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Associations of retrospective and concurrent lipid levels with subclinical atherosclerosis prediction after 20 years of follow-up: the Coronary Artery Risk Development in Young Adults (CARDIA) study

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Abstract

Purpose—Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we sought to determine how well lipids measured at baseline and at 20 years predict the presence of subclinical atherosclerosis.

Methods—Complete risk factor, coronary artery calcification (CAC), and carotid intima media thickness (CIMT) data were available for 2435 participants. Lipids were categorized into quartiles, CAC at Y20 was dichotomized as present/absent, and CIMT was dichotomized as ≥84 or <84th overall percentile. Multivariable logistic regression was used to model the association between lipids and CAC/CIMT. C statistics were used to assess the discriminative value of each lipid measure in predicting the presence of CAC or CIMT at Y20.

Results—Lipid levels measured in young adulthood as well as middle age were both associated with subclinical disease in middle age. The discriminatory value of lipids was virtually identical at baseline, when participants were 18–30 years of age, and 20 years later. Neither baseline nor Y20

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lipid data were strong predictors of Y20 subclinical disease despite statistically significant associations.

Conclusions—These results are consistent with a growing body of evidence that early-life exposure to nonoptimal lipids matters and lifestyle modifications administered earlier in the lifespan could slow the progress of the atherosclerotic plaques.

Keywords

Atherosclerosis; Lipids; Risk

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States, causing approximately 1 of every 6 deaths in 2008 [1]. CHD is a clinical manifestation of atherosclerosis, which begins in childhood with the accumulation of lipids in the intima of arteries to form fatty streaks and progresses to atherosclerotic plaques during adolescence [2]. Atherosclerotic burden can be diagnosed by B-mode ultrasound measurements of carotid intima media thickness (CIMT) and computed tomography–based measurements of coronary artery calcification (CAC). Multiple studies have shown that both CIMT and CAC are strong and independent predictors of future cardiovascular events [3].

Animal studies, laboratory investigations, and epidemiologic studies, including genetic forms of hypercholesterolemia, indicate that dyslipidemia is a major risk factor for CHD and atherosclerosis in middle-aged and older adults [3,4]. Furthermore, studies indicate that lipids measured in childhood and young adulthood are associated with CHD, CAC, and CIMT measured later in life [5–10]. In terms of risk prediction, the Coronary Artery Risk Development in Young Adults (CARDIA) study has previously shown that risk factors measured in young adults followed for 15 years predict future CAC better than risk factors measured concurrently [6].

The availability of both CAC and CIMT measures concurrently and in a middle-aged population allows us the unique opportunity to assess whether lipid levels measured in young adulthood are associated with both measures of subclinical disease later in life. Specifically, we used data from the CARDIA study, a large, biracial prospective cohort study, to determine how well several lipid measures measured in adults ages 18–30 years predicted the presence of CAC and CIMT ≥84th percentile measured 20 years later compared with concurrently measured lipids. We also assessed whether race or sex modified the association of lipids with CIMT and CAC.

Subjects and methods

Study population

The CARDIA study is a population-based cohort study of the development and determinants of cardiovascular risk factors in 5115 young adults, ages 18–30 years. It comprises a biracial population of black and white subjects recruited in equal numbers in 1985–1986 from four communities in the United States: Birmingham, AL; Chicago, IL; Minneapolis, MN; and

Oakland, CA. The study design, sampling strategies, and examination components and measurements have previously been described in detail [11]. The participants were reexamined 2 (1987–1988), 5 (1990–1991), 7 (1992–1993), 10 (1995–1996), 15 (2000–2001), 20 (2005–2006), and 25 (2010–2011) years after baseline, with 90%, 86%, 81% 79%, 74%, 72%, and 72%, respectively, of the surviving cohort retained. Examination protocols were approved by institutional review boards at each site, and informed consent was obtained from each participant at every examination.

Measurements

Participants were asked to fast for 12 hours before the clinical examination. Body height and weight were measured with a calibrated scale and a vertical ruler. Body mass index (BMI) was calculated as kg/m^2. Age, sex, physical activity, alcohol intake, educational attainment, and smoking habits were determined with the use of standardized questionnaires. Physical activity scores were computed by multiplying the frequency of participation by intensity of activity and reported as “exercise units.” Seated blood pressure was measured after 5 minutes of rest with a random-zero sphygmomanometer at year 0 and an automated device (Omron) at year 20; Omron values were recalibrated to random-zero values. Three blood pressure measurements were made and the mean of the second and third readings was used as measured blood pressure [11].

Blood was drawn from a vein in the antecubital fossa into a Vacutainer coated with ethylenediamine tetraaacetic acid for plasma. Samples were transported on dry ice to the Northwest Lipid Research Center in Seattle, Washington. Plasma concentrations of total cholesterol and triglycerides were made using an enzymatic assay, and high-density lipoprotein cholesterol (HDL-C) was determined after precipitation with dextran sulfate-magnesium chloride on the ABA 200 Biochromatic instrument (Abbott Laboratories, North Chicago, IL). Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation [12]. Serum glucose was measured at year 0 using the hexokinase ultraviolet method by American Bio-Science Laboratories (Van Nuys, CA) and at year 20 using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, MO).

CAC

There were two computed tomography (CT) scans made for each participant at the year 20 examination using electron beam CT (Imatron C-150, GE Medical Systems, Milwaukee, WI[Chicago and Oakland centers]) or multidetector CT (GE Lightspeed, GE Medical Systems [Birmingham center] or Volume Zoom, Siemens, Erlangen, Germany [Minneapolis center]) using a previously described methodology [13]. Forty consecutive images were read for each scan, from the root of the aorta to the apex of the heart.

The scans were read centrally by a trained reader and each participant’s scans were read independently. The reader was blinded to all the participant’s characteristics. The reader identified a region of interest for each potential focus of calcification, defined as four or adjacent pixels (1.87 mm^2) with a CT scan number greater than 130 Hounsfield units (field of view = 35 cm). Agatston scores were adjusted for between-center differences via a

standard calcium phantom scanned underneath each participant, and summed across the four major coronary arteries to compute a total calcium score [13]. Biweekly calibrations were conducted using a standard torso insert to guard against between center and temporal variability. The presence of calcification was defined as having a positive, non-zero Agatston score, using the average of two scans [14]. Discordant scans were adjudicated independently by two CARDIA investigators.

CIMT

High-resolution B-mode ultrasonography was used to capture images of the bilateral common carotid and internal carotid arteries using a Logiq 700 ultrasound machine (General Electric Medical Systems; Issaquoah, IL). A high-resolution M12 L transducer operating at a frequency of 13 MHz was used to image the common carotid artery, and a 9-MHz frequency for the carotidartery bulb and proximal internal carotid arteries. All sonographers were trained centrally and underwent a certification process.

Images were made at end diastole by a certified sonographer, who selected the image with the lowest arterial diameter and then saved the selected images on a super VHS videotape. The image series used to select the images were also recorded so that the selection could subsequently be confirmed during the reading process. One image was obtained, on both sides, at the level of the common carotid before the bifurcation. Two images were taken at the carotid artery bulb, and two images were obtained in the proximal 2 cm of the internal carotid arteries proper after the flow divider.

A certified reader reviewed the videotape and digitized images with the aid of an image analysis workstation. The software integrated validated image analysis algorithms interfaced with an Access database to store the IMT measurements. The high-resolution images of the different carotid artery segments were used to calculate the IMT of the far or near wall on each image after the operator traced the respective lumen–intima and media–adventitia interfaces over a 1-cm distance with the aid of a Wacom imaging tablet. Any atherosclerotic plaque was included as part of the intima-media interface and a note was made about the extent of stenosis that existed anywhere in the right or left carotid artery.

The maximum CIMT of the common carotid and internal carotid was defined as the mean of the maximum intima-media thickness of the near and far wall on both the left and right sides. A normalized composite CIMT measure was derived from combining the maximal CIMT of the common carotid and the internal carotid (consisting of the arithmetic average of all internal carotid and bulb measurements) by averaging these two measurements after standardization (subtraction of the mean and division by the standard deviation for the measurement). This analysis used the aggregate mean maximum measure of CIMT. Because the focus of these analyses was on subclinical disease measurements, and CAC and CIMT were only measured concurrently at Y20, we did not use Y25 data.

Exclusions

Individuals who completed the year 20 (Y20) examination (n = 3549) were excluded from analysis if they were missing CAC data at Y20 (n = 422), CIMT data at Y20 (n = 241), Y0 risk factors (n = 62), Y20 risk factors (n = 155), or if they were taking cholesterol-lowering

medications at Y0 (n = 0) or Y20 (n = 234). Complete risk factor, CAC, and CIMT data, therefore, were available for 2435 participants.

Statistical analyses

Plasma lipids assessed at Y0 and Y20 were the exposures of interest and included total cholesterol, LDL-C, HDL-C, triglycerides, and the ratio of total cholesterol to HDL-C. Lipids at Y0 were categorized into quartiles and Y20 lipids were subsequently divided by the Y0 quartile ranges for comparability in lipid categories across exams.

The presence of CAC at Y20 was defined as an Agatston score greater than 0. Measures of Y20 CIMT were dichotomized as 84 or greater or less than 84th overall percentile, a cutpoint that includes a reasonable proportion of participants at the upper end of the CIMT distribution, to create a variable that was comparable with CAC for expressing the presence/absence of subclinical carotid atherosclerosis. Covariates included the following clinical and demographic characteristics: age, sex, race, field center, education (dichotomized as ≥/<12 years), BMI, physical activity, smoking status (never/former/current), alcohol consumption (mL per day), hypertension (≥140 mmHg for systolic blood pressure, ≥90 mmHg for diastolic blood pressure or use of anti-hypertensive medications), diabetes (≥126 mg/dL or use of diabetes medications). Baseline characteristics were calculated as medians or percentage by the presence/absence of CAC and CIMT ≥/< 84th percentile, and differences between CAC and CIMT categories were tested using either the Wilcoxon rank sum test or a χ^2 statistic, respectively.

Multivariable logistic regression was used to model the association between lipids and CAC or CIMT. Models assessing the association between Y0 lipid levels and Y20 outcomes were adjusted for sex, race, center and Y0 values for age, education, BMI, physical activity, smoking status, alcohol consumption, and hypertension. Models assessing the association between Y20 lipid levels and outcomes were adjusted for sex, race, center, and Y20 values for age, education, BMI, physical activity, smoking status, alcohol consumption, hypertension, and diabetes.

Statistical interactions were included for sex and race as multiplicative terms in the model. To determine whether there was a significant graded increase in risk of CAC/CIMT with increasing lipid quartiles, the *P* value for the linear trend across lipid quartiles was estimated using a 1 df Wald χ^2 test. C statistics were used to assess the discriminative value of each lipid measure in predicting the presence of CAC or CIMT at Y20. Y0 and Y20 models were compared using a nonparametric test of correlated c-statistics [15]. All analyses were conducted using SAS v9.2 (SAS Institute Inc., Cary, NC). A two-sided $P < .05$ was considered statistically significant.

Results

Of the 2435 participants with data, 16% had detectable CAC at year 20 with 16% of CIMT 84th percentile or greater as defined (Table 1). Participants with CAC were more likely to be older and men. Furthermore, on average they were more likely to have a high school education or less, greater BMI scores, be current smokers, and drink more alcohol compared

with those without CAC for both Y0 and Y20 covariates. At Y0, those with CAC had greater mean physical activity levels and at Y20 those with CAC were more likely to have diabetes or hypertension (Table 1). Participants with CIMT 84th or greater percentile were more likely to be older, African American, and men. For both Y0 and Y20 covariates, they were more likely to have a high school education or less, have greater BMI scores, and be current smokers compared with those with lower CIMT. At Y20, those with greater CIMT were more likely have diabetes or hypertension (Table 1).

Y0 and Y20 lipids were categorized into four groups using cutpoints created from Y0 lipid quartiles (Table 2). As expected, by Y20 individuals often shifted into greater quartiles of total cholesterol, LDL-C, triglycerides, and total cholesterol to HDL-C ratios and into lower categories of HDL-C. For example, 40% at Y20 were above the greatest Y0 quartile cutpoint for total cholesterol (≥194 mg/dL) whereas only 14% were below the lowest Y0 quartile cutpoint. The pattern was more variable for HDL-C, with 28% at Y20 falling into the lowest Y0 quartile (≤44 mg/dL) and 30% at Y20 moving into the greatest Y0 quartile (≥62 mg/dL). The odds ratios for CAC and CIMT were largely similar between Y0 and Y20 lipid quartiles in the unadjusted models (all p for trends <0.0001), although not all individual quartile comparisons were statistically significant. Furthermore, the c statistics were generally similar between Y0 and Y20, whether the outcome was CAC or CIMT, ranging from 0.56 to 0.64 in these unadjusted models. None of the nonparametric tests of correlated c-statistics, used to compare Y0 and Y20, were statistically significant.

Associations between CAC adjusted for Y0 covariates with Y0 total cholesterol, LDL-C, and triglycerides were markedly stronger and statistically significant only in the greatest compared with the lowest quartile (Table 3), suggesting a nonlinear association. All of the total cholesterol to HDL-C quartiles were significant; however, the associations between Y0 HDL-C and CAC were inconsistent across quartiles. At Y20, associations between total cholesterol, LDL-C, and the total cholesterol to HDL-C ratio with CAC also were statistically significant for the greatest quartiles after we adjusted for Y20 covariates (Table 3). At Y20, none of the HDL-C or triglyceride quartiles were statistically significantly associated with the presence of CAC. The c statistics were comparable for models containing either Y0 or Y20 lipid measures and associated covariates and ranged between 0.74 and 0.75. There were no statistically significant interactions with sex or race (all $P > .05$).

A different pattern of associations was observed for CIMT. At Y0, all cholesterol and LDL-C quartiles were significantly associated with CIMT 84th percentile or greater after we adjusted for covariates. Two of the total cholesterol-to-HDL-C ratio quartiles were statistically significantly associated with CIMT, but none of the HDL-C or triglyceride quartiles was significantly associated (Table 4). At Y20, the quartiles of total cholesterol and LDL-C remained statistically significantly associated with CIMT; however, only the greatest quartile of the total cholesterol to HDL-C ratio was statistically significantly associated with elevated CIMT when compared to the lowest quartile (Table 4). None of the Y20 HDL-C or triglycerides quartiles was associated with Y20 CIMT. As observed with CAC, there were no statistically significant interactions with sex or race for the associations between lipids and CIMT (all $P > .05$). In sensitivity analyses with the lipids modeling continuously, there

were nearly identical c-statistics and associated 95% confidence intervals for both CAC and CIMT when compared to the models that included lipid quartiles.

Discussion

This study found that lipid levels measured in young adulthood as well as middle age are both associated with two established measures of subclinical disease in middle age. The discriminatory value of lipids was virtually identical at baseline, when participants were 18–30 years of age, and 20 years later; however, both baseline and Y20 lipid data were only modest predictors of Y20 subclinical disease, based on unadjusted c statistics of 0.56–0.64, despite statistically significant associations. Baseline levels of all lipids measured predicted CAC and CIMT as well as lipids measured at Y20. In 18- to 30-year-old subjects, a total cholesterol 194 mg/dL or greater and LDL-C 126 mg/dL or greater were associated with greater odds of having CAC 20 years later. At the same age, lower lipid levels were associated with relatively greater odds of having increased CIMT 20 years later (total cholesterol ≥153 mg/dL and LDL-C ≥87 mg/dL).

The associations between LDL-C and HDL-C and CAC confirm patterns already established in earlier CARDIA studies and suggest a nonlinear increase in the odds of the subclinical disease with greater lipid levels. Pletcher et al. [7] found that the time-averaged exposures of nonoptimal levels of LDL-C and HDL-C during young adulthood were independently associated with Y20 CAC measured in middle age in CARDIA; however, there was not a statistically significant association with triglycerides. Loria et al. [6] found that Y0 measures of LDL-C and HDL-C and Y15 measures of LDL-C were associated with CAC. Loria et al. also found that a baseline multivariable model, which included measures of LDL-C and HDL-C, were as strong a predictor of CAC based on c statistics as the Y15 multivariable model with concurrent measures of LDL-C and HDL-C [6]. This study extends these findings by examining additional lipid parameters as they relate to CAC with 5 more years of follow up, and more importantly, presenting new data on the relationship between lipids and CIMT. The findings presented here also are consistent with results from other cohort studies that indicate that lipid levels measured in childhood and young adulthood are associated with both CAC and CIMT later in life [8,10,16].

Studies have found that modifiable risk factors, such as plasma lipids, “track” in an individual over time [17,18]. Thus unless clinical interventions are initiated, individuals with elevated lipid levels in childhood or young adulthood will have a higher absolute risk of atherosclerosis and coronary heart disease later in life. Autopsy studies have shown that fatty streaks begin in childhood and progress to atherosclerosis by young adulthood [19]. We show that adverse associations exist between lipid levels and subclinical disease when measured in young adulthood, and that the associations do not change over time, suggesting that adverse levels in young adulthood may be important in initiating future atherosclerotic disease.

We were also interested in whether race or sex would affect the relationships between lipids and CAC and/or CIMT, and found no differences. Although observational studies have limitations in terms of measurement error leading to residual confounding in covariates,

especially those that are self-reported, a central strength of this study is its generalizability, large sample size, and high retention rate.

Our findings suggest that lipid risk reduction during young adulthood may provide benefits in terms of preventing atherosclerosis and cardiovascular events later in life. Lipid levels measured when individuals were 18–30 years of age predicted subclinical measures of atherosclerosis comparably to those measured when the individuals were 38–50 years of age. Although our data do not suggest a difference in risk prediction over time for lipids, they suggest that young adulthood is not too early to improve cardiovascular health through lifestyle modification, one small component of which is improving lipid profiles. Guidelines from the National Heart, Lung, and Blood Institute National Cholesterol Education Program's Adult Treatment Panel III recommend that all adults age 20 years and older obtain a lipid profile every 5 years. Recently released guidelines for screening and treatment in children recommend that lipid levels be measured at least once between the ages of 17 and 21, in addition to measures obtained earlier in childhood to counter progression of lipid risk factors [20,21]. Lipid treatment guidelines generally recommend lifestyle changes as the first treatment option, especially in children. The effectiveness and safety of long-term lipid-lowering therapy in children and young adults is limited, making it difficult to develop evidence-based recommendations for such treatment at these ages [22–24]. Clinical trial evidence proving that treatment early in life reduces CHD events much later in life will be difficult to obtain; therefore, gathering evidence via observational studies like this one will be critically important to inform guidelines. Our findings are consistent with a growing body of evidence that early life exposure to non-optimal lipids matters.

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Table 1

Baseline and year 20 characteristics by CAC and CIMT status prevalence in the CARDIA study

	Year 0						Year 20					
	No CAC	**CAC**	***P* value for difference**	**CIMT <84th percentile**	**CIMT ≥84th percentile**	***P* value for difference**	**No CAC**	**CAC**	***P* value for difference**	**CIMT <84th percentile**	**CIMT ≥84th percentile**	***P* value for difference**
N	2057 (84)	378 (16)		2045 (84)	390 (16)							
Age, yrs *	25.0 (3.6)	27.0 (3.4)	<.0001	25.0 (3.6)	27.0 (3.2)	<.0001	45.0 (3.6)	47.0 (3.7)	<.0001	45.0 (3.6)	47.0 (3.1)	<.0001
Men, %	36.4	65.3	<.0001	37.0	56.4	<.0001						
White race, %	54.5	59.5	.08	56.5	49.0	.006						
Education ≤ high school, %	32.5	39.2	.01	32.6	38.2	.03	20.7	29.4	.0002	20.5	29.7	<.0001
Hypertension, %	1.0	2.1	.06	1.0	1.8	.19	18.4	25.7	.001	17.9	28.5	<.0001
Diabetes, %							4.2	7.7	.003	3.8	9.5	<.0001
BMI, kg/m2	22.9 (4.4)	24.4 (4.4)	<.0001	23.7 (4.5)	24.5 (4.8)	<.0001	27.5 (6.3)	28.7 (6.7)	.002	27.3 (6.3)	29.4 (6.2)	<.0001
Physical activity (EU)	356.0 (293.5)	410.0 (301.0)	.007	362.0 (291.7)	367.0 (312.1)	.93	273.0 (276.7)	301.5 (301.5)	.27	282.0 (276.7)	267.0 (268.6)	.16
Current smoker, %	22.4	38.1	<.0001	23.6	31.3	.0001	15.6	32.0	<.0001	16.6	25.9	<.0001
Alcohol, mL per day	2.7 (18.0)	9.5 (24.9)	<.0001	4.8 (19.1)	4.8 (20.9)	.12	2.4 (20.0)	4.8 (30.3)	.01	2.4 (21.4)	2.4 (24.8)	.99

BMI = body mass index; CAC = coronary artery calcification; CARDIA = Coronary Artery Development in Young Adults; CIMT = carotid intima media thickness; EU = exercise units.

*Continuous variables are reported as median (SD).

Table 2

Crude associations between lipid cutpoints as defined at Y0 and CAC and CIMT at Y0 and Y20

	Year 0 quartile cutpoints	Year 0					Year 20				
		Y0 N (%)	CAC OR (95% CI)	C statistic	CIMT OR (95% CI)	C statistic	Y20 N (%)	CAC OR (95% CI)	C statistic	CIMT OR (95% CI)	C statistic
Total cholesterol, mg/dL	≤152	594 (24)	Ref	0.59	Ref	0.58	338 (14)	Ref	0.58	Ref	0.59
	153–172	635 (26)	1.13 (0.80–1.60)		1.54 (1.09–2.17)		504 (21)	1.05 (0.68–1.62)		1.55 (0.98–2.46)	
	173–193	589 (24)	1.42 (1.01–2.00)		1.94 (1,38–2.72)		615 (25)	1.27 (0.84–1.91)		1.85 (1.19–2.87)	
	≥194	617 (25)	2.33 (1.70–3.20)		2.27 (1.63–3.15)		978 (40)	1.99 (1.37–2.88)		2.84 (1.89–4.29)	
LDL cholesterol, mg/dL	≤86	597 (25)	Ref	0.61	Ref	0.59	529 (22)	Ref	0.60	Ref	0.63
	87–104	629 (26)	1.06 (0.74–1.51)		1.68 (1.18–2.38)		537 (22)	1.25 (0.86–1.82)		1.55 (1.03–2.31)	
	105–125	610 (25)	1.44 (1.02–2.02)		2.15 (1.52–3.03)		631 (26)	1.33 (0.92–1.90)		2.03 (1.39–2.95)	
	≥126	599 (25)	2.74 (2.00–3.76)		2.68 (1.91–3.75)		738 (30)	2.61 (1.88–3.61)		3.61 (2.54–5.13)	
HDL cholesterol, mg/dL	≤44	591 (24)	Ref	0.60	Ref	0.58	689 (28)	Ref	0.61	Ref	0.58
	45–52	602 (25)	0.59 (0.44–0.79)		0.84 (0.64–1.12)		523 (21)	0.85 (0.64–1.12)		0.83 (0.62–1.10)	
	53–61	631 (26)	0.60 (0.45–0.81)		0.55 (0.41–0.75)		494 (20)	0.44 (0.31–0.61)		0.65 (0.49–0.89)	
	≥62	611 (25)	0.34 (0.24–0.47)		0.48 (0.35–0.66)		729 (30)	0.40 (0.29–0.54)		0.48 (0.36–0.65)	
Triglycerides, mg/dL	≤44	609 (25)	Ref	0.58	Ref	0.56	183 (8)	Ref	0.59	Ref	0.57
	45–59	612 (25)	1.19 (0.85–1.69)		1.19 (0.86–1.64)		376 (15)	1.20 (0.63–2.30)		1.33 (0.74–2.39)	
	60–80	616 (25)	1.52 (1.09–2.11)		1.10 (0.80–1.53)		553 (23)	1.74 (0.96–3.17)		1.60 (0.92–2.79)	
	≥81	598 (25)	2.23 (1.62–3.06)		1.82 (1.35–2.47)		1323 (54)	2.95 (1.68–5.17)		2.28 (1.36–3.82)	
Cholesterol-to-HDL cholesterol ratio, mg/dL	≤2.72	609 (25)	Ref	0.64	Ref	0.60	589 (24)	Ref	0.64	Ref	0.62
	2.73–3.22 mg/dL	608 (25)	1.65 (1.14–2.39)		148 (1 04–2 10)		446 (18)	0 87 (0 57–1 34)		0.91 (0.60–1.37)	
	3.23–3.91 mg/dL	609 (25)	1.63 (1.12–2.36)		1.64 (1.16–2.31)		526 (22)	1.43 (0.99–2.08)		1.41 (0.98–2.02)	
	≥ 3.92 mg/dL	609 (25)	4.17 (2.98–5.84)		2.91 (2.10–4.02)		874 (36)	3.01 (2.20–4.12)		2.69 (1.98–3.65)	

CAC = coronary artery calcification; CI = confidence interval; CIMT = carotid intima media thickness; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio.

Table 3

Associations between lipid quartiles as defined at Y0 and the odds of CAC in multivariable models

	Year 0*					Year 20†				
	OR	**95% CI**	***p* for trend**	**C statistic**	**95% CI**	**OR**	**95% CI**	***p* for trend**	**C statistic**	**95% CI**
Cholesterol			<0.0001	0.75	(0.72–0.77)			<0.0001	0.75	(0.72–0.78)
Q2	1.23	(0.86–1.77)				1.14	(0.72–1.81)			
Q3	1.34	(0.94–1.91)				1.31	(0.85–2.01)			
Q4	2.36	(1.68–3.31)				2.00	(1.35–2.97)			
LDL-C			<0.0001	0.75	(0.72–0.78)			<0.0001	0.75	(0.73–0.78)
Q2	1.07	(0.74–1.55)				1.31	(0.88–1.96)			
Q3	1.32	(0.92–1.89)				1.18	(0.80–1.73)			
Q4	2.53	(1.80–3.55)				2.20	(1.55–3.13)			
HDL-C			0.003	0.74	(0.71–0.76)			0.09	0.74	(0.72–0.77)
Q2	0.69	(0.50–0.94)				1.11	(0.82–1.51)			
Q3	0.81	(0.59–1.12)				0.79	(0.55–1.15)			
Q4	0.51	(0.35–0.75)				0.77	(0.53–1.10)			
Triglycerides			0.02	0.74	(0.71–0.76)			0.02	0.74	(0.72–0.77)
Q2	1.12	(0.78–1.60)				1.32	(0.67–2.60)			
Q3	1.31	(0.92–1.86)				1.45	(0.77–2.70)			
Q4	1.48	(1.05–2.10)				1.78	(0.98–3.22)			
Ratio of cholesterol to HDL-C			<0.0001	0.75	(0.73–0.78)			0.0003	0.75	(0.72–0.78)
Q2	1.79	(1.21–2.63)				0.79	(0.50–1.23)			
Q3	1.55	(1.05–2.29)				1.15	(0.78–1.71)			
Q4	3.24	(2.23–4.71)				1.68	(1.17–2.42)			

CAC = coronary artery calcification; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio.

*Y0 is adjusted for the Y0 covariates age, sex, race, center, education, body mass index, physical activity, smoking, alcohol consumption, and hypertension.

†Year 20 is adjusted for sex, race, center plus the Y20 covariates age, education, body mass index, physical activity, smoking, alcohol consumption, hypertension, and diabetes.

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Table 4

Associations between lipid quartiles as defined at Y0 and the odds of CIMT in multivariable models

	Year 0*					Year 20†				
	OR	**95% CI**	***p* for trend**	**C statistic**	**95% CI**	**OR**	**95% CI**	***p* for trend**	**C statistic**	**95% CI**
Cholesterol			0.0001	0.71	(0.69–0.74)			<0.0001	0.74	(0.71–0.76)
Q2	1.67	(1.18–2.38)				1.81	(1.12–2.94)			
Q3	1.80	(1.27–2.56)				1.99	(1.26–3.16)			
Q4	2.01	(1.42–2.83)				3.13	(2.04–4.82)			
LDL-C			<0.0001	0.72	(0.69–0.74)			<0.0001	0.74	(0.71–0.77)
Q2	1.69	(1.17–2.43)				1.59	(1.04–2.42)			
Q3	1.88	(1.32–2.69)				1.93	(1.30–2.87)			
Q4	2.13	(1.50–3.03)				3.19	(2.20–4.61)			
HDL-C			0.02	0.71	(0.68–0.74)			0.49	0.72	(0.69–0.74)
Q2	1.03	(0.76–1.39)				1.06	(0.78–1.44)			
Q3	0.73	(0.53–1.01)				1.09	(0.77–1.55)			
Q4	0.72	(0.51–1.03)				0.90	(0.63–1.27)			
Triglycerides			0.13	0.71	(0.68–0.74)			0.26	0.72	(0.69–0.75)
Q2	1.14	(0.82–1.59)				1.39	(0.75–2.55)			
Q3	0.97	(0.69–1.37)				1.31	(0.74–2.33)			
Q4	1.37	(0.98–1.91)				1.44	(0.84–2.49)			
Ratio of total cholesterol to HDL-C			0.0005	0.71	(0.69–0.74)			0.0005	0.73	(0.70–0.75)
Q2	1.46	(1.02–2.10)				0.79	(0.51–1.20)			
Q3	1.42	(0.99–2.04)				1.05	(0.72–1.54)			
Q4	1.95	(1.37–2.78)				1.62	(1.15–2.30)			

CI = confidence interval; CIMT = carotid intima media thickness; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio.

*Y0 is adjusted for the Y0 covariates age, sex, race, center, education, body mass index, physical activity, smoking, alcohol consumption, and hypertension.

†Year 20 is adjusted for sex, race, center plus the Y20 covariate sage, education, body mass index, physical activity, smoking, alcohol consumption, hypertension, and diabetes.