.2% at concentrations of 90, 106, and 129 mg/dL, respectively) [20], triacylglycerols (TG, enzymatic assay, day-to-day variability 1.8 and 1.7% at concentrations of 84.0 and 202 mg/dL, respectively) [21], and high-sensitivity CRP (immunoturbidimetric assay, day-to-day variability 2.8, 1.6, and 1.1% at concentrations of 0.9, 3.1, and 13.4 mg/L, respectively) [22]. All biomarkers were analyzed using a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN) and reagents from Roche Diagnostics (total cholesterol, LDL cholesterol, HDL cholesterol, and TG) and Denka Seiken (Niigata, Japan) (CRP). As a summary measure we calculated the ratio of LDL to HDL cholesterol.

2.4. Statistical Analysis

We first calculated means or percentages of demographic, lifestyle, and dietary covariates by quintiles of dietary GI and dietary GL. Linear regression was used to calculate p-values for continuous variables and χ^2 tests for categorical variables. We computed mean total cholesterol, HDL cholesterol, LDL cholesterol, and LDL:HDL cholesterol ratio by quintiles of dietary GI and GL. The means were adjusted first for age alone (5-year categories), and then additionally adjusted for BMI (< 21 kg/m^2, 21-22.9 kg/m^2, 23-24.9 kg/m^2, 25-26.9 kg/m^2, 27-28.9 kg/m^2, 29-30.9 kg/m^2, ≥ 31 kg/m^2), strenuous exercise (rarely/never, < 1 times/week, 1-3 times/week, ≥ 4 times/week), history of hypertension (yes, no), postmenopausal hormone use (current, past, never), smoking status (current, past, never), multivitamin use (current, past, never), and intakes of protein, saturated fat, trans fat, polyunsaturated fat, alcohol, cholesterol, fiber, magnesium, folate, and total energy (quintiles). Controlling for randomized treatment assignment did not alter results. Because the distributions of TG and CRP were skewed toward high values, we took natural logarithms of TG and CRP to normalize the distributions. We calculated the means of natural logarithm-transformed TG and CRP adjusted for age and additionally adjusted for the other covariates as described above. Back transforming the resulting values produced geometric means of TG and CRP. We tested for linear trends by entering the median intake in each quintile as a predictor in the models. We then stratified our analysis by overweight (BMI < 25 kg/m^2 or ≥ 25 kg/m^2). Formal tests of interaction were performed by entering the product of the overweight indicator variable and the median intake of the quintile as a predictor in the multivariate-adjusted model. Because use of postmenopausal

hormones increases CRP [23], HDL cholesterol, and TG and decreases LDL cholesterol [24], we examined whether the associations of the carbohydrate measures with blood lipids and CRP varied by such use. Analysis was performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); a two-sided P-value < 0.05 was considered significant for all tests.

3. Results

Dietary GI and dietary GL were moderately correlated in this population ($r = 0.53$, $p < 0.001$). Dietary GL was highly correlated with carbohydrate intake ($r = 0.94$, $p < 0.001$), and the correlation between dietary GI and carbohydrate intake was lower ($r = 0.23$, $p < 0.001$). Women with high dietary GI tended to be less physically active, and to have lower intakes of alcohol, folate and magnesium compared to women with low dietary GI (Table 1). In contrast, women with high dietary GL tended to be thinner, more physically active, less likely to have hypertension or to smoke than women with lower dietary GL. Additionally, they had lower average fat, protein, and cholesterol intake and higher average folate and magnesium intakes. In multivariable-adjusted analysis, dietary GI was associated with small increases in LDL cholesterol, LDL:HDL cholesterol ratio, TG, and CRP and with a small decrease in HDL cholesterol (Table 2). Dietary GL was associated with higher LDL:HDL cholesterol ratio and TG concentration and lower HDL cholesterol (Table 3).

Forty-seven percent of the women in this population were overweight (BMI $\geq$ 25 kg/m^2). We found that the relationship between dietary GL and HDL cholesterol was slightly stronger among normal weight women than among overweight women (BMI < 25 kg/m^2, difference between top and bottom quintile = -5.6, 95% CI: -7.2, -4.0; BMI $\geq$ 25 kg/m^2, difference between top and bottom quintile = -4.0, 95% CI: -5.5, -2.5; *P* for interaction < 0.001). Associations between dietary GI, GL, and other biomarkers did not vary significantly by overweight status. Dietary GI was not associated with total cholesterol among the 10,199 women who were not taking postmenopausal hormones (difference between top and bottom quintile = 0.07, 95% CI: -2.8, 2.9) but there was an association between dietary GI and total cholesterol among current postmenopausal hormone users (difference between top and bottom quintile = 3.7, 95% CI: 0.5, 6.8; *P* for interaction = 0.01). We did not find evidence for interactions of dietary GL with postmenopausal hormone use.

4. Discussion

In this large cross-sectional study of nondiabetic middle-aged and older women, dietary GI and GL were associated with small differences in concentrations of blood lipids and CRP. Because dietary GL describes both carbohydrate quantity and propensity to raise blood glucose, we expected that dietary GL would be the best predictor of the markers of cardiovascular risk. Dietary GL was a stronger predictor of HDL cholesterol and LDL:HDL cholesterol ratio than dietary GI. However, dietary GI, but not dietary GL, was associated with LDL cholesterol and CRP. In this population, we did not find evidence to suggest that diets high in GI or GL had a more adverse effect on lipids among overweight than normal weight women. In fact, dietary GL appeared to have a slightly stronger inverse relationship with HDL cholesterol in normal weight women.

Several cross-sectional studies in the general population have examined the association of dietary GI and GL with blood lipids. While not all investigators have found significant associations [25], in most studies, high dietary GI or dietary GL was associated with lower HDL cholesterol [6-8,26,27], higher TG concentrations [6,26], and increased prevalence of metabolic syndrome [28]. Other observational studies have not found significant associations of dietary GI or GL with LDL cholesterol [7,25], perhaps because of smaller sample sizes leading to lower power to detect a modest association. In diet trials, low GI diets decreased

TG, LDL cholesterol, and the total:HDL cholesterol ratio [29-32]. In a previous analysis of 244 participants in the Women's Health Study, dietary GI and dietary GL were associated with CRP [9], and among diabetic participants in the Nurses' Health Study dietary GI, but not dietary GL, also was significantly associated with CRP [33]. Additionally, trial data indicate that low GL weight-loss diets may reduce CRP more than high GL weight-loss diets [34].

The association of dietary GI and dietary GL with cardiovascular disease has been found to be stronger in overweight than in normal weight participants in prospective studies [3,4,35]. In a cross-sectional study, the associations of high GL diets with HDL cholesterol and TG were also stronger in overweight individuals [6]; this was observed for CRP in a sample of 244 women in Women's Health Study [9]. However, in the present analysis and in another large population [8], the associations with lipids were similar across groups or slightly stronger in normal weight participants. While underlying insulin resistance may exacerbate the effects of elevated concentrations of insulin and glucose following a high GL meal [36], the current study does not provide evidence to support the hypothesis that the effects on blood lipids and inflammation are greater in overweight women.

Physiologic responses to meals that raise blood glucose may explain the observed associations with blood lipids and CRP. During the period just after a meal with a high GI, glucose and insulin concentrations are elevated, but 4 to 6 hours later, glucose can dip into the hypoglycemic range, stimulating the release of counterregulatory hormones that increase the concentrations of both glucose and free fatty acids [29]. Elevated insulin, glucose, and free fatty acids have been shown to induce insulin resistance [29,37-39]. Insulin resistance seems to cause increases in TG and inflammatory mediators and decreases in HDL cholesterol [40]. Additionally, hyperglycemia results in oxidative stress, which may increase inflammation [29].

Although the absolute differences in lipids and CRP between extreme quintiles of dietary GI and dietary GL were small, they may be associated with differences in cardiovascular risk of clinical and public health importance. Based on our results, the -4.9 mg/dL difference in HDL cholesterol between extreme quintiles of dietary GL would be expected to increase risk of coronary heart disease by approximately 22%, while 0.24 unit difference in LDL:HDL cholesterol ratio would increase risk by approximately 14%, and the 13 mg/dL difference in TG would increase risk by approximately 7% [41]. Moreover, these estimates only consider the associations between diets with a propensity to raise blood glucose and lipids; they do not fully address the cardiovascular effects of these diets through other mechanisms. For example, in the OmniHeart Study, blood pressures were lower during the higher fat and protein diet periods than during the higher carbohydrate diet periods [42].

Potential measurement error is a significant limitation of this study. Although many high GL foods are known to be relatively well measured, dietary GI and dietary GL derived from questionnaires are likely to have substantial errors. The errors may arise both from the FFQ and from the GI values used for the foods. Because of scarcity of data, it was necessary to use GI values measured in other countries for some foods; the properties of foods with the same names may vary across countries [43]. Additionally, we have only one measurement of the blood lipids and CRP, which may lead to misclassification due to random variability. If the errors in dietary factors and biomarkers are not correlated, the measurement errors are likely to result in underestimation of the associations. Although we controlled for many determinants of blood lipids and CRP, we cannot rule out residual confounding.

In conclusion, this study suggests that the quantity and quality of carbohydrates consumed may influence blood lipid concentrations and inflammation in nondiabetic women. Diets characterized by lower GI and GL were associated with somewhat more favorable lipid profiles

and lower CRP. Although the absolute differences were small, they may translate into meaningful differences in cardiovascular risk.

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Table 1

Characteristics of 18,137 participants in the Women's Health Study (means or %) by quintile of carbohydrate variables

	Quintile dietary glycemic index				Quintile dietary glycemic load			
	1 (lowest)	3	5 (highest)	p[1]	1 (lowest)	3	5 (highest)	p[1]
Age (y)[2]	55.2	55.0	54.3	<0.001	54.3	54.8	55.3	<0.001
Body mass index (kg/m^2)	25.6	25.6	26.0	<0.001	26.3	25.8	25.0	<0.001
History of hypertension (%)	23.0	24.3	25.3	0.20	25.9	23.9	22.9	0.04
Strenuous exercise (%)				<0.001				<0.001
Rarely or never	30.5	36.2	44.6		41.4	36.2	34.2	
<1 times/week	17.8	20.2	20.5		21.0	20.0	16.8	
1-3 times/week	35.8	32.4	26.6		28.7	32.6	33.7	
≥4 times/week	15.9	11.2	8.8		8.9	11.2	15.2	
Postmenopausal hormone use (%)				0.50				0.01
Current	45.5	43.6	42.6		41.6	45.0	44.3	
Past	9.6	10.1	10.4		10.1	9.0	11.0	
Never	44.9	46.4	47.0		48.4	46.0	44.7	
Smoking (%)				<0.001				<0.001
Current	13.4	10.6	12.0		20.4	9.5	7.7	
Past	41.5	37.1	31.5		40.3	36.7	33.0	
Never	45.1	52.3	56.5		39.3	53.8	59.4	
Multivitamin use (%)				0.11				<0.001
Current	29.9	29.1	27.7		25.5	30.2	31.4	
Past	56.7	57.9	56.2		60.2	57.4	55.1	
Never	13.4	13.0	13.2		14.3	12.4	13.5	
Nutrient intakes								
Carbohydrate (g/d)[3] [% energy]	213 [49.2]	222 [51.3]	234 [54.1]	<0.001	177 [41.0]	222 [51.4]	267 [61.9]	<0.001
Protein (g/d)[3] [% energy]	85.5 [19.9]	80.9 [18.8]	75.6 [17.6]	<0.001	88.3 [20.6]	82.1 [19.0]	70.7 [16.5]	<0.001
Saturated fat (g/d)[3] [% energy]	20.2 [10.5]	19.7 [10.3]	18.7 [9.7]	<0.001	23.8 [12.4]	19.7 [10.3]	15.0 [7.8]	<0.001
Trans fat (g/d)[3] [% energy]	2.0 [1.1]	2.3 [1.2]	2.4 [1.3]	<0.001	2.6 [1.4]	2.3 [1.2]	1.8 [0.9]	<0.001
Monounsaturated fat (g/d)[3] [% energy]	21.3 [11.1]	21.7 [11.3]	21.1 [11.0]	0.23	25.9 [13.4]	21.5 [11.2]	16.7 [8.7]	<0.001
Polyunsaturated fat (g/d)[3] [% energy]	11.2 [5.8]	11.2 [5.8]	10.8 [5.6]	<0.001	12.6 [6.5]	11.1 [5.8]	9.5 [4.9]	<0.001
Alcohol (g/d)[3]	7.1	4.5	2.8	<0.001	10.2	3.9	2.1	<0.001
Cholesterol (mg/d)[3]	230	224	214	<0.001	275	224	166	<0.001
Fiber (g/d)[3]	20.5	19.2	17.3	<0.001	15.8	19.1	22.5	<0.001
Magnesium (mg/d)[3]	370	340	305	<0.001	321	342	353	<0.001
Folate (μg/d)[3]	452	431	404	<0.001	384	433	473	<0.001
Total energy (kcal/d)	1690	1777	1666	0.08	1691	1771	1684	0.20

[1] P-values from linear regression (continuous variables) or $\chi 2$ test (categorical variables)

[2] Means or percents

[3] Energy-adjusted using the residuals method

Table 2

Arithmetic or geometric mean concentrations of blood lipids and high-sensitivity C-reactive protein by quintile of dietary glycemic index

	Dietary glycemic index [median]						
	Quintile 1 [49]	**Quintile 2 [51]**	**Quintile 3 [53]**	**Quintile 4 [54]**	**Quintile 5 [57]**		**p for linear trend**
	Arithmetic mean					Difference between quintile 5 and quintile 1 (95% CI)	
Total cholesterol (mg/dL)							
Age-adjusted[1]	210	212	211	213	213	2.4 (0.5, 4.3)	0.007
Multivariate-adjusted[2]	210	212	211	212	212	1.6 (-0.5, 3.7)	0.10
High-density lipoprotein cholesterol (mg/dL)							
Age-adjusted	56.6	55.3	54.1	53.4	52.0	-4.6 (-5.3, -3.9)	< 0.001
Multivariate-adjusted	55.7	54.8	54.0	53.9	53.1	-2.6 (-3.3, -2.0)	< 0.001
Low-density lipoprotein cholesterol (mg/dL)							
Age-adjusted	122	124	125	126	127	4.1 (2.6, 5.7)	< 0.001
Multivariate-adjusted	123	125	125	126	126	2.2 (0.5, 4.0)	0.004
Low-density to high-density lipoprotein cholesterol ratio							
Age-adjusted	2.33	2.42	2.48	2.54	2.61	0.28 (0.24, 0.33)	< 0.001
Multivariate-adjusted	2.39	2.44	2.48	2.51	2.55	0.16 (0.12, 0.21)	< 0.001
	Geometric mean					Ratio of quintile 5 to quintile 1 (95% CI)	
Triglyceride (mg/dL)							
Age-adjusted	107	113	115	119	125	1.17 (1.14, 1.19)	< 0.001
Multivariate-adjusted	109	114	116	118	121	1.11 (1.08, 1.14)	< 0.001
High-sensitivity C-reactive protein (mg/L)							
Age-adjusted	1.63	1.80	1.80	1.84	1.97	1.21 (1.14, 1.28)	< 0.001
Multivariate-adjusted	1.69	1.83	1.82	1.79	1.90	1.12 (1.06, 1.18)	< 0.001

[1] Adjusted for age (five year categories)

[2] Adjusted for age (five year categories), BMI (< 21 kg/m^2, 21-22.9 kg/m^2, 23-24.9 kg/m^2, 25-26.9 kg/m^2, 27-28.9 kg/m^2, 29-30.9 kg/m^2, ≥ 31 kg/m^2), strenuous exercise (rarely/never, < 1 times/week, 1-3 times/week, ≥ 4 times/week), history of hypertension (yes, no), postmenopausal hormone use (current, past never), smoking status (current, past, never), and intakes of protein, saturated fat, trans fat, polyunsaturated fat, alcohol, cholesterol, fiber, magnesium, folate, and total energy (quintiles)

Table 3

Arithmetic or geometric mean concentrations of blood lipids and high-sensitivity C-reactive protein by quintile of dietary glycemic load

	Dietary glycemic load [median]						
	Quintile 1 [92]	**Quintile 2 [107]**	**Quintile 3 [117]**	**Quintile 4 [127]**	**Quintile 5 [143]**		**p for linear trend**
	Arithmetic mean					Difference between quintile 5 and quintile 1 (95% CI)	
Total cholesterol (mg/dL)							
Age-adjusted[1]	213	212	211	210	211	-1.6 (-3.5, 0.3)	0.02
Multivariate-adjusted[2]	213	213	211	210	212	-1.0 (-4.3, 2.3)	0.36
High-density lipoprotein cholesterol (mg/dL)							
Age-adjusted	56.2	54.7	54.2	53.7	52.7	-3.6 (-4.2, -2.9)	< 0.001
Multivariate-adjusted	56.9	55.1	54.1	53.4	51.9	-4.9 (-6.0, -3.8)	< 0.001
Low-density lipoprotein cholesterol (mg/dL)							
Age-adjusted	125	126	124	124	126	0.7 (-0.9, 2.2)	0.83
Multivariate-adjusted	124	125	125	124	126	1.4 (-1.3, 4.1)	0.49
Low-density to high-density lipoprotein cholesterol ratio							
Age-adjusted	2.41	2.47	2.46	2.48	2.55	0.14 (0.10, 0.18)	< 0.001
Multivariate-adjusted	2.36	2.45	2.47	2.50	2.60	0.24 (0.17, 0.31)	< 0.001
	Geometric mean					Ratio of quintile 5 to quintile 1 (95% CI)	
Triglyceride (mg/dL)							
Age-adjusted	111	114	116	117	121	1.09 (1.07, 1.11)	< 0.001
Multivariate-adjusted	109	113	116	118	122	1.13 (1.08, 1.17)	< 0.001
High-sensitivity C-reactive protein (mg/L)							
Age-adjusted	1.95	1.87	1.81	1.74	1.66	0.84 (0.78, 0.89)	< 0.001
Multivariate-adjusted	1.78	1.77	1.80	1.81	1.86	1.05 (0.97, 1.14)	0.23

[1] Adjusted for age (five year categories)

[2] Adjusted for age (five year categories), BMI (< 21 kg/m^2, 21-22.9 kg/m^2, 23-24.9 kg/m^2, 25-26.9 kg/m^2, 27-28.9 kg/m^2, 29-30.9 kg/m^2, ≥ 31 kg/m^2), strenuous exercise (rarely/never, < 1 times/week, 1-3 times/week, ≥ 4 times/week), history of hypertension (yes, no), postmenopausal hormone use (current, past never), smoking status (current, past, never), and intakes of protein, saturated fat, trans fat, polyunsaturated fat, alcohol, cholesterol, fiber, magnesium, folate, and total energy (quintiles)