Lipoprotein(a) and coronary artery calcium in comparison with other lipid biomarkers: The multi-ethnic study of atherosclerosis

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Abstract

Background: Coronary artery calcium (CAC) scoring is often used for atherosclerotic cardiovascular disease (ASCVD) risk stratification in individuals with elevated lipoprotein(a) [Lp(a)].

Objective: To evaluate associations between Lp(a) and baseline CAC (volume/density) and CAC progression compared to other lipid biomarkers.

Methods: We utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study of individuals without clinical ASCVD, excluding statin users. We evaluated

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the associations between Lp(a), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, total cholesterol, apolipoproteinB, and non-HDL-C with baseline CAC and annual CAC progression using multivariable ordinal regression with adjustment for ASCVD risk factors. Analyses were also stratified by median age.

Results: In 5,597 participants (2,726 at median 9.5-year follow-up), Lp(a) was not associated with baseline CAC volume or density and was modestly associated with volume progression (OR 1.11, 95% CI 1.03–1.21). However, other biomarkers were positively associated with baseline volume and volume progression (LDL-C: OR 1.26, 95% CI: 1.19–1.33 and OR 1.22, 95% CI: 1.15–1.30, respectively), except HDL-C which was inversely associated. LDL-C, total cholesterol and non-HDL-C were inversely associated with baseline density. In participants <62 years of age, Lp(a) was modestly associated with baseline CAC volume (OR 1.10, 95% CI: 1.00–1.20) and volume progression (OR 1.16 95% CI: 1.04–1.30).

Conclusions: In contrast to other lipid biomarkers, Lp(a) was not associated with baseline CAC volume or density and was only modestly associated with volume progression. Our findings suggest that Lp(a) is not as robustly associated with CAC as other lipid biomarkers.

Introduction

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL)-like particle composed of apolipoprotein B-100 (apoB) linked by a disulfide bond to apolipoprotein(a) (apo(a)).[1] Elevated Lp(a) levels are associated with an increased risk for several cardiovascular diseases.[2] Traditional risk scoring methods do not account for Lp(a),[3] however, and coronary artery calcium (CAC) scoring is often used clinically to clarify risk in individuals with elevated Lp(a).[4]

CAC is a robust marker of subclinical atherosclerosis and for predicting atherosclerotic cardiovascular disease (ASCVD) risk.[5] Prior studies have demonstrated an association between elevated Lp(a) and CAC.[6–14] However, these studies were performed in heterogenous populations, and several demonstrated only modest associations, primarily using the Agatston score. There are limited data comparing the association between Lp(a) and CAC with other lipid biomarkers, and using CAC volume and density,[15] though volume and density improve risk prediction over the Agatston score.[16]

In this study, we investigated the association between Lp(a) and CAC measures (Agatston score, volume, density) at baseline and follow-up in comparison with other lipid biomarkers in individuals free of clinical ASCVD from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study population

The design of the MESA has been described previously.[17] Briefly, the MESA recruited 6,814 individuals from 2000–2002 between 45–84 years of age from 6 centers across the United States and 4 ethnic groups (Caucasian, African American, Hispanic, Chinese) who were free of clinically apparent cardiovascular disease (CVD). MESA was approved by the institutional review boards at each center, and all participants provided written informed consent. For this study, those with missing data for Lp(a) or ASCVD risk factors were excluded. For the analysis of CAC progression, we additionally excluded individuals without follow-up CAC scoring. For the primary analysis, baseline statin users were excluded due to the known effects of statins on CAC, particularly density. For analyses of density, only participants with detectable CAC at baseline were included due to the need for the presence of CAC to calculate density.

CAC measurement

Participants underwent cardiac computed tomography (CT) scans for CAC scoring at baseline, at short-term follow-up (half from 2002–2004, half from 2004–2005) and long-term follow-up (2010–2011 in a subset of participants). Calcification was defined by the presence of plaque $\geq$ 1 mm^2 with a density of $\geq$ 130 Hounsfield Units (HU). The Agatston score was calculated as the product of total calcified plaque area and a peak calcium density weighting factor defined by plaque attenuation in HU.[18] CAC density was calculated for all participants by dividing the Agatston score by the area score (volume score / CT scanner slice thickness), as previously described.[19] Progression in CAC measurements was determined by calculating the yearly change in CAC measurements from baseline to follow-up.

ASCVD risk factors and lipid biomarkers

Participants underwent standardized questionnaires, vital sign measurement and laboratory testing for characterization at baseline. For this study, relevant covariates included baseline demographics (age, sex, race/ethnicity), systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), apoB, non-HDL-C, body mass index (BMI), diabetes mellitus, smoking status, hypertension, use of anti-hypertensive medications, and use of statins. Lp(a) was measured using a latex-enhanced turbidimetric immunoassay (Denka Seiken) of mass concentration and reported in mg/dL. LDL-C was calculated by the Friede-wald equation.

Statistical analysis

Baseline characteristics were compared across 3 categories of CAC volume (0, 1–100, > 100 mm^3) and CAC density (1–1.9, 2–2.9, 3–4). Continuous variables were compared using analysis of variance (ANOVA) or Kruskal-Wallis testing, and categorical variables were compared using Chi-squared tests.

For analyses of lipid biomarkers, Lp(a), total cholesterol, HDL-C, LDL-C, TG, and apoB were natural log (ln)-transformed. For the baseline analysis, the association between

baseline lipid biomarkers and baseline CAC Agatston score, CAC volume, and CAC density were evaluated using multivariable ordinal regression models due to non-linearity in the associations between Lp(a) and CAC measures. For Agatston and volume, the categories were: 0, 1–100 and > 100 Agatston units (AU) and mm^3, respectively. For density, the categories were 1–1.9, 2–2.9, and 3–4 (unitless). Models evaluated each biomarker individually with adjustment for ASCVD risk factors (age, sex, race/ethnicity, SBP, diabetes, smoking, hypertension treatment). For Lp(a) and LDL-C, models were also evaluated with additional adjustment for HDL-C and TG. Overlapping biomarkers (such as Lp(a) and LDL-C or total cholesterol / apoB / non-HDL-C and Lp(a) / LDL-C / HDL-C / TG) were not included in the same models. Models for density were additionally adjusted for CAC volume. Odds ratios (OR) are presented per standard deviation (SD).

For the progression analysis, the association between Lp(a), other lipid biomarkers, and progression of CAC at short-term and long-term follow-up was evaluated using multivariable ordinal regression. For Agatston and volume, categories of annual change of 0, 1–20, > 20 AU or mm^3, respectively, were used. For density, categories of annual change were 0, 0–0.25 and > 0.25 (unitless). Again, categories were chosen due to the non-linear association between lipid biomarkers and annual change in CAC. Model 1 and Model 2 included the same covariates as for the baseline analysis. OR are presented per SD.

Given the associations between Lp(a), premature ASCVD, and race/ethnicity we also performed the baseline and progression analysis stratified by the median age in the cohort (62 years) and by race/ethnicity. The multiplicative interactions between Lp(a) level and age and between Lp(a) and race/ethnicity were tested in the baseline ordinal regression models used above for volume and density. As an additional sensitivity analysis, we performed the baseline and progression analyses including individuals with baseline statin use; in this analysis, models were additionally adjusted for baseline statin use. Of note, apoB was only available in non-statin users and was not included in this sensitivity analysis. We also performed an additional sensitivity analysis using quartiles of baseline CAC measures and quartiles of CAC change as the outcomes for the primary analyses.

Results

MESA included 6,814 participants. After excluding participants with pre-baseline events, missing Lp(a) data or missing covariates, there were 6,566 participants. For the baseline analysis, there were 5,597 participants without statin use, 4,733 participants for the short-term progression analysis and 2,726 for the long-term progression analysis. For analyses involving density, only participants with CAC (ability to calculate density) were included for the baseline (n=2,625), short-term progression (n=2,150), and long-term progression (n=1,780) analyses (Figure 1).

Baseline characteristics

Table 1 shows the baseline characteristics of the study population stratified by CAC volume and CAC density. Participants with a higher CAC volume were more likely to have increased burden of CVD risk factors including older age, male sex, hypertension, diabetes, higher SBP, and higher 10-year ASCVD risk score. With increasing level of CAC volume, greater

total cholesterol, LDL-C, and TG, and lower HDL-C were observed, though trends were modest in magnitude. There was no difference in Lp(a) levels between different categories of CAC volume. Participants with higher CAC density similarly had increased burden of CVD risk factors including older age, male sex, hypertension, higher SBP and higher 10-year ASCVD risk score, but lower LDL-C. There was no difference in Lp(a) levels between different categories of CAC density.

Baseline CAC

At baseline, there were 2,972 participants with CAC volume = 0 mm^3, 1,448 with volume 1–100 mm^3, and 1,177 with volume > 100 mm^3. There were 344 participants with CAC density 1–1.9, 822 with density 2–2.9, and 1,459 with density 3–4. Lp(a) was not associated with Agatston score or CAC volume at baseline. Of the biomarkers evaluated, non-HDL-C had the strongest association with CAC volume (odds ratio (OR) per SD 1.29, 95% confidence interval (CI) 1.22–1.37). In addition, LDL-C (OR 1.26, 95% CI 1.19–1.33), TG (OR 1.13, 95% CI 1.06–1.20), total cholesterol (OR 1.22, 95% CI 1.15–1.29), and apoB (OR 1.25, 95% CI 1.17–1.34) were positively associated with CAC volume at baseline (Figure 2). HDL-C was inversely associated with volume at baseline (OR 0.84, 95% CI 0.79–0.89). Similar results were seen for the Agatston score. Lp(a) was not associated with baseline CAC density, while LDL-C (OR 0.91, 95% CI 0.83–0.99), total cholesterol (OR 0.90, 95% CI 0.83–0.99) and non-HDL-C (OR 0.90, 95% CI 0.82–0.99) were all inversely associated (Table 2). When quartiles of CAC measures were used as the outcome, results were similar, except that apoB was now significantly associated with baseline density (Table S1). When statin users were included in a sensitivity analysis, Lp(a) was associated with baseline CAC volume (OR 1.06, 95% CI 1.01–1.11, Table S2).

CAC progression

Median short-term follow-up was 2.4 [IQR 1.6, 3.1] years. At follow-up, there were 2,466 participants with yearly CAC volume progression of 0 mm^3, 1325 with progression of 1–20 mm^3, and 942 with progression of > 20 mm^3. Lp(a) was not associated with progression of CAC volume. Non-HDL-C was most strongly associated with volume progression (OR per SD 1.26, 95% CI 1.19–1.35). LDL-C (OR 1.22, 95% CI 1.15–1.30), TG (OR 1.16, 95% CI 1.09–1.24), total cholesterol (OR 1.20, 95% CI 1.13–1.27), and apoB (OR 1.21, 95% CI 1.13–1.30) were also positively associated with volume progression. HDL-C was inversely associated with volume progression (OR 0.84, 95% CI 0.79–0.90, Figure 3). Similar results were seen for the Agatston score. None of the biomarkers evaluated were significantly associated with density progression (Table 3).

Median long-term follow-up was 9.5 [IQR 9.2, 10.0] years. At follow-up, there were 937 participants with yearly CAC volume progression of 0 mm^3, 1,210 with progression of 1–20 mm^3, and 579 with progression of > 2 mm^3. In general, the magnitude of associations between lipid biomarkers and CAC progression was greater at long-term follow-up than short-term follow-up. Lp(a) was significantly associated with progression of CAC volume (OR 1.11 per SD, 95% CI 1.03–1.21). Non-HDL-C was again most strongly associated with volume progression (OR per SD 1.44, 95% CI 1.33–1.57). LDL-C (OR 1.35, 95% CI 1.25–1.47), TG (OR 1.23, 95% CI 1.13–1.33), total cholesterol (OR 1.35, 95% CI 1.24–

1.46), and apoB (OR 1.36, 95% CI 1.24–1.48) were also positively associated with volume progression. HDL-C was again inversely associated with volume progression (OR 0.80, 95% CI 0.73–0.87, Figure 3). Similar results were seen for the Agatston score. None of the biomarkers evaluated were significantly associated with density progression (Table 3). Results were similar when quartiles of annual CAC change were used as the outcome (Table S1). When statin users were included in a sensitivity analysis, no significant differences were noted for Lp(a) (Table S3).

Baseline CAC and progression of CAC stratified by age

There was a borderline statistically significant interaction between age and Lp(a) for baseline CAC density (p=0.05), but not CAC volume (p=0.323). Among those with age below the median of 62 years, Lp(a) was associated with baseline CAC volume (OR 1.10, 95% CI 1.00–1.20) but not CAC density. Of the other biomarkers evaluated, LDL-C, total cholesterol, apoB and non-HDL-C were all positively associated with CAC volume in younger participants, while HDL-C was inversely associated; the strongest positive association was observed with non-HDL-C (OR 1.30, 95% CI 1.18–1.42). HDL-C was positively associated with baseline CAC density (OR 1.19, 95% CI 1.02–1.39). None of the other biomarkers were associated with CAC density. In older participants (age ≥ 62 years), Lp(a) was not associated with baseline CAC volume or density. Of the other biomarkers evaluated, LDL-C, TG, total cholesterol, apoB and non-HDL-C were all positively associated with CAC volume in older participants, while HDL-C was inversely associated; the strongest positive association was observed with non-HDL-C (OR 1.29, 95% CI 1.19–1.39). LDL-C was borderline inversely associated (OR 0.89, 95% CI 0.80–1.00) and total cholesterol was significantly inversely associated (OR 0.88, 95% CI 0.79–0.99) with CAC density. None of the other biomarkers were associated with CAC density. In general, the strength of associations were similar for CAC volume in younger and older participants, while there were differential associations with CAC density (Table 4).

Lp(a) was associated with long-term CAC volume progression in younger participants (OR per SD 1.16, 95% CI 1.04–1.30). Of the other biomarkers evaluated, LDL-C, TG, total cholesterol, apoB and non-HDL-C were all positively associated with CAC volume progression in younger participants, while HDL-C was inversely associated; the strongest positive association was observed with non-HDL-C (OR 1.51, 95% CI 1.36–1.68). None of the biomarkers were associated with CAC density progression in younger individuals. In older participants (age ≥ 62 years), Lp(a) was not associated with CAC volume progression. LDL-C, TG, total cholesterol, apoB and non-HDL-C were all positively associated with CAC volume progression in older participants, while HDL-C was inversely associated; the strongest positive association was observed with non-HDL-C (OR 1.36, 95% CI 1.21–1.55). None of the biomarkers were associated with CAC density progression in older individuals. In general, the strength of associations was greater in younger participants than in older participants (Table S4). When short-term follow-up was evaluated, Lp(a) was not associated with CAC volume progression but was inversely associated with density progression in younger individuals (OR 0.85, 95% CI 0.73–0.98).

Baseline CAC and progression of CAC stratified by race/ethnicity

There was not a significant interaction between Lp(a) and race/ethnicity for baseline volume (p=0.944), baseline density (0.426), volume progression (p=0.322) or density progression (0.253). In general, results were consistent across racial/ethnic groups as Lp(a) was not associated with baseline CAC volume or density across groups. Similarly, Lp(a) was positively associated with volume progression across groups but was only statistically significant in Hispanic individuals (OR per SD 1.26, 95% CI 1.07–1.48). Similarly, Lp(a) was not significantly associated with density progression except in Hispanic individuals (OR per SD 0.71, 95% CI 0.52–0.95, Fig. S1).

Discussion

Individuals with elevated Lp(a) are at significantly increased risk for several cardiovascular diseases. CAC scoring is used clinically to evaluate and individualize overall ASCVD risk. In our study, however, Lp(a) was not associated with baseline CAC volume or density and was weakly associated with CAC volume progression. In younger individuals, Lp(a) was only modestly associated with baseline CAC volume and CAC volume progression, and was the only biomarker associated (inversely) with density progression (over short-term follow-up). This is in contrast to other lipid biomarkers which were more strongly associated with CAC. Our findings suggest that Lp(a) is not as robustly associated with CAC as other lipid biomarkers.

Given that Lp(a) is strongly associated with ASCVD risk, it may be surprising that it is, at best, modestly associated with CAC, which represents subclinical atherosclerosis and is also strongly associated with ASCVD risk. A recent study utilizing coronary computed tomography angiography (CCTA) may help explain these results. In this study of 191 individuals, those with high Lp(a) 70 mg/dL had accelerated progression of low attenuation plaque volume (density <30 HU), which is a marker for necrotic core and a powerful predictor of future events.[20] In another study evaluating young patients with acute coronary syndrome (ACS) who had higher levels of Lp(a) than age-matched healthy controls, individuals with higher levels of Lp(a) had decreased fibrous cap thickness on optical coherence tomography (OCT) imaging compared to those with lower Lp(a) levels.[21] Thus, it is possible that Lp(a) is more associated with non-calcified or low attenuation plaque, which is associated with increased risk but not captured by CAC scoring. This is reflected by the inverse association between Lp(a) and CAC density progression in younger individuals in our study.

Indeed, these results align with another recent study involving data from MESA and the Dallas Heart Study (DHS). In asymptomatic individuals, elevated Lp(a) and CAC were independently associated with ASCVD risk without a significant interaction between the two. Additionally, when elevated Lp(a) and CAC were present, they appeared to be additive for risk.[22] Together, these findings suggest that CAC may not be sufficient to risk stratify individuals with elevated Lp(a), as Lp(a) was independently associated with risk and is associated with low-attenuation plaque, as noted above. Furthermore, Lp(a) has additional properties associated with atherosclerotic risk, which may not be captured by CAC, including the pro-thrombotic and pro-inflammatory properties associated with

apo(a) and oxidized phospholipids (OxPL).[23] In a recent study, high Lp(a) was found to be associated with various high-risk characteristics on CCTA, including not only higher total plaque volume but also inflammatory attributes reflected by a higher fat attenuation index. Causal mediation analyses also showed that approximately 40% of the prognostic effect of Lp(a) was mediated by high-risk attributes such as high-risk plaque, high-risk inflammatory attributes, and high-risk physiological attributes.[24]

Lp(a) is a risk factor for premature ASCVD. We observed a borderline statistically significant interaction between Lp(a) and age for CAC density but not volume. This may be due to density representing plaque age / stability (i.e. older participants with elevated Lp(a) may be more likely to have denser plaque than younger participants). Thus, the age-stratified results are particularly relevant given the potential selection bias as individuals who were older with elevated Lp(a) at the time of MESA recruitment may have been selected out due to already having an ASCVD event. We observed that Lp(a) was associated with baseline CAC volume and volume progression in younger individuals but not older individuals. Again, this association was modest, particularly when compared to other lipid biomarkers. Interestingly, Lp(a) was also inversely associated with density progression in younger individuals over short-term follow-up. This aligns with the previously discussed propensity for Lp(a) to develop less dense plaque and with higher density being inversely associated with ASCVD risk.

Prior studies have observed an association between Lp(a) and CAC, and many have methodologic differences from the present study. Most of these studies used the Agatston score[8–10, 12, 13, 25–28] and the associations were generally modest. These studies were also performed in varied populations including individuals with chest pain,[9] randomly selected individuals,[25] specific racial/ethnic groups,[10, 26] individuals with familial hypercholesterolemia,[8] or those with family history of ASCVD.[27] One study utilized single-nucleotide polymorphisms of the LPA gene rather than Lp(a) levels.[28] Additionally, some of these studies did not include extensive multivariable adjustment.[9, 10, 26] A recent study from the atherosclerosis risk in communities study (ARIC) demonstrated a stronger association between Lp(a) > 50 mg/dL and CAC[14]; there are several potential reasons for the differences from our study – in MESA, Lp(a) testing was performed on baseline blood samples during the same time period as baseline CAC scoring and repeat CAC scoring was performed at subsequent exams. In the ARIC study, Lp(a) was measured at visit 4 and CAC scoring was performed at visit 7, participants were significantly older in ARIC when undergoing CAC scoring with a much higher prevalence of CAC, and a large number of participants did not undergo CAC scoring. Conversely, other studies have failed to show an association between Lp(a) and prevalent CAC.[28, 29] A study from MESA observed that elevated Lp(a) was not associated with prevalent CAC but was associated with more rapid CAC progression, again using the Agatston score.[11] In this study, progression was only assessed among those with a change in CAC score, while our study included those with no change in CAC. Another study in MESA demonstrated that elevated Lp(a) was associated with modest progression in CAC volume but not density.[15] This study, however, did not report the association with baseline measures of CAC, and used different statistical methods. Our study focused on individuals free of known ASCVD, for whom CAC scoring is most appropriate, and utilized CAC volume and density which are stronger predictors of risk than the Agatston score.

Additionally, our study provides context for our findings by contrasting the negative or modest associations between Lp(a) with CAC to the robust associations seen with other lipid biomarkers. Our study also stratified by age as Lp(a) is a risk factor for premature ASCVD.

Our study has limitations. As previously mentioned, our results may be subject to selection bias. Given that individuals with elevated Lp(a) are at risk for premature ASCVD and may have events at a younger age, such individuals may not have been eligible for recruitment in MESA. We attempted to address this potential bias by performing analyses stratified by age. Our study utilized a peak density factor based on the available data in MESA. However, use of a continuous assessment of mean density may be more predictive.[30] Additionally, though CAC volume and density provide better risk assessment than the Agatston score, the Agatston score is the current clinical standard. However, results for CAC volume were generally consistent with results for CAC Agatston and may be similarly applied. Additionally, Lp(a) has a more skewed distribution than other lipid biomarkers, which may have impacted our ability to detect significant associations. Furthermore, as an observational study, there is the potential for residual confounding.

Conclusions

In this study of individuals free of clinical ASCVD, Lp(a) was not associated with baseline CAC volume or density and was modestly associated with CAC volume progression. In younger individuals, Lp(a) was associated with baseline CAC volume and volume progression, but this association was much more modest compared with other lipid biomarkers, and Lp(a) was the only biomarker inversely associated with CAC density progression (over the short-term). Our findings suggest that Lp(a) is not strongly associated with CAC, particularly when compared to other lipid biomarkers. Further studies are needed to identify the most effective ways to risk stratify this population and to guide the use of preventive therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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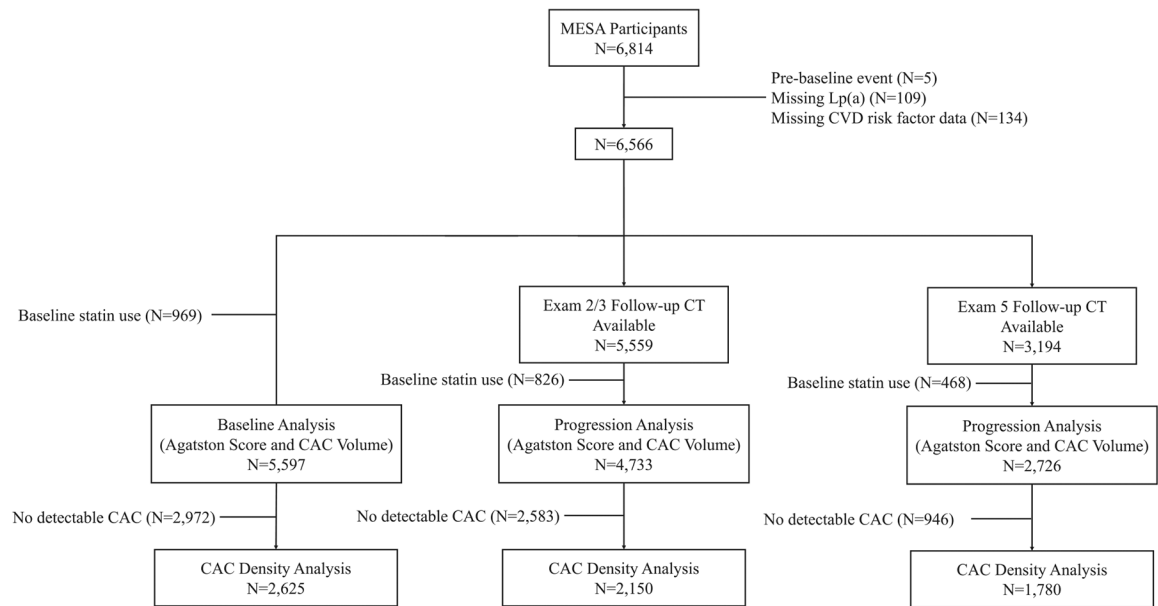
Figure 1.

Flow diagram of study population.

Abbreviations: CAC, coronary artery calcium; CT, computed tomography; CVD, cardiovascular disease; Lp(a), lipoprotein(a); MESA, Multi-Ethnic Study of Atherosclerosis.

Figure 2.
Association between lipid biomarkers and baseline coronary artery calcium (CAC) volume and density.

Abbreviations: CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B; Lp(a), lipoprotein (a); TG, triglycerides.
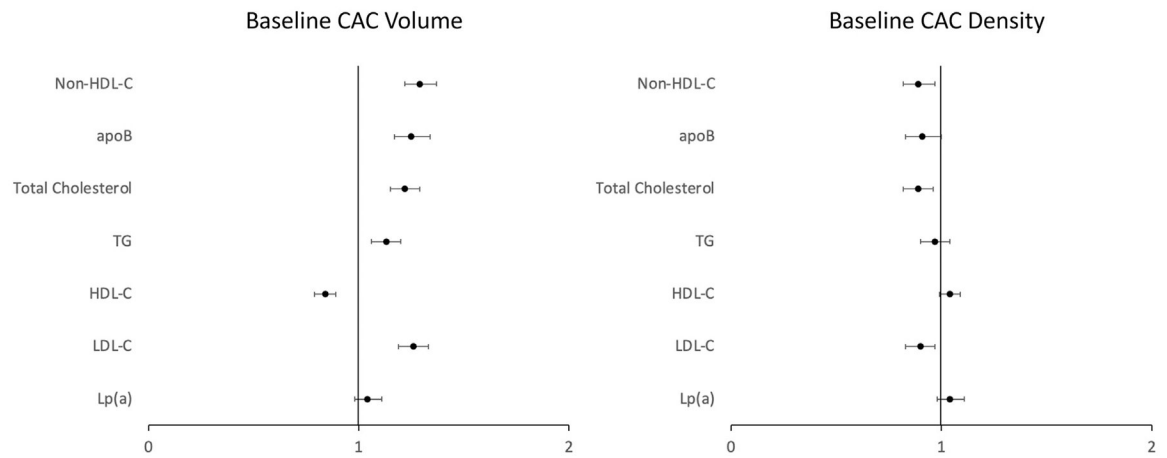
Figure 3.

Association between lipid biomarkers and coronary artery calcium (CAC) volume progression.

Abbreviations: CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B; Lp(a), lipoprotein (a); TG, triglycerides.
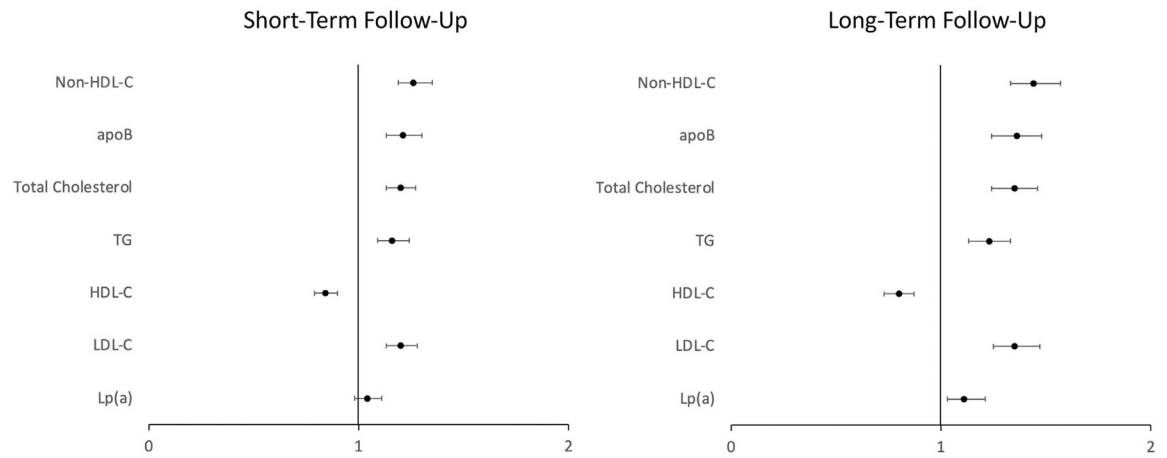
Table 1

Baseline Characteristics of Study Cohort by Baseline CAC Volume and Density.

	CAC Volume 0 mm³ (n=2972)	CAC Volume 1–100 mm³ (n=1448)	CAC Volume >100 mm³ (n=1177)	P
Age, years	57.49 (9.11)	63.52 (9.86)	69.11 (8.73)	<0.001
Female sex, n (%)	1879 (63.2)	674 (46.5)	403 (34.2)	<0.001
Race / ethnicity, n (%)				<0.001
Black, African-American	900 (30.3)	373 (25.8)	255 (21.7)	
Chinese	351 (11.8)	212 (14.6)	116 (9.9)	
Hispanic	733 (24.7)	315 (21.8)	227 (19.3)	
White, Caucasian	988 (33.2)	548 (37.8)	579 (49.2)	
Hypertension, n (%)	978 (32.9)	671 (46.3)	666 (56.6)	<0.001
Diabetes, n (%)	242 (8.1)	169 (11.7)	189 (16.1)	<0.001
Current smoking, n (%)	401 (13.5)	198 (13.7)	151 (12.8)	0.800
Hypertension medication use, n (%)	773 (26.0)	526 (36.3)	542 (46.0)	<0.001
Systolic blood pressure, mmHg	121.76 (20.34)	128.46 (21.71)	132.72 (21.41)	<0.001
Total cholesterol, mg/dL	193.00 [171.00, 215.00]	195.00 [175.00, 218.00]	195.00 [173.00, 219.00]	0.007
HDL cholesterol, mg/dL	50.00 [42.00, 61.00]	47.00 [39.00, 57.00]	46.00 [39.00, 57.00]	<0.001
LDL cholesterol, mg/dL	116.00 [97.00, 136.00]	122.00 [101.00, 140.00]	120.00 [102.00, 142.00]	<0.001
Triglycerides, mg/dL	104.00 [73.00, 152.00]	113.50 [82.00, 161.00]	116.00 [80.00, 164.00]	<0.001
apoB, mg/dL	104.65 [88.77, 122.03]	108.60 [93.25, 126.40]	109.80 [94.55, 127.25]	<0.001
Non-HDL-cholesterol, mg/dL	140.00 [118.00, 163.00]	147.00 [125.00, 168.00]	147.00 [125.00, 169.00]	<0.001
Lp(a), mg/dL	18.10 [7.80, 40.32]	17.00 [7.98, 37.40]	15.30 [6.80, 38.50]	0.062
ASCVD 10-year risk score, %	7.98 (9.18)	14.71 (13.05)	22.44 (14.58)	<0.001

	CAC Density 1–1.9 (n=344)	CAC Density 2–2.9 (n=822)	CAC Density 3–4 (n=1459)	P
Age, years	61.04 (10.28)	65.27 (9.90)	67.63 (9.11)	<0.001
Female sex, n (%)	155 (45.1)	356 (43.3)	566 (38.8)	0.029
Race / ethnicity, n (%)				0.016
Black, African-American	75 (21.8)	194 (23.6)	359 (24.6)	
Chinese	44 (12.8)	99 (12.0)	185 (12.7)	
Hispanic	77 (22.4)	202 (24.6)	263 (18.0)	

				p-value
White, Caucasian	148 (43.0)	327 (39.8)	652 (44.7)	
Hypertension, n (%)	143 (41.6)	429 (52.2)	765 (52.4)	**0.001**
Diabetes, n (%)	42 (12.2)	97 (11.8)	219 (15.0)	0.071
Current smoking, n (%)	46 (13.4)	112 (13.6)	191 (13.1)	0.936
Hypertension medication use, n (%)	110 (32.0)	341 (41.5)	617 (42.3)	**0.002**
Systolic blood pressure, mmHg	126.82 (20.92)	130.35 (21.71)	131.22 (21.76)	**0.003**
Total cholesterol, mg/dL	197.00 [175.75, 219.25]	197.00 [178.00, 220.00]	194.00 [172.00, 218.00]	0.078
HDL cholesterol, mg/dL	46.00 [39.00, 55.25]	46.00 [39.00, 57.00]	47.00 [39.00, 58.00]	0.510
LDL cholesterol, mg/dL	124.00 [104.00, 141.00]	123.00 [103.00, 142.00]	119.00 [100.00, 140.00]	**0.025**
Triglycerides, mg/dL	117.00 [84.00, 167.25]	115.50 [82.00, 160.00]	113.00 [79.00, 162.00]	0.597
apoB, mg/dL	110.80 [94.40, 130.60]	110.60 [93.93, 127.38]	107.70 [93.40, 125.50]	0.122
Non-HDL–cholesterol, mg/dL	147.00 [128.00, 172.00]	149.00 [126.00, 169.00]	145.00 [124.00, 167.00]	**0.042**
Lp(a), mg/dL	15.30 [6.73, 33.22]	15.80 [7.30, 38.90]	16.70 [7.70, 38.25]	0.279
ASCVD 10-year risk score, %	12.84 (13.03)	17.29 (14.07)	19.93 (14.33)	**<0.001**

Data presented as n (%), mean (SD) or median [IQR].

Abbreviations: CAC, coronary artery calcium; HDL, high-density lipoprotein; LDL, low-density lipoprotein; apoB, apolipoprotein B; Lp(a), lipoprotein (a); ASCVD, atherosclerotic cardiovascular disease.

Table 2

Association of lipid biomarkers with baseline CAC.

	Agatston Score			Volume Score			Density Score		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Lp(a)	1.04	0.98, 1.10	0.237	1.04	0.98, 1.11	0.176	1.04	0.95, 1.15	0.365
Lp(a) with adjustment for HDL–C and TG	1.05	0.99, 1.11	0.140	1.05	0.99, 1.12	0.095	1.04	0.95, 1.15	0.374
LDL-C	1.26	1.19, 1.33	<0.001	1.26	1.19, 1.33	<0.001	0.91	0.83, 0.99	0.030
LDL-C with adjustment for HDL–C and TG	1.25	1.18, 1.32	<0.001	1.25	1.18, 1.32	<0.001	0.91	0.83, 0.99	0.031
HDL-C	0.85	0.80, 0.90	<0.001	0.84	0.79, 0.89	<0.001	1.03	0.94, 1.13	0.551
TG	1.11	1.05, 1.18	<0.001	1.13	1.06, 1.20	<0.001	0.98	0.89, 1.07	0.663
Total cholesterol	1.22	1.15, 1.29	<0.001	1.22	1.15, 1.29	<0.001	0.90	0.83, 0.99	0.028
apoB (n=4,582)	1.24	1.16, 1.33	<0.001	1.25	1.17, 1.34	<0.001	0.92	0.83, 1.01	0.082
Non-HDL-C	1.28	1.21, 1.36	<0.001	1.29	1.22, 1.37	<0.001	0.90	0.82, 0.99	0.025

All lipid biomarkers were ln-transformed. OR are presented per standard deviation. Models included individual biomarkers + CVD risk factors (age, sex, race/ethnicity, SBP, DM, smoking, hypertension treatment); For Lp(a) and LDL–C, models with additional adjustment for HDL–C and TG are shown. Models for density are adjusted for volume. Abbreviations: ApoB, apolipoprotein B; CAC, coronary artery calcium; CI, confidence interval; HDL–C, high-density lipoprotein cholesterol; LDL–C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); OR, odds ratio; TG, triglycerides.

Table 3

Association of lipid biomarkers with yearly CAC progression.

Short-Term Follow-Up

	Agatston Score			Volume Score			Density Score		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Lp(a)	1.04	0.98, 1.11	0.188	1.03	0.97, 1.10	0.309	0.93	0.85, 1.01	0.088
Lp(a) with adjustment for HDL–C and TG	1.05	0.99, 1.12	0.106	1.04	0.98, 1.11	0.179	0.93	0.85, 1.01	0.094
LDL-C	1.20	1.13, 1.28	**<0.001**	1.22	1.15, 1.30	**<0.001**	0.96	0.89, 1.04	0.354
LDL–C with adjustment for HDL–C and TG	1.19	1.12, 1.27	**<0.001**	1.20	1.13, 1.28	**<0.001**	0.96	0.88, 1.04	0.303
HDL-C	0.86	0.80, 0.92	**<0.001**	0.84	0.79, 0.90	**<0.001**	1.03	0.94, 1.12	0.547
TG	1.14	1.08, 1.22	**<0.001**	1.16	1.09, 1.24	**<0.001**	1.05	0.97, 1.15	0.217
Total cholesterol	1.19	1.12, 1.26	**<0.001**	1.20	1.13, 1.27	**<0.001**	1.01	0.93, 1.10	0.794
apoB (n=3,851)	1.19	1.11, 1.28	**<0.001**	1.21	1.13, 1.30	**<0.001**	1.02	0.94, 1.11	0.587
Non-HDL-C	1.25	1.17, 1.33	**<0.001**	1.26	1.19, 1.35	**<0.001**	0.99	0.91, 1.08	0.790

Long-Term Follow-Up

	Agatston Score			Volume Score			Density Score		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Lp(a)	1.11	1.02, 1.20	**0.011**	1.09	1.00, 1.18	**0.043**	0.95	0.82, 1.10	0.459
Lp(a) with adjustment for HDL–C and TG	1.13	1.05, 1.23	**0.002**	1.11	1.03, 1.21	**0.010**	0.95	0.82, 1.09	0.452
LDL-C	1.35	1.25, 1.46	**<0.001**	1.38	1.27, 1.50	**<0.001**	1.02	0.88, 1.18	0.792
LDL–C with adjustment for HDL–C and TG	1.33	1.22, 1.44	**<0.001**	1.35	1.25, 1.47	**<0.001**	1.02	0.88, 1.18	0.784
HDL-C	0.81	0.74, 0.88	**<0.001**	0.80	0.73, 0.87	**<0.001**	1.04	0.90, 1.20	0.604
TG	1.18	1.09, 1.27	**<0.001**	1.23	1.13, 1.33	**<0.001**	0.99	0.86, 1.14	0.902
Total cholesterol	1.31	1.21, 1.42	**<0.001**	1.35	1.24, 1.46	**<0.001**	1.04	0.90, 1.20	0.568
apoB (n=2,135)	1.32	1.21, 1.44	**<0.001**	1.36	1.24, 1.48	**<0.001**	0.99	0.85, 1.15	0.875
Non-HDL-C	1.40	1.29, 1.51	**<0.001**	1.44	1.33, 1.57	**<0.001**	1.02	0.88, 1.17	0.825

All lipid biomarkers were ln-transformed. OR and beta coefficients are presented per standard deviation. Models included individual biomarkers + CVD risk factors (age, sex, race/ethnicity, SBP, DM, smoking, hypertension treatment); For Lp(a) and LDL-C, models with additional adjustment for HDL-C and TG are shown. Models for density are adjusted for baseline volume. Abbreviations: ApoB, apolipoprotein B; CAC, coronary artery calcium; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); OR, odds ratio; TG, triglycerides.

Table 4

Association of lipid biomarkers with baseline CAC stratified by age.

Age < 62 years (n=2,872)

	Agatston Score			Volume Score			Density Score		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Lp(a)	1.08	0.98, 1.18	0.103	1.09	0.99, 1.19	0.073	1.13	0.97, 1.32	0.121
Lp(a) with adjustment for HDL-C and TG	1.09	0.99, 1.20	0.065	1.10	1.00, 1.20	**0.043**	1.13	0.96, 1.32	0.138
LDL-C	1.26	1.15, 1.38	**<0.001**	1.27	1.16, 1.39	**<0.001**	0.91	0.78, 1.06	0.220
LDL-C with adjustment for HDL-C and TG	1.25	1.15, 1.37	**<0.001**	1.27	1.16, 1.39	**<0.001**	0.91	0.78, 1.06	0.219
HDL-C	0.86	0.78, 0.94	**0.002**	0.85	0.77, 0.93	**<0.001**	1.19	1.02, 1.39	**0.028**
TG	1.07	0.98, 1.17	0.142	1.08	0.99, 1.18	0.100	0.89	0.76, 1.05	0.173
Total cholesterol	1.22	1.12, 1.34	**<0.001**	1.23	1.13, 1.35	**<0.001**	0.93	0.80, 1.08	0.328
apoB	1.23	1.11, 1.36	**<0.001**	1.24	1.12, 1.37	**<0.001**	0.86	0.71, 1.03	0.091
Non-HDL-C	1.28	1.17, 1.40	**<0.001**	1.30	1.18, 1.42	**<0.001**	0.87	0.74, 1.02	0.083

Age ≥ 62 years (n=2,725)

	Agatston Score			Volume Score			Density Score		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Lp(a)	1.01	0.93, 1.10	0.792	1.01	0.94, 1.10	0.738	0.99	0.88, 1.11	0.842
Lp(a) with adjustment for HDL-C and TG	1.02	0.94, 1.10	0.655	1.02	0.94, 1.11	0.586	0.99	0.88, 1.11	0.863
LDL-C	1.25	1.16, 1.35	**<0.001**	1.25	1.16, 1.35	**<0.001**	0.90	0.80, 1.00	0.060
LDL-C with adjustment for HDL-C and TG	1.24	1.15, 1.34	**<0.001**	1.23	1.14, 1.33	**<0.001**	0.89	0.80, 1.00	0.053
HDL-C	0.84	0.78, 0.91	**<0.001**	0.83	0.76, 0.90	**<0.001**	0.95	0.84, 1.06	0.354
TG	1.14	1.05, 1.23	**<0.001**	1.16	1.07, 1.25	**<0.001**	1.03	0.92, 1.16	0.579
Total cholesterol	1.21	1.12, 1.31	**<0.001**	1.21	1.12, 1.30	**<0.001**	0.88	0.79, 0.99	**0.036**
apoB	1.25	1.14, 1.37	**<0.001**	1.26	1.16, 1.39	**<0.001**	0.95	0.84, 1.06	0.348
Non-HDL-C	1.28	1.19, 1.38	**<0.001**	1.29	1.19, 1.39	**<0.001**	0.91	0.81, 1.02	0.111

All lipid biomarkers were ln-transformed. OR are presented per standard deviation. Models included individual biomarkers + CVD risk factors (age, sex, race/ethnicity, SBP, DM, smoking, hypertension treatment); For Lp(a) and LDL-C, models with additional adjustment for HDL-C and TG are shown. Models for density are adjusted for volume. Abbreviations: ApoB, apolipoprotein B; CAC, coronary artery calcium; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); OR, odds ratio; TG, triglycerides.