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Lipoprotein (a) and Coronary Artery Calcification: Prospective study assessing interactions with other risk factors

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Abstract

Background: Elevated plasma lipoprotein (a) [Lp(a)] and coronary artery calcification (CAC) are established cardiovascular risk factors that correlate with each other. We hypothesized that other cardiovascular risk factors could affect their relationship.

Methods: We tested for interactions of 24 study variables related to dyslipidemia, diabetes, insulin resistance, hypertension, inflammation and coagulation with baseline Lp(a) on change in CAC volume and density over 9.5 years in 5975 Multi-Ethnic Study of Atherosclerosis (MESA) participants, free of apparent cardiovascular disease at baseline.

Results: Elevated Lp(a) was associated with larger absolute increase in CAC volume (3.21 and 4.45 mm^3/year higher for Lp(a) ≥30 versus <30 mg/dL, and Lp(a) ≥50 versus <50 mg/dL, respectively), but not relative change in CAC volume. No association was found with change in

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Author contributions

K.L.O., R.L.M., M.A.A., M.C. and F.T. participated in the study design. K.L.O. participated in data analysis. K.L.O. and F.T. wrote the manuscript. M.Y.T. measured the Lp(a) levels in the MESA cohort. All authors participated in data interpretation and critical revision of the manuscript.

Conflict of interest

The authors have no conflicts of interest to disclose.

CAC density when assessing continuous ln-transformed Lp(a). The association between elevated Lp(a) (≥30 mg/dL) and absolute change in CAC volume was greater in participants with higher circulating levels of interleukin-2 soluble receptor α, soluble tumor necrosis factor alpha receptor 1 and fibrinogen (15.33, 11.81 and 7.02 mm^3/year in quartile 4, compared to −3.44, −0.59 and 1.91 mm^3/year in quartile 1, respectively). No significant interaction was found for other study variables. Similar interactions were seen when assessing Lp(a) levels ≥50 mg/dL.

Conclusions: Elevated Lp(a) was associated with an absolute increase in CAC volume, especially in participants with higher levels of selected markers of inflammation and coagulation. These results suggest Lp(a) as a potential biomarker for CAC volume progression.

Keywords

Blood coagulation; Coronary artery calcification; Inflammation; Lipoprotein (a); Multi-Ethnic Study of Atherosclerosis

1. Introduction

Lipoprotein (a) [Lp(a)] is a plasma lipoprotein composed of a low-density lipoprotein (LDL)-like particle that contains a single apolipoprotein B100 molecule linked via a single disulphide bond to the large polymorphic glycoprotein, apolipoprotein (a) [1,2]. Elevated Lp(a) has been recognized as a highly prevalent genetic risk factor for cardiovascular disease (CVD) and calcific aortic valve disease [3]. Several meta-analyses of prospective studies have demonstrated that Lp(a) >30 mg/dL is associated with an increased risk of coronary heart disease and myocardial infarction, and Lp(a) >50 mg/dL is associated with an increased risk of ischemic stroke [4–7].

Multiple studies have demonstrated a positive correlation between Lp(a) levels and coronary artery calcification (CAC), which is a marker of coronary artery disease [8,9]. A recent MESA study from our group showed that elevated Lp(a) was associated with a higher risk of rapid CAC progression [10]. This study assessed CAC as a non-zero Agatston score. However, the density and volume of CAC predict CVD risk better than CAC Agatston score [11]. More importantly, CAC density and volume represent two distinct aspects of plaque development. A higher CAC volume indicates a larger lesion area, which is associated with a higher CVD risk, whereas a higher CAC density at a given CAC volume indicates a higher calcification of pre-existing lesions, which is associated with a lower CVD risk due to increased plaque stability [12]. Therefore, in this study, we investigated the association of Lp(a) with the progression of CAC density and volume separately in participants free of clinically apparent CVD at baseline from the Multi-Ethnic Study of Atherosclerosis (MESA). As CVD risk factors such as dyslipidemia, diabetes, hypertension, and increased propensity to inflammation and coagulation can also accelerate plaque calcification [13–15], we also assessed the association of Lp(a) with these factors and whether they could modify the association between baseline Lp(a) and the progression of CAC volume and density.

2. Materials and methods

2.1. Study participants

Details of the MESA study objectives, design, and protocol have been described previously [16]. Briefly, the MESA cohort consisted of 6814 men and women aged 45–84 years in four major ethnic groups (Caucasian, African American, Hispanic American, and Chinese American). All participants were free of clinically apparently CVD, when recruited from six United States communities at baseline (visit 1) between July 2000 and August 2002. Over a follow-up period of 8.0–11.4 years (mean = 9.5 years), participants attended up to four in-person clinic visits (2, 3, 4, and 5). A total of 6233, 5947, 5818, and 4716 participants were assessed at clinic visits 2 (2002–2004), 3 (2004–2005), 4 (2005–2007), and 5 (2010–2012), respectively. The study was approved by institutional review boards at all participating centres. All participants provided informed written consent.

Among 6814 participants at baseline, 6705 participants had available data on both plasma Lp(a) level and CAC at baseline. A total of 5975 participants had at least one follow-up visit with CAC measurement and were included in this analysis.

2.2. Measurement of Lp(a) levels

At baseline, venous blood samples were obtained by certified technicians from each participant after a 12-hour fast. Lp(a) mass was measured in serum by Health Diagnostics Laboratory (Richmond, Virginia) using a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) as described previously [17,18], which controlled for the heterogeneous sizes of apo(a) [19], with a total imprecision <5%.

2.3. CAC measurement

At baseline and follow-up exams, participants underwent computed tomography scans of the chest for CAC as described previously [20]. Calcification was defined as the presence of a plaque of ≥1 mm^2 with a density of ≥130 Hounsfield units. The Agatston scoring method was used to quantify the extent of calcification, which was calculated by multiplying the calcified plaque area of a given lesion within a given computed tomography slice by a calcium density factor. Agatston and volume scores were provided in the original MESA dataset. CAC density scores were calculated from Agatston and volume scores as described previously [11,12].

2.4. Other variables of interest

Information on age, gender, race/ethnicity, education, smoking, current alcohol use, physical activity, medical history and medication use were obtained from standardized questionnaires. Body mass index (BMI) was calculated from height and weight. Physical activity was measured as the total number of reported hours of moderate and vigorous activities per week, multiplied by metabolic equivalent level.

Blood pressure was measured three times in a resting seated position and the average of the last two readings was used in the analyses. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg or use of any anti-

hypertensive medication along with a self-reported diagnosis of hypertension. Diabetes was defined as fasting blood glucose ≥126 mg/dL or use of any glucose-lowering medication. Insulin resistance was estimated using the homeostasis model assessment index (HOMA-IR), according to the updated computer model [21]. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation [22].

Lipid profile (including total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides), glucose and insulin, were measured on fasting blood samples in the full cohort. As total cholesterol and LDL cholesterol includes the cholesterol contained in Lp(a) particles, we also assessed non-Lp(a) total cholesterol and non-Lp(a) LDL cholesterol as a sensitivity analysis in a sub-sample of 4676 participants. Lp(a) cholesterol was measured by Health Diagnostics Laboratory (Richmond, Virginia) [23], in which the major lipoprotein classes were separated by gradient gel electrophoresis and the lipoproteins bands were stained with enzymic reagents and their cholesterol content quantitated by densitometric scanning. Non-Lp(a) total cholesterol and non-Lp(a) LDL cholesterol were calculated by subtracting Lp(a) cholesterol from total cholesterol and LDL cholesterol respectively. Other biomarkers were measured in the full cohort or subsets. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity and mass were measured by diaDexus Inc (South San Francisco, CA) in 5353 and 5273 participants respectively (less than full cohort due to lack of consent by some participants for research involving a commercial entity) [24]. Lp-PLA_2 activity was measured using a radiometric assay with a tritium-labelled platelet-activating factor as the substrate, whereas Lp-PLA_2 mass was measured using the second-generation PLACT^M Test, a sandwich enzyme immunoassay [24]. Interleukin (IL)-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN) in the full cohort [25]. Soluble intercellular adhesion molecule-1 (sICAM-1) was measured by ELISA (Parameter Human sICAM-1 Immunoassay; R&D Systems, Minneapolis, MN) in the first one-third of MESA participants and a random sample of 1000 participants (n=2683) [26]. Soluble tumor necrosis factor receptor 1 (sTNF-R1), interleukin-2 soluble receptor α (IL-2 sRα) and IL-10 were measured in a race/ethnicity-balanced sub-sample through the MESA Family Ancillary Study (n = 2871, 2861 and 2814, respectively). sTNF-R1 and IL-2 sRα were measured by ultra-sensitive ELISA assays (Quantikine Human sTNF RI Immunoassay and Quantikine Human IL-2 sRα Immunoassay respectively; R&D Systems, Minneapolis, MN) [27,28]. Interleukin-10 was measured using the MilliplexMAP Human Cardiovascular Disease Panel 3 (Millipore Corpora-tion; Billerica, MA) and run as a single-plex assay [25]. Total plasma homocysteine was measured by a fluorescence polarization immunoassay (IMx Homocysteine Assay, Axis Biochemicals ASA, Oslo, Norway) in the full cohort [29]. C-reactive protein (CRP), fibrinogen, factor VIII, fibrin fragment D-dimer, and plasmin-antiplasmin complex (PAP), a marker of plasmin generation, were measured in the full cohort [26].

2.5. Statistical analysis

Data were presented as mean (standard deviation [SD]) and percentage (number), where appropriate. For variables with a skewed distribution, data were presented as median

(interquartile range) and natural log (ln)-transformed before analysis. Comparison of clinical characteristics and biomarker levels between participants with and without elevated Lp(a) levels was performed by chi-square tests for categorical variables and independent t-tests for continuous variables. For skewed variables, data were analyzed after natural log (ln) transformation. Participants with missing data for a variable were excluded from the analysis of that variable.

The cross-sectional association of Lp(a) levels with 24 study variables related to dyslipidemia, diabetes, insulin resistance, hypertension, and laboratory biomarkers at baseline was assessed using multivariable linear regression analysis for continuous variables, and multivariable logistic regression analysis for binary categorical variables. Robust standard error estimation was used. Data was adjusted for demographic and lifestyle factors (age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use and physical activity), established cardiovascular risk factors (BMI, ln-transformed fasting glucose, SBP, HDL cholesterol, LDL cholesterol, ln-transformed triglycerides, use of lipid-lowering medication, use of hypertensive medication, use of glucose lowering medication, family history of heart attack, eGFR) at baseline. In all of these analyses, no multi-collinearity issues were detected in the adjusted models (all variance inflation factors <3.0). Elevated Lp(a) was defined using both clinical cut-off points, ≥30 and ≥50 mg/dL [30,31]. In a separate analysis, Lp(a) levels were assessed as a continuous variable among all the participants as the relationship of Lp(a) with CVD risk has been suggested to extend to lower threshold, even <30 mg/dL [32]. In all the analysis, multiple testing corrections for 24 study variables were performed using false discovery rate with the study-wide false discovery rate set at 0.05.

For CAC at the baseline exam, detectable calcium was defined as a CAC score >0. Progression of CAC was considered as the annual absolute change in CAC volume and density between the baseline visit and the last follow-up visit among all participants with and without CAC at baseline. The association of continuous and elevated Lp(a) levels with annual absolute changes in CAC volume and density were assessed using multivariable linear regression analysis with robust standard error estimation. For the analysis of annual absolute change in CAC density, data were further adjusted for baseline CAC volume and annual absolute change in CAC volume. This was because change in CAC volume can affect CAC density as the development of new and less dense lesions (i.e. increase in CAC volume) could reduce the average CAC density. In a separate analysis, the annual relative change in CAC volume and density between the baseline visit and the last follow-up visit was assessed among all participants with CAC at baseline.

The *p*-values for interactions were estimated by including the interaction term in the multivariable regression models in full sample after adjusting for the main effects of all covariates. When the *p*-value for interaction was <0.05, analysis was then performed separately for each of the sub-groups.

Data analysis was performed using SPSS (version 25, IBM, Armonk, NY, USA) or STATA (version 16, StataCorp, College Station, TX, USA). A two-tailed *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of the participants with and without elevated Lp(a), defined as a level ≥30 mg/dL and Supplementary Table 1 shows the baseline characteristics of these participants with and without Lp(a) ≥50 mg/dL. Compared to participants without elevated Lp(a), participants with elevated Lp(a) (≥30 or ≥50 mg/dL) were more likely to be women, African American, more educated, obese, and hypertensive They also had higher total cholesterol, LDL cholesterol, HDL cholesterol, CRP, IL-6, fibrinogen, factor VIII, D-dimer and PAP levels, but lower triglycerides, fasting insulin, HOMA-IR, IL-2 sRα and sICAM levels. Among these 5975 participants, 4137 participants had Lp(a) cholesterol measured. Participants with elevated Lp(a) (≥30 or ≥50 mg/dL) were more likely to have higher non-Lp(a) total cholesterol and non-Lp(a) LDL cholesterol than those without elevated Lp(a) (Supplementary Table 2).

3.2. Association of Lp(a) with study variables

As shown in Table 2, ln-transformed Lp(a) was related to several study variables related to dyslipidemia, diabetes, insulin resistance, inflammation and coagulation, but not hypertension. Higher ln-transformed Lp(a) levels were associated with higher total cholesterol, LDL cholesterol, Lp-PLA_2 mass, CRP, fibrinogen, D-dimer and PAP, and lower triglycerides, fasting glucose, fasting insulin and HOMA-IR. All these associations remained significant after multiple testing correction of 24 study variables. Although higher ln-transformed Lp(a) levels were nominally associated with higher HDL cholesterol, such associations did not pass the multiple testing correction. When assessing elevated Lp(a) using both Lp(a) levels ≥30 or ≥50 mg/dL as the cut-off values, elevated Lp(a) was still associated with higher total cholesterol, LDL cholesterol and fibrinogen, and lower triglycerides, fasting insulin and HOMA-IR after multiple testing correction. In a sensitivity analysis, similar results were obtained when assessing the relationship of Lp(a) levels with non-Lp(a) total cholesterol and non-Lp(a) LDL cholesterol (Supplementary Table 3). Higher ln-transformed Lp(a) or categorical elevated Lp(a) were associated significantly with higher levels of non-Lp(a) total cholesterol and non-Lp(a) LDL cholesterol.

3.3. Relationship of Lp(a) with progression of CAC volume and density

As shown in Table 3, elevated baseline Lp(a) (≥30 or ≥50 mg/dL) was associated with larger annual absolute increase in CAC volume. There was a significant racial/ethnic difference in such association, in which the association of Lp(a) with absolute change in CAC volume was more prominent in African Americans and Hispanic Americans, than in Caucasian and Chinese Americans (Table 4). When assessing continuous ln-transformed Lp(a), no significant association was found with annual absolute increase in CAC volume although a similar racial/ethnic difference was observed (Tables 3 and 4). No association was found when assessing the annual relative change in CAC volume, nor annual absolute or relative change in CAC density.

3.4. Interaction with different study variables for change in CAC volume

As shown in Supplementary Table 4, when assessing elevated Lp(a) using ≥30 mg/dL as the cut-off point, a significant interaction was found for continuous fibrinogen, ln-transformed IL-2 sRα, and ln-transformed sTNF-R1 levels after multiple testing correction of 24 study variables. When participants were categorized according to the quartiles of these biomarker levels, the association of elevated Lp(a) with larger annual absolute increase in CAC score tended to be more prominent in participants with the highest quartile 4 of IL-2 sRα, sTNF-R1, and fibrinogen levels, compared to those with the lowest quartile 1 (Table 5). Similar trends were obtained when assessing elevated Lp(a) using ≥50 mg/dL as the cut-off point, although only the interaction with continuous ln-transformed IL-2 sRα, but not fibrinogen and ln-transformed sTNF-R1 levels, remained significant after multiple testing correction (Tables 4 and 5). No significant interactions were found with other study variables related to dyslipidemia, diabetes and insulin resistance, hypertension, and other markers of inflammation and coagulation. No significant interaction was found with any study variable after multiple testing correction when assessing continuous ln-transformed Lp(a) (Supplementary Table 4). No significant interaction with any study variable was found after multiple testing correction when assessing annual relative change in CAC volume (Supplementary Table 5), annual absolute change in CAC density (Supplementary Table 6) and annual relative change in CAC density (Supplementary Table 7).

4. Discussion

The main finding of this study was that higher Lp(a) levels were associated with larger annual increases in CAC volume, but not density over 9.5 years, and cross-sectionally with a variety of laboratory biomarkers. The longitudinal associations with CAC volume were more prominent in African and Hispanic Americans, compared to Caucasian and Chinese Americans, as well as in participants with higher levels of IL-2 sRα, sTNF-R1 and fibrinogen, but did not differ by levels of other biomarker and clinical risk factors.

Elevated Lp(a) is an established CVD risk factor and has been suggested as a therapeutic target for reducing CVD risk [2,3]. Mendelian randomization studies also suggest a causal role of Lp(a) in the development of CVD [33]. Consistent with these, multiple studies have reported Lp(a) as an independent risk factor and predictor for CAC. A European study with 1560 patients showed that circulating Lp(a) correlated positively with CAC [9]. In another Korean study with 2611 participants, elevated levels of Lp(a) (≥ 50mg/dL) were associated with the progression of CAC (defined as change in CAC score >0 over four years) [34]. In another study of 937 asymptomatic individuals with a family history of premature atherosclerotic CVD in the Netherlands, elevated levels of Lp(a) (≥50 mg/dL) were associated with higher CAC score [35]. In a recent MESA study, elevated levels of Lp(a) (both ≥30 and ≥50 mg/dL) were associated with a higher risk of rapid CAC progression (defined as ≥100 units/year) [10]. The present study extends these findings by showing that elevated levels of Lp(a) (both ≥30 and ≥50 mg/dL) were associated with a larger annual absolute increase in CAC volume, but not CAC density. The association of Lp(a) with absolute increase in CAC volume was more prominent when assessing elevated Lp(a) using clinical cut-off points (≥30 or ≥50 mg/dL), rather than continuous values. This is unlikely

due to the highly skewness of Lp(a) distribution in the study cohort as ln-transformation was used to improve the normality of the Lp(a) values. More importantly, this may suggest a potential threshold effect of Lp(a), which supports the use of clinical cut-off points of Lp(a) for CVD risk stratification in clinical guidelines [30,31]. Nevertheless, further larger independent studies are needed to validate this finding.

Ethnic difference in Lp(a) levels have been reported previously, with the highest levels in African Americans [18]. Previous MESA studies have also demonstrated ethnic difference in the association of Lp(a) with risk of carotid plaque progression and heart failure, with the association being significant only in Caucasians, but not in other racial/ethnic groups [17,18]. In the present study, however, the association of elevated Lp(a) with progression of CAC volume was more prominent in African Americans and Hispanic Americans, than in Caucasian and Chinese Americans. This suggests that the pathophysiological role of Lp(a) in CAC, may differ from that in carotid plaque progression and heart failure. In fact, in the REGARDS study, Lp(a) tends to be a significant risk factor for stroke in African Americans, but not Caucasians [36]. Further studies are needed to elucidate how Lp(a) is related to CAC volume progression.

CAC has been associated with hyperlipidemia, hypertension, diabetes, inflammation and coagulation [13–15]. It is therefore expected that in the present study, higher Lp(a) levels are associated with higher total cholesterol, LDL cholesterol and fibrinogen levels, which are all associated with higher CVD risk. However, in this study higher Lp(a) levels were associated with lower plasma triglycerides, fasting insulin, and HOMA-IR. These results are unexpected as these metabolic conditions are usually associated with lower CVD risk. Similar to our study, previous studies reported lower Lp(a) with diabetes and insulin resistance [37,38] and the positive association of Lp(a) with lower triglycerides levels was also previously reported but only in a hyperlipidemic population [39,40]. It is not known why elevated Lp(a) is associated with these favorable CVD risk parameters, but a Mendelian randomization study does not support any causal role of lowering Lp(a) levels for increasing diabetes risk [41]. Further studies are needed to elucidate the inverse relationship between Lp(a) with glycemic parameters and triglycerides; and whether this inverse relationship is maintained under disease conditions. It is also possible that the lack of association of Lp(a) with some CVD risk factors may be due to its circulating levels being mainly determined by genetic factors [2,3].

In the present study, Lp(a) was associated with CAC volume, but not CAC density change. This may suggest Lp(a) was more related to lesion size regardless of the density of these plaques. The association of Lp(a) with absolute but not relative CAC volume change suggests that the strength of association is similar regardless of the baseline CAC volume values. However, it should be noted that the analysis of relative changes in CAC volume was performed among participants with non-zero CAC score at baseline. Therefore, the association of Lp(a) with CAC volume progression may be less prominent once the CAC development is initiated. However, we could not exclude the possibility that the lack of significant association for relative changes could be due to a lower sample size and hence statistical power.

The association of Lp(a) with the absolute CAC volume change did not significantly differ among participants with different levels of dyslipidemia, diabetes, insulin resistance, and hypertension markers. However, the association was more prominent in participants with higher levels of pro-inflammatory cytokines, especially IL-2 sRα and sTNF-R1, and fibrinogen. These inflammation and coagulation markers have been previously shown to predict CVD outcome events in MESA studies [42,43]. IL-2 sRα is a biomarker for a broad range of inflammatory diseases and immune system activation [44], and its elevated circulating levels have been reported to be associated with CAC [45,46], although this association was not observed in MESA (Table 2). sTNF-R1 is produced by the shedding of the extracellular domains of TNF receptor 1. Its circulating levels are elevated in inflammation, and it binds to and neutralizes the cytotoxic effects of TNF-α [47]. In fact, previous studies have demonstrated a role of TNF-α and TNF-R1 in aortic calcium accumulation [48,49], with the lipid-lowering drug, simvastatin suppressing aortic calcification by inhibiting TNF-α and TNF-R1 in human aortic smooth muscle cells [50].

Fibrinogen, an acute phase reactant, is important in coagulation and is associated with higher CVD risk [51]. In the present study, a higher fibrinogen level was also associated with higher a Lp(a) level, thus the interaction we observed may be particularly important. In fact, Lp(a) has prothrombotic properties and inhibit fibrinolysis [2]. An interaction between Lp(a) and fibrinogen has been reported to increase the combined risk of mortality from coronary heart disease and stroke [52]. However, the underlying mechanism for such interaction effect between Lp(a) and fibrinogen level is not clear. In fact, a recent study has demonstrated that reduction in Lp(a) by antisense oligonucleotide in patients with very high Lp(a) levels does not affect the *ex vivo* fibrinolysis [53]. Further studies are therefore needed to assess whether Lp(a) interacts with IL-2 sRα, sTNF-R1 and fibrinogen in the association with clinical CVD outcome events.

Our study has the advantage of making use of data from the large well-established and well-characterized MESA cohort with standardized assessments of CAC and Lp(a), and availability of data on many biomarkers of dyslipidemia, inflammation and hemostasis. The prospective study design can help to determine the temporal relationship of baseline CAC with change in CAC volume and density. The assessment of Lp(a) with CAC volume and density separately can help to delineate the role of Lp(a) in atherosclerotic lesion development. However, there are also several limitations. Because of the descriptive nature and observational design of the study, no causal relationship between Lp(a) and CAC progression could be inferred. Some biomarkers were measured only in a sub-set of participants and this limited the study power for interaction testing, which may lead to false negative results. Moreover, Lp(a) was measured only at baseline, so the relationship between change in Lp(a) and changes in CAC density and volume over follow-up could not be assessed. As participants were aware of their CAC score at baseline, we could not exclude the possibility that those participants with higher score may undergo more intensive intervention to reduce their CVD risk, as the present study did not take into account of any changes in lifestyle factors and use of medications during follow-up which may confound the findings of the present study. This could either diminish the magnitude of the association. Moreover, we could not exclude the possibility of residual confounding due to factors, such as dietary factors, which have not been analyzed in the present study. There are

also some limitations for the analysis of CAC density in the MESA study. The CAC density was originally measured as a continuous value ranging from 130 to >3000 Hounsfield units, but was categorized by the arbitrary 4-point scale used in the Agatston score. The highest score (4) on the 4-point scale represented all CAC densities ≥400 HU and this may reduce the scale of changes in CAC density and hence the study power of the analysis of change in CAC density. The CAC density used in this study was the average density for each participant without considering the range of density score. This may reduce the statistical power to detect a significant association between baseline Lp(a) and change in CAC density in this study.

In conclusion, this study shows that elevated Lp(a) is associated with an absolute increase in CAC volume among participants with elevated pro-inflammatory and pro-coagulant biomarkers, including IL-2 sRα, sTNF-R1, and fibrinogen levels (Figure 1). Our findings suggest that Lp(a) could be a useful biomarker for CAC volume progression, especially in people with inflammatory and coagulation conditions. Further independent studies are needed to validate the findings of the present study and to assess whether the association of elevated Lp(a) with CVD events and other CVD risk factors are more prominent in cohorts with pro-inflammatory conditions and disorders of coagulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CAC	coronary artery calcification
CRP	C-reactive protein
CVD	cardiovascular disease

DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment index of insulin resistance
IL	interleukin
IL-2 sRα	interleukin-2 soluble receptor α
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
Lp-PLA$_2$	lipoprotein-associated phospholipase A_2
MESA	Multi-Ethnic Study of Atherosclerosis
PAP	plasmin-antiplasmin complex
SBP	systolic blood pressure
SD	standard deviation
sICAM-1	soluble intercellular adhesion molecule-1
sTNF-R1	soluble tumor necrosis factor receptor 1

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Highlights

- Higher Lp(a) was related to a higher annual absolute increase in CAC volume.
- The relationship was stronger in participants with inflammation and procoagulation.
- Baseline Lp(a) was not related to change in the density of CAC.

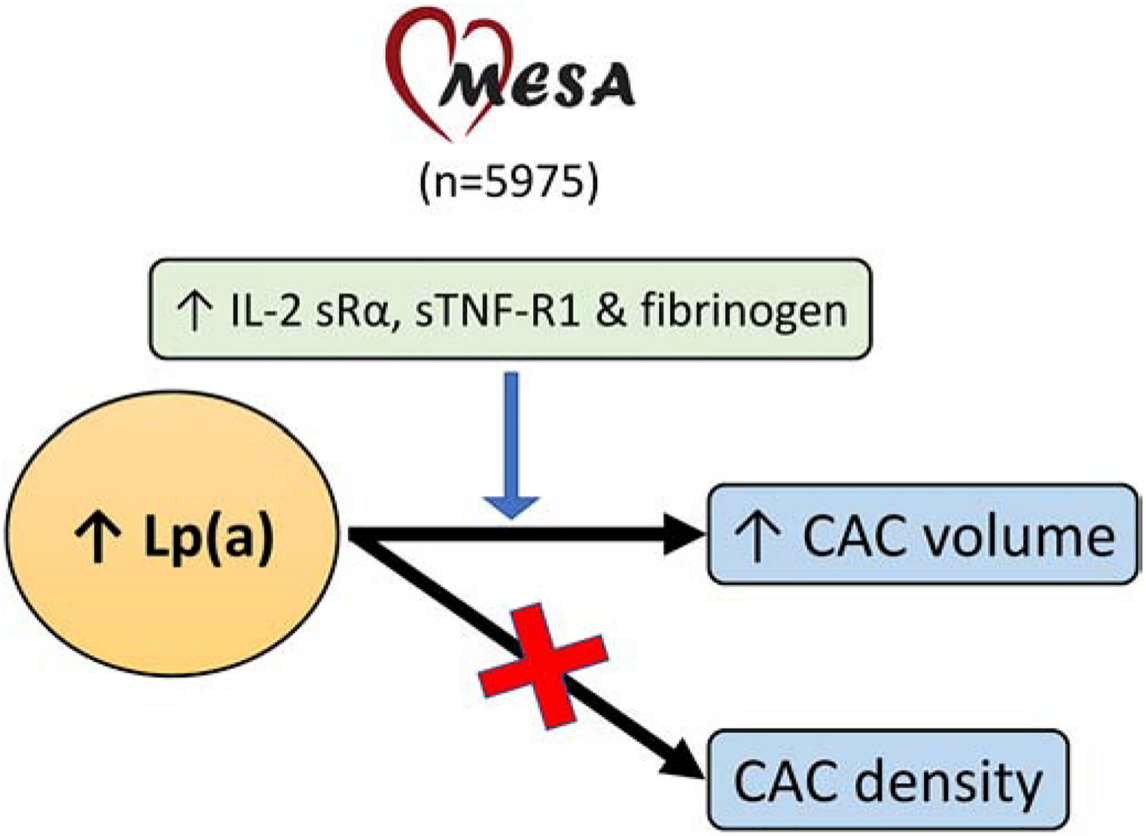

Fig. 1.

Summary of the findings from the present study. Elevated lipoprotein (a) [Lp(a)] was associated with progression of coronary artery calcification (CAC) volume, but not CAC density in 5975 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). The association of elevated Lp(a) with progression of CAC volume was greater in participants with higher circulating levels of interleukin-2 soluble receptor α (IL-2 sRα), soluble tumor necrosis factor (sTNF-R1).

Table 1.

Baseline clinical characteristics of participants with and without elevated Lp(a) (≥30 mg/dL) at baseline

Characteristic	n	Lp(a) <30 mg/dL	Lp(a) ≥30 mg/dL	*p*-value
n	5975	4017	1958	-
Age (years)	5975	61.7 (10.2)	61.8 (10.0)	0.75
Women, n (%)	5975	2020 (50.3)	1110 (56.7)	<0.001
Race/ethnicity, n (%)				
Caucasian	2367	1781 (44.3)	586 (29.9)	<0.001
African American	1602	692 (17.2)	910 (46.5)	
Hispanic American	1303	972 (24.2)	331 (16.9)	
Chinese American	703	572 (14.2)	131 (6.7)	
Education, n (%)				
<High school	1001	700 (17.5)	301 (15.5)	0.04
High school	2463	1617 (40.3)	846 (43.4)	
>High school	2493	1692 (42.2)	801 (41.1)	
BMI (kg/m^2)	5975	5.3 (28.1)	5.6 (28.7)	<0.001
Smoking, n (%)				
Never	3009	2030 (50.6)	979 (50.3)	0.05
Former	2197	1502 (37.5)	695 (35.7)	
Current	752	478 (11.9)	274 (14.1)	
Pack-years of smoking	5898	11.3 (21.5)	10.4 (18.4)	0.09
Current alcohol intake, n (%)	5935	2274 (56.9)	1092 (56.3)	0.64
Physical activity (MET-hours/weeks)	5960	96.4 (100.9)	99.8 (92.2)	0.21
Family history of heart attack, n (%)	5615	1582 (41.9)	818 (44.5)	0.06
eGFR ($mL/min/1.73m^2$)	5969	77.9 (15.7)	77.9 (16.5)	0.89
Lipid-lowering medications, n (%)	5960	631 (15.7)	337 (17.3)	0.14
Glucose-lowering medication, n (%)	5960	343 (8.6)	188 (9.6)	0.18
Anti-hypertensive medication, n (%)	5972	1402 (34.9)	764 (39.0)	0.002
Total cholesterol (mg/dL)	5969	191 (35)	200 (36)	<0.001
LDL cholesterol (mg/dL)	5897	114 (30)	124 (31)	<0.001
HDL cholesterol (mg/dL)	5966	50 (15)	52.6 (15)	<0.001
Triglycerides (mg/dL)[a]	5969	117 (80–169)	99 (73–142)	<0.001
Lp-PLA_2 mass (ng/mL)	4699	178 (47)	177 (41)	0.60
Lp-PLA_2 activity (nmol/min/mL)	4765	150 (36)	147 (36)	0.001
Fasting glucose (mg/dL)[a]	5969	90 (83–99)	89 (83–99)	0.06
Fasting insulin (mU/L)[a]	5966	8.4 (6.0–12.4)	7.7 (5.8–11.5)	<0.001
HOMA-IR[a]	5958	0.96 (0.68–1.41)	0.88 (0.65–1.30)	<0.001
Diabetes (%)	5969	453 (11.3)	248 (12.7)	0.12
SBP (mm Hg)	5973	125 (21)	127 (22)	<0.001
DBP (mm Hg)	5973	72 (10)	72 (10)	0.001
Hypertension, n (%)	5975	1682 (41.9)	931 (47.5)	<0.001

Characteristic	n	Lp(a) <30 mg/dL	Lp(a) ≥30 mg/dL	*p*-value
CRP (mg/L)[a]	5956	1.78 (0.78–4.05)	2.10 (0.96–4.46)	<0.001
IL-2 sRα (ng/mL)[a]	2490	0.894 (0.723–1.152)	0.887 (0.716–1.091)	0.01
IL-6 (pg/mL)[a]	5851	1.17 (0.75–1.83)	1.22 (0.79–1.90)	0.02
IL-10 (pg/mL)[a]	2466	7.48 (5.48–10.40)	7.51 (5.61–10.93)	0.19
sICAM (ng/mL)	2420	275 (88)	257 (91)	<0.001
Homocysteine (μmol/L)[a]	5971	8.6 (7.3–10.4)	8.6 (7.2–10.4)	0.62
sTNF-R1 (ng/mL)[a]	2502	1.29 (1.10–1.54)	1.27 (1.10–1.49)	0.16
Fibrinogen (mg/dL)	5959	338 (70)	360 (77)	<0.001
Factor VIII (%)	5958	97 (36)	101 (39)	<0.001
D-dimer (μg/ml)[a]	5961	0.20 (0.13–0.35)	0.23 (0.13–0.42)	<0.001
PAP (nM)[a]	5838	4.21 (3.31–5.39)	4.62 (3.63–5.97)	<0.001

Data are expressed as mean (SD), n (%), or median (interquartile range).

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment index of insulin resistance; IL, interleukin; IL-2 sRα, interleukin-2 soluble receptor α; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); Lp-PLA2, lipoprotein-associated phospholipase A2; PAP, plasmin-antiplasmin complex; SBP, systolic blood pressure; SD, standard deviation; sICAM-1, soluble intercellular adhesion molecule-1; sTNF-R1, soluble tumor necrosis factor receptor 1.

[a] *P* values were estimated using ln-transformed data.

Table 2.

Multivariable-adjusted associations of baseline Lp(a) levels with study variables

Study variable	Per SD of ln Lp(a)		Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
	B / OR (95% CI)	*p*-value	B / OR (95% CI)	*p*-value	B / OR (95% CI)	*p*-value
Dyslipidemia						
Total cholesterol (mg/dL)	7.39 (6.51, 8.27)	**<0.001** *	11.38 (9.56, 13.20)	**<0.001** *	13.72 (11.61, 15.83)	**<0.001** *
LDL cholesterol (mg/dL)	7.20 (6.35, 8.05)	**<0.001** *	11.33 (9.53, 13.13)	**<0.001** *	13.59 (11.54, 15.65)	**<0.001** *
HDL cholesterol (mg/dL)	0.37 (0.03, 0.72)	**0.03**	0.64 (−0.08, 1.34)	0.08	1.31 (0.45, 2.17)	**0.003** *
Triglycerides (mg/dL)[a]	−0.028 (−0.040, −0.016)	**<0.001** *	−0.040 (−0.068, −0.017)	**0.001** *	−0.042 (−0.071, −0.013)	**0.005** *
Lp-PLA_2 mass (ng/mL)	1.91 (0.71, 3.12)	**0.002** *	2.32 (−0.41, 5.07)	0.10	3.50 (0.45, 6.55)	**0.02**
Lp-PLA_2 activity (nmol/min/mL)	−0.24 (−1.09, 0.61)	0.58	−0.29 (−2.06, 1.49)	0.75	0.20 (−1.86, 2.27)	0.85
Diabetes and insulin resistance						
Fasting glucose (mg/dL)[a]	−0.006 (−0.011, −0.002)	**0.01** *	−0.012 (−0.022, −0.002)	**0.02**	−0.010 (−0.021, 0.001)	0.08
Fasting insulin (mU/L)[a]	−0.030 (−0.042, −0.017)	**<0.001** *	−0.044 (−0.070, −0.002)	**<0.001** *	−0.044 (−0.075, −0.014)	**0.004** *
HOMA-IR[a]	−0.032 (−0.045, −0.020)	**<0.001** *	−0.053 (−0.078, −0.028)	**<0.001** *	−0.050 (−0.079, −0.020)	**<0.001** *
Diabetes	1.01 (0.91, 1.13)	0.79	1.21 (0.99, 1.49)	0.06	1.33 (1.06, 1.67)	**0.01** *
Hypertension						
SBP (mm Hg)	−0.25 (−0.78, 0.28)	0.35	0.24 (−0.89, 1.37	0.68	0.01 (−1.32, 1.34)	0.99
DBP (mm Hg)	−0.06 (−0.33, 0.21)	0.67	0.12 (−0.45, 0.70)	0.67	−0.08 (−0.74, 0.58)	0.82
Hypertension	1.00 (0.93, 1.07)	0.93	1.02 (0.89, 1.18)	0.73	1.02 (0.87, 1.19)	0.84
Inflammation						
CRP (mg/L)[a]	0.045 (0.015, 0.075)	**0.003** *	0.066 (0.005, 0.127)	**0.04**	0.045 (−0.025, 0.116)	0.21
IL-2 sRα (ng/mL)[a]	−0.001 (−0.016, 0.013)	0.85	−0.008 (−0.040, 0.023)	0.61	−0.020 (−0.057, 0.017)	0.28
IL-6 (pg/mL)[a]	0.017 (0.000, 0.034)	0.05	0.032 (−0.004, 0.068)	0.08	0.040 (−0.001, 0.082)	0.06
IL-10 (pg/mL)[a]	0.019 (−0.012, 0.049)	0.23	0.061 (−0.004, 0.125)	0.07	0.061 (−0.013, 0.135)	0.10
sICAM (ng/mL)	−0.50 (−3.97, 2.98)	0.78	−4.83 (−12.85, 3.19)	0.24	1.92 (−6.97, 10.81)	0.67
Homocysteine (μmol/L)[a]	−0.007 (−0.015, 0.000)	0.07	−0.016 (−0.032, −0.001)	**0.04**	−0.010 (−0.028, 0.007)	0.25

Study variable	Per SD of ln Lp(a)		Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
	B / OR (95% CI)	*p*-value	B / OR (95% CI)	*p*-value	B / OR (95% CI)	*p*-value
sTNF-R1 (ng/mL)[a]	0.004 (−0.005, 0.013)	0.39	0.007 (−0.012, 0.026)	0.46	−0.002 (−0.025, 0.020)	0.84
Coagulation						
Fibrinogen (mg/dL)	8.06 (6.13, 9.98)	**<0.001** *	13.50 (9.42, 17.59)	**<0.001** *	10.54 (5.89, 15.18)	**<0.001**
Factor VIII (%)	0.266 (−0.766, 1.299)	0.61	1.795 (−0.365, 3.957)	0.10	1.308 (−1.250, 3.865)	0.32
D-dimer (μg/ml)[a]	0.041 (0.016, 0.066)	**0.001** *	0.037 (−0.016, 0.089)	0.17	0.045 (−0.016, 0.106)	0.15
PAP (nM)[a]	0.015 (0.005, 0.025)	**0.003** *	0.033 (0.012, 0.055)	**0.002** *	0.024 (−0.001, 0.049)	0.06

Among 5975 participants, 1958 participants had Lp(a) ≥30 mg/dL and 1181 participants had Lp(a) ≥50 mg/dL.

Lp(a) was modeled as a continuous variable (per SD increase [1.144] in ln-transformed values) and by clinical cutoff values, 30 and 50 mg/dL.

Data are shown as odds ratio for diabetes and hypertension, and regression coefficient (B) (i.e. absolute change) for other parameters.

All data were adjusted for age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use, physical activity, BMI, ln-transformed fasting glucose (except for analysis of HOMA-IR and diabetes), SBP (except for analysis of blood pressure and hypertension), HDL cholesterol, LDL cholesterol (except for analysis of total cholesterol), ln-transformed triglycerides, use of lipid-lowering medication, use of hypertensive medication (except for analysis of hypertension), use of glucose lowering medication (except for analysis of diabetes), family history of heart attack, and eGFR.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment index of insulin resistance; IL, interleukin; IL-2 sRα, interleukin-2 soluble receptor α; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); Lp-PLA2, lipoprotein-associated phospholipase A2; PAP, plasmin-antiplasmin complex; SBP, systolic blood pressure; SD, standard deviation; sICAM-1, soluble intercellular adhesion molecule-1; sTNF-R1, soluble tumor necrosis factor receptor 1.

[a]Data were ln-transformed before analysis.

**P* values that remained significant after multiple testing correction of 24 study variables.

Table 3.

Association of baseline Lp(a) levels with annual changes in CAC volume and density

Parameter	Mean change (SD) in CAC volume/density	Model 1		Model 2		*p*-value for race/ ethnicity interaction
		B (95% CI)	*p*-value	B (95% CI)	*p*-value	
CAC volume						
Absolute change (mm^3/year, n=5975)						
Lp(a) (per SD in ln-transformed unit)	20.4 (48.0)	0.66 (−0.66, 1.98)	0.33	0.83 (−0.51, 2.17)	0.23	0.02
Lp(a) ≥30 mg/dL						
No	19.9 (46.0)	-	-	-	-	0.02
Yes	21.4 (51.9)	3.43 (0.77, 6.09)	0.01	3.21 (0.56, 5.87)	0.02	
Lp(a) ≥50 mg/dL						
No	19.6 (45.5)	-	-	-	-	0.03
Yes	23.7 (57.0)	5.67 (2.24, 9.11)	0.001	4.45 (0.97, 7.92)	0.01	
Relative change (%/year, n=2902)[a]						
Lp(a) (per SD in ln-transformed unit)	47.4 (99.3)	0.54 (−3.13, 4.21)	0.77	0.54 (−3.72, 4.80)	0.80	0.48
Lp(a) ≥30 mg/dL						
No	45.0 (97.8)	-	-	-	-	0.51
Yes	52.6 (102.4)	3.15 (−4.59, 10.89)	0.42	3.28 (−5.25, 11.81)	0.45	
Lp(a) ≥50 mg/dL						
No	46.6 (100.3)	-	-	-	-	0.88
Yes	50.7 (95.2)	2.16 (−7.06, 11.38)	0.65	1.36 (−9.00, 11.73)	0.80	
CAC density						
Absolute change (Hu category unit/year, n=5975)						
Lp(a) (per SD in ln-transformed unit)	0.069 (0.229)	0.001 (−0.005, 0.006)	0.83	0.002 (−0.005, 0.008)	0.58	0.79
Lp(a) ≥30 mg/dL						
No	0.067 (0.236)	-	-	-	-	0.97
Yes	0.073 (0.213)	0.002 (−0.010, 0.015)	0.70	0.007 (−0.006, 0.021)	0.31	
Lp(a) ≥50 mg/dL						
No	0.068 (0.232)	-	-	-	-	0.73
Yes	0.074 (0.218)	0.004 (−0.011, 0.018)	0.62	0.008 (−0.007, 0.024)	0.31	
Relative change (%/year, n=2902)[a]						

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Parameter	Mean change (SD) in CAC volume/density	Model 1		Model 2		*p*-value for race/ ethnicity interaction
		B (95% CI)	*p*-value	B (95% CI)	*p*-value	
Lp(a) (per SD in ln-transformed unit)	1.72 (11.42)	0.08 (−0.33, 0.49)	0.70	0.09 (−0.34, 0.52)	0.68	0.80
Lp(a) ≥30 mg/dL						
No	1.68 (11.71)	-	-	-	-	0.82
Yes	1.80 (10.78)	0.14 (−0.76, 1.04)	0.76	0.15 (−0.79, 1.10)	0.75	
Lp(a) ≥50 mg/dL						
No	1.82 (11.86)	-	-	-	-	0.32
Yes	1.30 (9.39)	−0.55 (−1.52, 0.42)	0.27	−0.48 (−1.50, 0.53)	0.35	

For continuous Lp(a) levels, regression coefficient (B) is expressed as change in CAC volume or density related to one SD unit (1.144) increase in ln-transformed Lp(a) levels (mg/dL).

Model 1: Adjusted for demographic and lifestyle factors, including age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use and physical activity at baseline.

Model 2: Further adjusted for cardiovascular risk factors, including BMI, ln-transformed fasting glucose, SBP, HDL cholesterol, LDL cholesterol, ln-transformed triglycerides, use of lipid-lowering medication, use of hypertensive medication, use of glucose lowering medication, family history of heart attack, and eGFR at baseline. For change in CAC density, data were further adjusted for baseline CAC volume and change in CAC volume.

Abbreviations: BMI, body mass index; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); SBP, systolic blood pressure; SD, standard deviation.

[a]For relative change, analysis was performed among participants with CAC at baseline.

Table 4.

Association of baseline Lp(a) levels with annual absolute change in CAC volume by race/ethnicity

Sub-group	n	Mean change (SD) in CAC volume, mm^3/year	B (95% CI)	*p*-value
Lp(a) (per SD in ln-transformed unit)				
Caucasian	2367	23.5 (51.8)	−1.16 (−3.24, 0.94)	0.28
African American	1602	18.4 (46.8)	2.72 (−0.09, 5.53)	0.06
Hispanic American	1303	18.7 (46.0)	3.01 (0.38, 5.64)	0.02
Chinese American	703	17.3 (40.0)	0.26 (−3.22, 3.74)	0.88
Lp(a) ≥30 mg/dL				
Caucasian				
No	1781	24.2 (51.9)	-	-
Yes	586	21.5 (51.6)	−1.45 (−6.17, 3.27)	0.55
African American				
No	692	14.7 (36.7)	-	-
Yes	910	21.3 (53.0)	4.72 (0.69, 8.74)	0.02
Hispanic American				
No	972	17.2 (42.7)	-	-
Yes	331	23.3 (54.4)	8.76 (2.61, 14.91)	0.005
Chinese American				
No	572	17.5 (40.9)	-	-
Yes	131	16.5 (35.7)	−0.83 (−7.26, 5.59)	0.80
Lp(a) ≥50 mg/dL				
Caucasian				
No	1996	23.6 (51.0)	-	-
Yes	371	23.2 (55.9)	−1.06 (−6.98, 4.86)	0.73
African American				
No	1059	16.0 (40.3)	-	-
Yes	543	23.2 (57.0)	4.47 (−0.61, 9.55)	0.08
Hispanic American				
No	1104	16.9 (41.6)	-	-
Yes	199	28.8 (64.5)	13.98 (4.92, 23.03)	0.003

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Sub-group	n	Mean change (SD) in CAC volume, mm^3/year	B (95% CI)	*p*-value
Chinese American				
No	635	17.5 (40.4)	-	-
Yes	68	15.6 (35.2)	−0.96 (−9.31, 7.39)	0.82

For continuous Lp(a) levels, regression coefficient (B) is expressed as change in CAC volume or density related to one SD unit (1.144) increase in ln-transformed Lp(a) levels (mg/dL).

All data were adjusted for demographic and lifestyle factors, including age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use, physical activity, BMI, ln-transformed fasting glucose, SBP, HDL cholesterol, LDL cholesterol, ln-transformed triglycerides, use of lipid-lowering medication, use of hypertensive medication, use of glucose lowering medication, family history of heart attack, and eGFR at baseline.

Abbreviations: BMI, body mass index; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); SBP, systolic blood pressure; SD, standard deviation.

Table 5.

Association of baseline Lp(a) levels with annual absolute change in CAC volume

Parameter	N		B (95% CI) for change in CAC volume	*p*-value
	With elevated Lp(a)	Without elevated Lp(a)		
Using Lp(a) ≥30 mg/dL to define elevated Lp(a)				
IL-2 sRα (ng/mL)				
Quartile 1 (≤0.72)	204	437	−3.44 (−7.98, 1.11)	0.14
Quartile 2 (0.73–0.89)	182	434	−2.43 (−7.49, 2.63)	0.35
Quartile 3 (0.90–1.13)	202	406	7.59 (0.05, 15.13)	0.05
Quartile 4 (≥1.14)	166	459	15.33 (4.61, 26.04)	0.005
sTNF-R1 (ng/mL)				
Quartile 1 (≤1.10)	195	445	−0.59 (−5.20, 4.02)	0.80
Quartile 2 (1.11–1.28)	207	416	1.13 (−4.40, 6.65)	0.69
Quartile 3 (1.29–1.52)	190	427	2.31 (−3.82, 8.44)	0.46
Quartile 4 (≥1.53)	169	453	11.81 (0.48, 23.13)	0.04
Fibrinogen (mg/dL)				
Quartile 1 (≤294)	374	1138	1.91 (−3.51, 7.34)	0.49
Quartile 2 (295–337)	426	1053	−1.62 (−6.38, 3.13)	0.50
Quartile 3 (338–387)	524	954	4.63 (−0.85, 10.10)	0.10
Quartile 4 (≥388)	626	864	7.02 (1.79, 12.24)	0.008
Using Lp(a) ≥50 mg/dL to define elevated Lp(a)				
IL-2 sRα (ng/mL)				
Quartile 1 (≤0.72)	125	516	−3.80 (−9.18, 1.57)	0.17
Quartile 2 (0.73–0.89)	109	507	4.89 (−1.60, 11.39)	0.14
Quartile 3 (0.90–1.13)	121	487	11.04 (0.57, 21.52)	0.04
Quartile 4 (≥1.14)	92	533	18.61 (6.04, 31.18)	0.004

For continuous Lp(a) levels, regression coefficient (B) is expressed as annual absolute change in CAC score related to one unit increase in ln-transformed Lp(a) levels (mg/dL).

Data were adjusted for age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use, physical activity, BMI, ln-transformed fasting glucose, SBP, HDL cholesterol, LDL cholesterol, ln-transformed triglycerides, use of lipid-lowering medication, use of hypertensive medication, use of glucose lowering medication, family history of heart attack, and eGFR at baseline.

Abbreviations: BMI, body mass index; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IL-2 sRα, interleukin-2 soluble receptor α; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); SBP, systolic blood pressure; SD, standard deviation; sTNF-R1, soluble tumor necrosis factor receptor 1.