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Associations of serum LDL particle concentration with carotid intima-media thickness and coronary artery calcification

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CONFLICT OF INTEREST
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Abstract

Background—Low-density lipoprotein particle (LDL-P) has recently been found to be a stronger predictor of cardiovascular disease (CVD) than LDL cholesterol (LDL-C).

Objective—Whether LDL-P is associated with subclinical atherosclerosis, independent of LDL-C, as well as other lipid measures has not been fully examined. We aimed to analyze LDL-P associations with measures of subclinical atherosclerosis.

Methods—We examined 870 Japanese men randomly selected from Kusatsu City, Shiga, Japan, aged 40–79 years from 2006–2008, free of clinical CVD and not using lipid-lowering medication. Cross-sectional associations of lipid measures with carotid intima-media thickness (cIMT) and coronary artery calcification (CAC) [>0 Agatston score] were examined.

Results—LDL-P was significantly positively associated with cIMT and maintained this association after adjustments for LDL-C and other lipid measures. While these lipid measures were positively associated with cIMT, model adjustment for LDL-P removed any significant relationships.

Higher LDL-P was associated with a significantly higher odds ratio of CAC and further adjustment for LDL-C did not affect this relationship. In contrast, the LDL-C association with CAC was no longer significant after adjustment for LDL-P. Other lipid measures attenuated associations of LDL-P with CAC. Likewise, associations of these measures with CAC were attenuated when model adjustments for LDL-P were made.

Conclusion—In a community-based sample of Japanese men, free of clinical CVD, LDL-P was a robust marker for subclinical atherosclerosis, with the former being independent of LDL-C and other lipid measures. Associations of LDL-C and other lipid measures with either cIMT or CAC were generally not independent of LDL-P.

Keywords

Low-density lipoprotein particle (LDL-P); Low-density lipoprotein cholesterol (LDL-C); Carotid intima-media thickness (cIMT); Coronary artery calcification (CAC); Subclinical atherosclerosis

INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) has been widely accepted as one of the main causal determinants of atherosclerosis and, thus, a commonly used lipid measure for cardiovascular disease (CVD) risk assessment[1, 2]. However, in CVD patients who achieve recommended LDL-C levels using statin medication, residual risk of cardiovascular disease (CVD) is still prominent[3, 4]. Thus, attention has been shifted towards alternate measures of LDL, specifically the total number of LDL particles (LDL-P), to better understand and measure this residual risk.

Recently, It has been shown that LDL-P is a stronger predictor of CVD risk than LDL-C[5, 6]. Despite the high correlation between LDL-P and LDL-C, the amount of cholesterol per LDL particle can vary as much as two-fold between individuals[5]. In situations where these two measures are discordant, ie. high levels of LDL-C do not coincide with high levels of LDL-P, CVD events are better predicted by LDL-P rather than LDL-C[6]. Thus, the sole reliance on LDL-C as a marker of CVD risk may be an inaccurate estimate of true risk.

Few studies have assessed LDL-P associations with risk of subclinical carotid or coronary atherosclerosis in randomly-selected healthy individuals[6, 7], and none, that we know of, have used stringent model adjustment to analyze robustness and independence of LDL-P from its cholesterol counterpart, LDL-C, as well as other lipid measures. Thus, in Japanese men, a population at low risk of CVD[8–10], we investigate whether LDL-P has cross-sectional associations with carotid intima-media thickness (cIMT) and coronary artery calcification (CAC), independent of select cardiovascular risk factors and lipid measures.

MATERIALS AND METHODS

Study Participants

Under Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), a population-based study of randomly selected Japanese men from Kusatsu City, Shiga, Japan[11, 12], from 2006 to 2008, a total of 1,094 men aged 40 to 79 years were recruited. Eligible participants for this present study met the following conditions: not taking lipid-lowering medication, free of CVD, and no missing information on lipid medication or LDL-P. A total of 870 Japanese males were analyzed in this study. This study adheres to *the Declaration of Helsinki*, was approved by the Institutional Review Board of Shiga University of Medical Science, Otsu, Japan (No. 17-19, 17-83) and each participant provided written informed consent.

Data on medical history, use of medication, smoking, alcohol intake, and other lifestyle factors were collected from each participant using a self-administered questionnaire. Trained technicians confirmed the completed questionnaire with participants.

Each participant underwent a physical examination for collection of information on weight, height, blood pressure, and other physical and measurable characteristics. Using an automated sphygmomanometer (BP-8800; Omron Colin, Tokyo, Japan) the mean of two consecutive measurements on the right arm were used to estimate blood pressure. Measurements were performed after participants sat motionless in a seated position for 5 minutes. Body mass index (BMI) was calculated using weight (kg) divided by height squared (m^2). Hypertension was defined as the use of antihypertensive medication, having systolic blood pressure (SBP) ≥140mm Hg, or having diastolic blood pressure (DBP) ≥90mm Hg. Diabetes mellitus (DM) was defined as the use of antidiabetic medication, a hemoglobin A1c (HbA1c) ≥ 6.1% (Japanese Diabetes Society criteria; equivalent to ≥ 6.5% under National Glycohemoglobin Standardization Program[13]), or having a fasting glucose ≥6.99 mmol/L (or 126 mg/dL).

Laboratory Measurements

After a 12-hour fast, blood samples from participants were drawn and centrifuged at 4°C and serum samples were stored at −80°C. Enzymatic techniques were used to measure standard lipids, such as triglycerides and total cholesterol. Heparin-calcium precipitation was used to measure high-density lipoprotein cholesterol (HDL-C). Measurements were standardized following the protocol of the US Center for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network (CDC/CRMLN)[14]. LDL-C levels were estimated using the Friedewald equation [LDL-C (mg/dL) = total cholesterol (mg/dL) – HDL-C (mg/dL) – triglyceride (mg/dL)/5]. In men with triglyceride >4.52 mmol/L (400 mg/dL), LDL-C was treated as missing (n=12). Non-HDL-C was calculated as total cholesterol (mg/dL) – HDL-C (mg/dL).

Serum LDL-P and HDL-P levels were measured using nuclear magnetic resonance (NMR) spectroscopy by LipoScience Inc (Raleigh, North Carolina, US). Amplitudes of distinct spectroscopic NMR signals of the lipid methyl group characteristic of each lipoprotein particle was used to obtain concentrations of the specified particle. LDL-P and HDL-P measurement by NMR have coefficient of variations of < 4%[15]. Small and large LDL-P were defined as LDL particles with sizes 18.3–21.2nm and 21.3–23nm, respectively.

Coronary artery calcification measurements

Coronary artery calcification (CAC) was measured either using 1) electron-beam computed tomography (EBCT) with a C-150 scanner (Imatron, South San Francisco, CA, US) or 2) a 16-channel multidetector-row computed tomography (MDCT) with an Aquilion scanner (Toshiba, Tokyo, Japan). EBCT and MDCT images accounted for 69.1% (n=601) and 30.9 % (n=269) of measured CAC, respectively. Starting from the root of the aorta, images were taken every 3 mm slice with a scan time of 100 millisecond for EBCT and 320 millisecond for MDCT. Using electrocardiogram triggering and during a single breath-hold, images were obtained at 70% of the cardiac cycle. CAC was calculated with AccuImage software (AccuImage Diagnostics, South San Francisco, CA, US). Presence of CAC was defined as a minimum of 3 contiguous pixels, an area of $1mm^2$, having a density of ≥130 Hounsefield units. At each high-density lesion of the epicardial coronary arteries, peak density and area were measured and used to calculate CAC as Agatston score[16]. All images were analyzed by one physician, who was trained in computed tomography at the Cardiovascular Institute of the University of Pittsburgh. The physician was blinded to the characteristics of participants. CAC measurement protocol was developed from a separate cohort study by our research group[12] in which scan reproducibility had an intraclass correlation of 0.98[17]. For all analyses, presence of CAC was defined as Agatston score > 0. Sensitivity analysis of CAC presence as Agatston score ≥10 was also performed. A total of 148 participants had Agatston score >0 and <10.

Carotid intima-media thickness measurements

Following the Ultrasound Research Laboratory guidelines at the University of Pittsburgh[11, 18], high-resolution B-mode ultrasound of the carotid arteries was used to scan both right and left carotid arteries using a Toshiba ZarioSSA-660A scanner (Toshiba Medical Systems, Japan), with a 7.5MHz linear-array imaging probe. The intima-media

thickness (IMT) of the carotid bulb, common carotid artery (CCA), and internal carotid artery were measured in both left and right arteries. Near and far walls of the CCA section were measured 1cm proximal to the bulb. Only far walls were examined for the bulb and internal carotid artery sections. The mean of the eight IMT values (four on each artery) was defined as cIMT.

Statistical Analyses

Characteristics of participants were analyzed per quartile of LDL-P. For trend P-values, LDL-P was treated as a continuous variable and linear regression was used for continuous variables and logistic regression was used for categorical variables.

Linear regression analysis was used to estimate excess in cIMT per 1 standard deviation (SD) higher LDL-P. All models were adjusted for base covariates: age (years), SBP (mmHg), hypertension medication (yes/no), current smoker (yes/no), alcohol intake (g/day) and DM (yes/no). LDL-P models were further adjusted for other lipid measures, such as HDL-C, HDL particle (HDL-P), triglycerides, total cholesterol (TC), LDL-C, LDL size and lipid measures: non-HDL-C, LDL-C/HDL-C ratio, and TC/HDL-C ratio. Associations of LDL-C and lipid measures with cIMT were also analyzed per 1 SD higher level of measure.

Logistic regression was used to determine odds ratio (OR) of CAC per 1 SD higher LDL-P, LDL-C and other lipid measures. Models were adjusted for base covariates and type of computed tomography scan (EBCT vs MDCT). Models were further adjusted for other cardiovascular risk factors.

Sensitivity analyses were performed for LDL-P associations with presence of CAC ≥10 Agatston score (to reduce false positive presence of CAC) and for associations of LDL-P size subclasses small and large with cIMT and CAC (>0 Agatston score).

SAS version 9.4 (SAS Institute, Cary, North Carolina) was used to for all analyses. Two-tailed *P*-values of <0.05 were considered significant.

RESULTS

Study participants and characteristic trends

Mean (SD) age and cIMT for participants were 63.3 (10) years and 834 (184) μm, respectively. CAC prevalence was 45.1% (n=392). Table 1 depicts characteristics of participants according to quartiles of LDL-P. Higher LDL-P levels were associated positively with traditional CVD risk markers (BMI, triglycerides and LDL-C) and lipid measures (non-HDL-C, LDL-C/HDL-C and TC/HDL-C). LDL-P levels were inversely associated with alcohol intake, HDL-C and HDL-P. Higher LDL-P levels were associated with higher cIMT and CAC levels.

LDL-P and lipid measure associations with cIMT

In Table 2, LDL-P associations with cIMT was assessed under multivariable model adjustments. In a model adjusted for base covariates, a 1 SD higher LDL-P was associated with 31μm higher cIMT (P<0.001). Model adjustment for LDL-C slightly affected the

association of LDL-P with cIMT, reducing it to a 24.6μm (P=0.010) higher cIMT per 1 SD higher LDL-P. LDL-P maintained significant positive associations with cIMT after adjustment for HDL-C or HDL-P. Adjustments for other lipid measures did not considerably affect associations of LDL-P with cIMT.

Independently, LDL-C, non-HDL-C, LDL-C/HDL-C, and TC/HDL-C were all positively associated with cIMT, ranging from 23.6μm – 28.9μm higher cIMT per 1 SD higher lipid measure. However, inclusion of LDL-P in the models removed these associations (Table 3).

LDL-P and lipid measure associations with CAC

Tables 4 and 5 depict OR of CAC per 1 SD higher LDL-P, LDL-C and lipid measure. A 1 SD higher LDL-P is associated with higher odds of CAC (1.36 OR [95% CI: 1.15, 1.61]) in a model adjusted for base covariates. LDL-C, triglycerides, TC, HDL-C, HDL-P and LDL size had little effect on the magnitude of association of LDL-P with CAC. Adjustments for either non-HDL-C, LDL-C/HDL-C, or TC/HDL-C attenuated the magnitude of associations of LDL-P with CAC, resulting in a loss of statistical significance. A similar trend was observed in a sensitivity analysis with CAC presence defined as ≥10 Agatston score (Supplementary Table I). A 1 SD higher LDL-C and other lipid measure were significantly associated with higher odds of CAC (>0 Agatston score), in models adjusted for base covariates. However, further adjustments for LDL-P attenuated associations of LDL-C, non-HDL-C and LDL-C/HDL-C with CAC. The ratios LDL-C/HDL-C and TC/HDL-C maintained a significant associations with CAC in the presence of LDL-P adjustment. In a sensitivity analyses with CAC ≥10 Agatston score, associations of these ratios or other lipid measures with CAC were not independent of LDL-P (Supplementary Table I).

DISCUSSION

LDL-P associations with subclinical carotid and coronary atherosclerosis

In a cross-sectional study of Japanese men, we investigated the associations of LDL-P with subclinical atherosclerosis and have identified robust positive associations of LDL-P with cIMT and CAC. LDL-P associations with cIMT persisted after model adjustment for LDL-C and other lipid measures. Analysis of LDL-C and lipid measure associations with cIMT revealed that these significant relationships were lost once adjustments for LDL-P were made. Of all the lipid measures assessed in this study, LDL-P, having the highest effect size of 31μm cIMT per 1 SD elevation, was the most strongly and robustly associated with cIMT. Likewise, in CAC analysis, LDL-P was significantly associated with CAC presence, independent of LDL-C. LDL-C association with CAC was not as strong, nor was it independent of LDL-P. These results suggest that of the two LDL measures, LDL-P is the stronger and more robust indicator of CAC presence. Adjustments for non-HDL-C, LDL-C/HDL-C and TC/HDL-C attenuated the association of LDL-P with CAC. Although the associations of LDL-C/HDL-C and TC/HDL-C ratios with CAC > 0 Agatston score appear independent of LDL-P, sensitivity analyses of CAC ≥ 10 Agatston score depicts otherwise (Supplementary Table I). Overall, our results suggest that associations of LDL-C and other lipid measures with subclinical carotid and coronary atherosclerosis are not independent of

LDL-P, and, more importantly, that LDL-P was associated with these subclinical diseases independent of most other lipid measures assessed.

We present consistent findings with other studies, where higher LDL-P was associated with thicker cIMT [19] and higher OR of CAC presence[20]. Furthermore, unlike its cholesterol counterpart, LDL-P was strongly associated with coronary heart disease progression[21] and incidence[5, 22].

Comparison of LDL-P to LDL-C and other lipid measures

LDL-P is an alternate LDL measure and although it is highly correlated with LDL-C, the cholesterol amount carried by each LDL particle varies[6]. LDL-P may identify a different measure, characteristic, or function of LDL that more closely relates to risk of subclinical atherosclerosis. Higher levels of circulating LDL-P may increase the chances of these particles damaging the arterial wall and entering into the intimal layer, where they become oxidized and initiate various plaque formation processes[23]. Whether LDL-P itself is an initiator of plaque formation or whether other mechanisms that lead to atherosclerosis also increase LDL-P are premature speculations and in need of further study.

Size subclasses of LDL have been associated with higher odds of incident cIMT[7]. The same was true in our study (Supplementary Table II), however, further model adjustment revealed that these associations were not independent of LDL-P. For presence of CAC, small LDL-P association with higher OR was attenuated with adjustment for LDL-P. Similarly, a study in adults at intermediate risk of CVD revealed that total LDL-P and small LDL-P were strong predictors of CAC, however only small LDL-P was further assessed for independence from other lipid measures[24]. We have shown that the relationship of LDL-P with CAC and cIMT is independent of LDL size and the relationship of small LDL-P with cIMT is not independent of LDL-P. These results suggest that LDL-P may be an important factor in the relationship of small LDL-P with subclinical atherosclerosis. Due to the strong correlation of total LDL-P with small LDL-P (Supplementary Table III), these findings should be considered with scrutiny.

Non-high-density lipoprotein cholesterol (non-HDL-C) has also recently been shown to be a strong indicator of CVD risk, superior to LDL-C[25]. Indeed, we observed that non-HDL-C was one of the strongest indicators of coronary artery calcification (CAC) presence in healthy Japanese men[26]. Non-HDL-C is a measure of cholesterol content in total putative atherogenic particles, mainly from LDL, very low-density lipoprotein (VLDL), and chylomicrons[27]. However, due to the cholesterol variability in lipoproteins, non-HDL-C may leave residual risk after treatment goals are met. This is evident in circumstances of discordance between non-HDL-C and apoB (the protein component and estimate of LDL-P) levels, where apoB is a more accurate indicator of CVD risk[28].

We have previously shown that HDL-P is robustly associated with lower cIMT, independent of other CVD risk factors, as well as its cholesterol counterpart, HDL-C[29]. In this study, we demonstrate that LDL-P association with cIMT is also robust and, furthermore, independent of HDL-P. Likewise, the association of HDL-P with cIMT is independent of LDL-P (data not shown). With regard to CAC, LDL-P maintained a significantly higher OR of prevalent

CAC than those of conventional lipid measures, also independent of HDL-P. In contrast, HDL-P was not associated with CAC in any model (data not shown). In general, we found that LDL-P, in comparison to HDL-P, LDL-C and other lipid measures is the more robust marker of subclinical atherosclerosis.

Comparison of CAC to cIMT

LDL-P is highly correlated with other lipid measures (Supplementary Table III) and these measures are also associated with CAC, the response variable (Table 5). Thus, overadjustment (ie lipid measures as intermediate variables on a causal pathway between LDL-P, or vice versa, and CAC) may provide an answer for the loss of associations, via the loss of precision, with CAC when any of these variables were combined in a model. In this situation, the reason for the loss of associations occurring only in CAC and not in cIMT warrants further study. Despite both cIMT and CAC being independent predictors of CVD events[30], they are slightly different measures of the pathogenesis of atherosclerosis. It is believed that cIMT is indicative of plaque burden in the carotid arteries[31], however cIMT was initially developed as a non-invasive surrogate for coronary atherosclerosis[32]. In comparison, CAC score is a more direct gauge of coronary burden and is highly correlated with the volume of coronary artery plaque[33]. It is important to note that not all plaques are calcified[34, 35]. Calcification in the coronary arteries is representative of the natural progression of plaques[34, 36], in which calcification occurs and increases with time. Thus, over time, it is possible that other factors, such as non-HDL-C and other atherogenic factors, may also play a role in plaque histology and composition that lead to calcification.

Limitations and Strengths

As is the case with cross-sectional studies, we cannot conclude causality in the associations of LDL-P with cIMT or CAC based on the results of our study. Also, as only Japanese men were analyzed, our results are restricted to men of a single ethnic group. However, population homogeneity reduces possible confounding from genetic variation and from cultural and environmental factors, including lifestyle behavior.

To our knowledge, we are the first to use stringent model adjustment for associations of LDL-P independent of LDL-C or other lipid measure with cIMT and CAC, suggesting that LDL-P may play an important role in pathogenesis of atherosclerosis. Also, we are the first to demonstrate that the associations of these lipid measures with cIMT were not independent of LDL-P.

Although the National Lipid Association endorses the use of LDL-P in identifying individuals who are likely to benefit from lipid therapy or from increased lipid therapy[37], the aim of our study was not to improve such prediction of CVD risk. Epidemiological studies, including cross-sectional ones, aim to direct and guide future basic research through attempts at uncovering putative causal associations between exposure and outcome. Thus, we hoped to better understand the associations of LDL-P and select lipid measures with subclinical atherosclerosis in an attempt to achieve insight into the driving lipid-related factors associated with atherosclerosis.

Conclusion

Overall, we demonstrate that LDL-P is a robust marker for subclinical carotid atherosclerosis in a community-based sample of CVD-free Japanese men. Associations of LDL-C and other lipid measures with either cIMT or CAC were not independent of LDL-P.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of SESSA Participants, 870 men aged 40–79 years (2006–2008)

Characteristic	Quartile of total LDL-P			
	1 (297 – 1002 nmol/L)	2 (1003–1259 nmol/L)	3 (1260 – 1534 nmol/L)	4 (1535 – 3156 nmol/L)
Age, years	64.2 ± 9.5	63 ± 10.4	63.4 ± 10.7	62.6 ± 9.4
Bodymass index, kg/m^2	22 ± 2.7	23.1 ± 2.8	23.9 ± 2.9	24.4 ± 3
SBP, mmHg	135 ± 19	134 ± 20	137 ± 20	138 ± 19
Alcohol intake (g/day)	34.2 ± 33.6	20.7 ± 21.3	21.9 ± 27.9	19.7 ± 25.3
Hypertension, %	50.7	47.5	51.4	54.6
Current smoker, %	32.3	33.8	31.9	35.8
Diabetes, % (Type 2)	15.7	16.4	19.4	21.6
EBCT, %	71	69.4	64.4	71.6
Triglyceride, mmol/L	1.3 ± 1.15	1.28 ± 0.93	1.39 ± 0.59	1.61 ± 0.85
LDL-C, mmol/L	2.41 ± 0.54	3.1 ± 0.49	3.41 ± 0.49	4.11 ± 0.62
HDL-C, mmol/L	1.76 ± 0.5	1.63 ± 0.44	1.43 ± 0.39	1.31 ± 0.29
HDL-P, µmol/L	36.3 ± 7.9	34.6 ± 6.3	33.5 ± 6.3	32.6 ± 5.6
Small LDL-P, nmol/L	171 ± 192	350 ± 256	620 ± 312	984 ± 340
Large LDL-P, nmol/L	528 ± 240	676 ± 284	652 ± 317	674 ± 309
LDL Size (mean), nm	21.2 ± 0.5	21.1 ± 0.5	20.8 ± 0.5	20.6 ± 0.5
Non-HDL-C, mmol/L	2.96 ± 0.66	3.67 ± 0.54	4.06 ± 0.53	4.84 ± 0.69
LDL-C/HDL-C	1.5 ± 0.5	2 ± 0.5	2.5 ± 0.6	3.3 ± 0.8
Total-C/HDL-C	2.9 ± 0.8	3.4 ± 0.8	4 ± 0.8	4.9 ± 1
cIMT, µm	800 ± 167	818 ± 183	852 ± 196	867 ± 182
CAC (Median), Agatston †	2.3 [0, 65]	3.6 [0, 59]	7.7 [0, 104]	10 [0, 58]

Values are mean ± SD or % (as indicated).

P-values for trend (P trend) of continuous and categorical variables were obtained using linear regression and logistic regression (for presence of characteristic), respectively, per 1 unit increase in LDL-P.

†CAC values are displayed as median [25th percentile, 75th percentile]. P value was obtained for presence of CAC (>0) per 1 unit increase in LDL-P.

SBP = systolic blood pressure, EBCT = electron-beam computed tomography, HDL-P = high-density lipoprotein particle, LDL-P = low-density lipoprotein, Total-C = total cholesterol, cIMT= carotid intima-media thickness, CAC = coronary artery calcification.

Table 2

Estimated excess in cIMT per 1 standard deviation (SD) elevation in LDL-P

Model	cIMT (μm)	95% CI	P-value
Base covt	31.0	20.4, 41.5	<0.001
Base covt + LDL-C	24.6	5.9, 43.3	0.010
Base covt + TG	31.6	21.0, 42.2	<0.001
Base covt + TC	31.0	17.3, 44.7	<0.001
Base covt + HDL-C	29.9	18.6, 41.2	<0.001
Base covt + HDL-P	27.4	16.7, 38.2	<0.001
Base covt + LDL size	32.1	20.5, 43.7	<0.001
Base covt + Non-HDL-C	28.1	10.6, 45.5	0.002
Base covt + LDL-C/HDL-C	26.8	9.5, 44.1	0.003
Base covt + TC/HDL-C	28.7	14.2, 43.2	<0.001

Base covariates (Base covt) include: age, SBP, hypertension medication (yes/no), and smoking status (yes/no), diabetes (yes/no) and alcohol intake. 1 SD of LDL-P = 393.8 nmol/L.

95% CI= 95% confidence interval, TG = triglycerides, TC = total cholesterol.

Table 3

Estimated excess in cIMT per 1 SD elevation in lipid measure

Parameter	Model	cIMT (μm)	95% CI	P-value
LDL-C	Base covt	28.9	18.0, 39.7	<0.001
	Base covt + LDL-P	8.7	−10.1, 27.5	0.366
Non-HDL-C	Base covt	26.2	15.5, 36.9	<0.001
	Base covt + LDL-P	3.7	−13.9, 21.3	0.681
LDL-C/HDL-C	Base covt	27.8	16.7, 38.8	<0.001
	Base covt + LDL-P	6.3	−11.4, 24.0	0.485
Total-C/HDL-C	Base covt	23.6	12.6, 34.5	<0.001
	Base covt + LDL-P	3.4	−11.5, 18.3	0.653

Base covariates (Base covt) include: age, SBP, hypertension medication (yes/no), and smoking status (yes/no), diabetes (yes/no) and alcohol intake. Models were further adjusted for HDL-P and LDL-P. 1 SD of LDL-C = 31.4mmol/L, non-HDL-C = 34.8mg/dL, LDL-C/HDL-C = 0.90, T-C/HDL-C= 1.12.

Table 4

Odds Ratio of CAC presence (Agatston score > 0) per 1 SD elevation in LDL-P

Model	OR	95% CI	P-value
Base covt	1.36	1.15, 1.61	<0.001
Base covt + LDL-C	1.55	1.15, 2.08	0.004
Base covt + TG	1.32	1.11, 1.56	0.001
Base covt + TC	1.37	1.10, 1.69	0.004
Base covt + HDL-C	1.28	1.08, 1.53	0.006
Base covt + HDL-P	1.33	1.12, 1.57	0.001
Base covt + LDL size	1.23	1.02, 1.48	0.028
Base covt + Non-HDL-C	1.16	0.89, 1.53	0.281
Base covt + LDL-C/HDL-C	1.11	0.84, 1.45	0.472
Base covt + TC/HDL-C	1.05	0.83, 1.32	0.685

Models were adjusted for base covariates (Base covt): age, SBP, hypertension medication (yes/no), smoking status (yes/no), diabetes (yes/no), alcohol intake, and type of CT scan.

OR = odds ratio.

Presence of CAC was defined as an Agatston score of > 0.

Table 5

Odds Ratio of CAC presence (Agatston Score > 0) per 1 SD elevation in lipid measure

Parameter	Model	OR	95% CI		P-value
LDL-C	Base covt	1.24	1.05	1.47	0.011
	Base covt + LDL-P	0.87	0.65	1.16	0.335
Non-HDL-C	Base covt	1.38	1.17	1.64	<0.001
	Base covt + LDL-P	1.23	0.93	1.62	0.150
LDL-C/HDL-C	Base covt	1.44	1.21	1.72	<0.001
	Base covt + LDL-P	1.33	1.00	1.76	0.049
TC/HDL-C	Base covt	1.54	1.29	1.83	<0.001
	Base covt + LDL-P	1.48	1.16	1.90	0.002

All models were adjusted for base covariates (Base covt): age, SBP, hypertension medication (yes/no), smoking status (yes/no), diabetes (yes/no), alcohol intake, and type of CT scan (EBCT vs MDCT).

Presence of CAC was defined as an Agatston score of > 0.