## Title

Lipoprotein(a) Levels Are Associated With Subclinical Calcific Aortic Valve Disease in White and Black Individuals



## Journal

Arteriosclerosis Thrombosis and Vascular Biology, 36(5)

## ISSN

1079-5642

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## Publication Date

2016-05-01

## DOI

10.1161/atvbaha.115.306683

Peer reviewed

Published in final edited form as:

*Arterioscler Thromb Vasc Biol*. 2016 May ; 36(5): 1003–1009. doi:10.1161/ATVBAHA.115.306683.

# Lipoprotein(a) levels are associated with subclinical calcific aortic valve disease in Caucasian and Black individuals: The Multi-Ethnic Study of Atherosclerosis

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## Abstract

**Objective—**Lipoprotein(a) [Lp(a)] is a risk factor for calcific aortic valve disease (CAVD) but has not been evaluated across multiple races/ethnicities. This study aimed to determine whether Lp(a) cut-off values used in clinical laboratories to assess risk of cardiovascular disease identify subclinical CAVD and its severity and whether significant relations are observed across race/ethnicity.

**Approach and Results—**Lp(a) concentrations were measured using a turbidimetric immunoassay, and subclinical CAVD was measured by quantifying aortic valve calcification (AVC) through computed tomography scanning in 4,678 participants of the Multi-Ethnic Study of Atherosclerosis. Relative risk (RR) and ordered logistic regression analysis determined cross-sectional associations of Lp(a) with AVC and its severity, respectively. The conventional 30 mg/dL Lp(a) clinical cut-off was associated with AVC in Caucasian (RR: 1.56; CI: 1.24–1.96) and was borderline significant (p=0.059) in Black study participants (RR: 1.55; CI: 0.98–2.44). Caucasians with levels ≥50 mg/dL also showed higher prevalence of AVC (RR: 1.72; CI: 1.36–2.17) than those below this level. Significant associations were observed between Lp(a) and degree of AVC in both Caucasians and Black individuals. The presence of existing coronary artery calcification

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**DISCLOSURES**

The authors have no conflicts of interest to disclose.

did not affect these associations of Lp(a) and CAVD. There were no significant findings in Hispanics or Chinese.

**Conclusions—**Lp(a) cut-off values that are currently used to assess cardiovascular risk appear to be applicable to CAVD, but our results suggest race/ethnicity may be important in cut-off selection. Further studies are warranted to determine whether race/ethnicity influences Lp(a) and risk of CAVD incidence and its progression.

## INTRODUCTION

Calcific aortic valve disease (CAVD) is a progressive disorder that encompasses a spectrum of valve pathologies ranging from calcification of valve leaflets to obstruction of blood outflow. Early subclinical stages of CAVD are characterized by aortic valve calcification (AVC) which has historically been considered a benign degenerative condition that occurs with advancing age, but is now recognized as a risk factor for cardiovascular disease. Indeed, AVC has been shown to independently predict cardiovascular events[1], increase risk of fatal coronary heart disease (CHD)[2], and may progress to valve stenosis—a stiffening or narrowing of the aortic valve and most common cause of valve replacement.[3] A number of factors have been identified that promote CAVD development that are largely shared with CHD including, but not limited to, age, gender, hypertension, smoking, type II diabetes, hypercholesterolemia,[4–7] and, more recently, elevated concentrations of lipoprotein (a) [Lp(a)].[7, 8]

Lp(a) particles are a subclass of low density lipoproteins (LDL) primarily distinguished by their apolipoprotein(a) [apo(a)] component. Similar to conventional LDL, elevated Lp(a) levels are an established independent risk factor for CHD as reported by case-control and prospective studies.[9–11] By comparison, evidence relating Lp(a) to CAVD and other valve disorders is less abundant, albeit consistent. Prospective and cross-sectional studies have reported positive associations of Lp(a) with both early and later stages of CAVD,[12–16] and Mendelian randomization studies indicate that Lp(a) directly contributes to disease[12,15]; however, there are critical aspects yet to be examined. First, race-based differences in median Lp(a) levels have been well-documented with Black individuals typically showing 2–3 fold higher levels compared to Caucasians or Hispanics.[17–19] Remarkably, these higher Lp(a) levels in Black individuals do *not* translate to a corresponding 2–3 fold higher risk of Lp(a)-associated disease—as shown in studies of CHD.[18, 19] Whether this phenomenon is evident in Lp(a)-associated CAVD or degree of calcification is unknown, but race/ethnicity may modify whether Lp(a) confers risk of CAVD.

In addition to a possible race/ethnicity-related modification of Lp(a) and valve disease, it remains unknown whether Lp(a) cut-off values used in clinical laboratories to assess cardiovascular risk (30 and 50 mg/dL) may be used in the context of CAVD. Notably, both the 30 and 50 mg/dL Lp(a) cut-offs have been shown to confer higher risk of CHD in Black individuals while only the 50 mg/dL cut-off was shown to associate with higher disease risk in Caucasians and Hispanics[18]—whether this phenomenon is also found in prevalent CAVD is unknown and is critical information for clinical laboratories. In the present analysis, we examined whether elevated levels of Lp(a) are related to the presence of subclinical CAVD

and degree of AVC among 1,347 Black, 1,708 Caucasian, 1,064 Hispanic, and 559 Chinese American participants of the Multi-Ethnic Study of Atherosclerosis (MESA). In addition to conventional risk factors, the presence of existing subclinical atherosclerosis as determined by coronary artery calcium (CAC) and serum phosphate levels were included as covariates.

## MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

## RESULTS

### Sample characteristics

Characteristics of MESA participants at baseline are shown in Table 1. Age and gender distributions were comparable. Chinese Americans had the lowest percentage of smokers and hypertensive participants, while Caucasians had the fewest diabetic participants. Blacks had higher prevalence of hypertension, lower levels of triglycerides, and significantly higher levels of Lp(a) compared to other groups. Caucasians had the highest prevalence (14.5%) of subclinical CAVD as assessed by AVC, while Chinese Americans had the lowest (6.6%). Caucasians showed the most severe AVC cases with 93 (5.4%) individuals having an AVC score of >100, while the Chinese Americans had the fewest cases with 9 individuals (1.6%).

### Continuous Lp(a) and prevalence of subclinical CAVD

Associations between log-transformed Lp(a) levels and the presence of AVC are shown in Table 2. A significant association (RR = 1.11; 95% CI: 1.02–1.21; p=0.02) was observed in the entire sample after adjusting for covariates including age, gender, systolic blood pressure (SBP), taking hypertension medication, smoking, education, diabetes, non-Lp(a)-LDL-C, HDL-C, triglycerides (log-transformed), serum phosphate levels, and the presence of CAC. When stratified by race/ethnicity, the association between Lp(a) and AVC remained significant in Caucasian participants (RR=1.19; 95% CI: 1.06–1.33; p=0.0023). No significant associations were observed in Hispanics or Chinese Americans, but approached significance in Black participants (RR= 1.26; 95% CI: 0.97–1.65; p=0.088). A formal interaction test suggested that the association of Lp(a) (per log unit) and the presence of AVC varies dependent on race/ethnicity ($p_{\text{interaction}}$=0.03).

### Lp(a) cut-offs and prevalence of subclinical CAVD

Lp(a) cut-off values were next evaluated to determine whether they differentially-associated with the presence of AVC across races. The 30 mg/dL cut-off identified higher prevalence of AVC in Caucasian individuals (RR=1.56; 95% CI: 1.24–1.96; p<0.001) compared to those below 30 mg/dL. This relationship was borderline significant in Black study participants (RR: 1.55; CI: 0.98–2.44; p=0.059). The 50 mg/dL cut-off identified higher prevalence of AVC in Caucasian MESA participants (RR=1.72; 95% CI: 1.36–2.17; p<0.001) but was not significant in Black participants (RR=1.24; 95% CI: 0.85–1.85; p=0.26). No significant associations were observed in Hispanics or Chinese Americans for either cutoff value.

### Lp(a) and AVC severity

Associations of Lp(a) and the degree of calcification on the aortic valve were examined as above, testing Lp(a) as a continuous or categorical variable (Table 3) with identical covariate adjustments; however, odds ratios were generated from ordered logistic regression in place of using a relative risk regression approach. Lp(a) (per 1 log unit) was associated with the severity of AVC in Black (OR = 1.48; 95% CI: 1.18–1.87) and Caucasian participants (OR = 1.33; 95% CI: 1.17–1.51). When examined using either 30 or 50 mg/dL dichotomizations, results were similar to the above. Caucasian individuals showed a greater likelihood of more severe AVC when Lp(a) exceeded 30 mg/dL (OR: 2.22; 95% CI: 1.59–3.10) or 50 mg/dL (OR: 2.95; 95% CI: 2.03–4.29). Likewise, Black individuals showed a greater likelihood of more severe AVC when Lp(a) exceeded 30 mg/dL (OR: 1.93; CI: 1.29–2.91) or 50 mg/dL (OR: 1.71; CI: 1.17–2.50). No significant associations were observed in Chinese or Hispanic subpopulations examining Lp(a) as a continuous variable or using either cutoff value; however, associations approached significance using the 50 mg/dL cut-off in both Chinese ($p=0.087$) and Hispanic study participants ($p=0.062$).

### Existing atherosclerosis and serum phosphate

Additional covariates were included in the above models that have been suggested to influence CAVD—specifically, levels of serum phosphate as well as the presence of atherosclerosis as estimated by CAC. Serum phosphate levels were weakly correlated with Lp(a) in Black (corr=0.099; $p<0.001$) and Caucasian participants (corr=0.059; $p=0.02$). Serum phosphate directly correlated with AVC in Black individuals (corr=0.010; $p<0.001$) but was inversely correlated in Caucasians (corr=−0.04; $p<0.001$). Direct correlations of serum phosphate with the exposure (Lp(a)) and outcome variables (AVC) in Black participants (but not in Caucasians) attenuated the associations of Lp(a) and AVC in this subgroup upon including it as a covariate.

In contrast, CAC was only associated with AVC in the subcohort using a regression model and adjusting for age, sex, education, diabetes, systolic blood pressure, hypertension meds, smoking, LDL, HDL, and triglycerides (RR=1.71; $p<0.001$). CAC was not associated with Lp(a) in the MESA dataset, and the inclusion of CAC into statistical models did not appreciably influence relations of Lp(a) and AVC in the subcohort or among races/ethnicities.

## DISCUSSION

In a subcohort of 4,678 MESA participants, higher Lp(a) levels were associated with the presence of subclinical CAVD and degree of valve calcification independent of age, gender, hypertension, smoking, education, diabetes, non-Lp(a)-LDL-C, HDL-C, triglycerides, serum phosphate and existing CAC with a significant race interaction. Applying Lp(a) cut-offs that are currently used in clinical laboratories to evaluate cardiovascular risk showed that Caucasian participants with levels exceeding 30 mg/dL had a higher prevalence of AVC and higher likelihood of more severe AVC than those below this level. Similarly, this cutoff value revealed a borderline significant relation with AVC ($p=0.059$) and more severe AVC in Black individuals. The 50 mg/dL cutoff identified higher prevalence of AVC in Caucasian

participants alone, but was associated with more severe valve calcification in both Black and Caucasian individuals.

## Lp(a) and aortic valve disease

Circulating concentrations of Lp(a) are largely determined by the apo(a)-encoding *LPA* gene,[20, 21] and initial studies of Lp(a) and aortic valve-related outcomes focused on *LPA* genotypes. The first study to suggest a role of Lp(a) in CAVD development was a genome wide-association analysis conducted in three cohorts, including MESA. Investigators showed that the *LPA* gene variant (rs10455872) was associated with AVC in both Caucasians and Black individuals. This relationship was further shown to be mediated by circulating Lp(a) concentrations—though only the European/Caucasian population was tested [12]. Two subsequent studies in the European Prospective Investigation into Cancer-Norfolk[15] and two Danish cohorts[14] also showed that elevated Lp(a) levels were associated with higher risk of CAVD incidence. Finally, and most recently, a cross-sectional analysis of 129 Dutch individuals with familial hypercholesterolemia showed that +10 mg/dL increments in Lp(a) were associated with 11% greater likelihood of CAVD (OR= 1.11; 95% CI = 1.01–1.20, $p$=0.03).[16] Collectively, these results indicate that higher Lp(a) levels are associated with CAVD.

The present analysis expands on previous studies by evaluating whether Lp(a) cut-off values detect the presence and severity of AVC among the four different races/ethnicities. In Caucasians, our results indicate that the 30 or 50 mg/dL cut off values reveal respective 56% and 72% significantly higher prevalence of AVC (p<0.001) as well as respective 122% and 195% higher likelihood of greater valve calcification than those below these cut-offs. Given these data and overlapping confidence intervals, either cut-off appears suitable to assess the presence or degree of AVC in Caucasians. Based on analysis of Lp(a) as a continuous variable, higher Lp(a) levels promote higher prevalence and severity of valve disease.

Black individuals showed a more complex relation of AVC with Lp(a) than Caucasians. The 30 mg/dL cut-off revealed a borderline significant 55% higher prevalence of AVC (p=0.059) and a 93% significantly higher likelihood of more severe valve calcification compared to Black participants below this cut-off. Unexpectedly, the 50 mg/dL cut-off value revealed a non-significant 24% higher prevalence of AVC, but a significant 71% higher likelihood of more severe AVC (p=0.005). In terms of overall disease prevalence, Black study participants had a lower prevalence of subclinical CAVD (11.7%) compared to Caucasians (14.5%) despite having 2–3 fold higher median Lp(a) levels (35.1 mg/dL) vs Caucasians (13.0 mg/dL). Based strictly on the significance values of the findings, the lower 30 mg/dL cut-off may be appropriate for Black individuals for identifying CAVD risk, but further research is needed to better characterize the relation of Lp(a) with CAVD in this population—with particular focus on determining whether Black individuals are protected from their relatively high levels of Lp(a) compared to Caucasians.

## Lp(a) and AVC in Hispanics and Chinese

Null findings in Hispanic participants were not anticipated. Indeed, an association of the *LPA* gene variant (rs10455872) with subclinical CAVD was previously reported in Hispanics

within the MESA population (odds ratio=2.75; $p$=0.004), and it has further been shown that the *LPA* gene accounts for 40–90% of the variation in Lp(a) levels depending on ethnicity.[20, 21] The lack of an association in Hispanic participants suggests that the genetic link between Lp(a) and valve calcification may not be mediated by plasma Lp(a) levels or there are additional modifying variables that must be considered.

In contrast to findings in Hispanics, null findings in Chinese American participants were expected based on previous findings showing inconsistent relations of Lp(a) levels with cardiovascular-related disease.[18, 23, 24] Indeed, it has been previously reported that Lp(a) does not associate with CHD incidence in the MESA Chinese subpopulation.[18] Despite the null finding in the present analysis, the wide confidence intervals in this group are remarkable. Ultimately, the above null findings should be replicated in other cohorts, but these initial observations coupled with the significant race interaction ($p$=0.03) when Lp(a) is treated as a continuous variable, suggest that it does not influence subclinical CAVD in Hispanics and Chinese individuals.

### Lp(a) and coronary artery calcium

Calcification of coronary arteries has previously been shown to associate with subclinical CAVD [25, 26], but relations among Lp(a), CAC, and CAVD have not been examined. The present study confirms previous findings that individuals with CAC have a higher prevalence of CAVD (RR=1.71; p<0.001). This association likely indicates that these pathophysiological processes share risk factors and/or the presence of one increases the risk for developing the other. In contrast, Lp(a) was not associated with CAC in this MESA subcohort in agreement with a number of previous studies [27–32], although not all. Upon including CAC as a covariate in our model, the relationship between Lp(a) and CAVD were not appreciably affected, suggesting that Lp(a) and CAC are independent risk factors of CAVD. Ultimately, further prospective and longitudinal studies will be better suited for identifying relations and temporality of CAC and CAVD than is possible using the present cross sectional design, but Lp(a) levels appear to be a risk factor for CAVD alone.

### Clinical Implications in Disease Development

Subclinical CAVD may be present in 15–40% of adults depending on age and race/ethnicity[33] and is projected to increase with the aging population.[34] Early CAVD may advance to valve stenosis and blockage[35], therefore assessing subclinical CAVD and its risk factors may identify advancement in valve disease. Although not regularly ordered by preventative cardiologists, AVC is readily available with routine chest CTs used for CAC detection. With respect to Lp(a), whether it is a viable clinical target or may otherwise inform clinical decisions regarding risk management of valve disease remains unclear. Lp(a) is still considered an unmodifiable lipoprotein risk factor at present, but development of Lp(a)-lowering therapies are currently underway.[36, 37]

### Strengths and limitations

This study provides the first large-scale cross-sectional evaluation of Lp(a) concentrations and subclinical CAVD across four different races/ethnic groups. To avoid the inherent issues in accurately measuring Lp(a), mass concentrations were quantified using a latex-enhanced

turbidimetric immunoassay that controls for the heterogeneous sizes of the apolipoprotein(a) component of Lp(a).[38] In terms of study limitations, the relatively few cases of subclinical CAVD in Chinese participants compared to other subpopulations limited statistical power, and null findings in Hispanic and Chinese subpopulations need to be interpreted with caution and confirmed by additional cohort studies. The cross-sectional study design prohibits the determination of temporality, but findings support a role for Lp(a) in aortic disease when coupled with other prospective analyses. Additional research using longitudinal approaches will better characterize whether high Lp(a) levels increase risk of CAVD in these different subpopulations.

### Conclusions

In summary, significant associations of Lp(a) and subclinical CAVD were observed in Black and Caucasian individuals in a subcohort of 4,678 MESA participants. Together with the presence of a significant race interaction, race/ethnicity may influence whether elevated levels of Lp(a) increase risk of subclinical CAVD, but further studies are warranted to determine whether Lp(a) levels increase risk of incident CAVD and its progression and whether certain races/ethnicities may be protected from the pathogenic influence of Lp(a).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

**SOURCES OF FUNDING**

This research was supported by R01 HL071739 and contracts N01-HC-95159 through N01-HC-95165 and N01 HC 95169 from the National Heart, Lung, and Blood Institute, and the Multi-Ethnic Study of Atherosclerosis and Air Pollution, funded by the Environmental Protection Agency (EPA) Science to Achieve Results (STAR) Program (grant RD 831697).

## NONSTANDARD ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **CAVD** | Calcific Aortic Valve Disease |
| **AVC** | Aortic Valve Calcification |
| **Lp(a)** | Lipoprotein(a) |
| **MESA** | Multi-Ethnic Study of Atherosclerosis |
| **CAC** | Coronary Artery Calcium |
| **Apo(a)** | Apolipoprotein(a) |
| **RR** | Relative Risk |
| **OR** | Odds Ratio |

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## SIGNIFICANCE

Lipoprotein(a) [Lp(a)] is an LDL particle subclass recently found to increase risk of subclinical calcific aortic valve disease (CAVD) which may contribute to aortic valve stenosis or heart disease. Notably, there are significant race-based differences in Lp(a), and it remains unknown whether this may influence valvular disease development. In this study of 4,679 study participants, higher Lp(a) was found to associate with higher prevalence of subclinical CAVD in Caucasian participants. Applying Lp(a) clinical laboratory cut-offs likewise showed that Caucasian participants with levels ≥30 mg/dL or ≥50 mg/dL had a higher prevalence of CAVD and more severe aortic valve calcification, while both cutoffs were only associated with more severe aortic valve calcification in Black study participants. No relationship between Lp(a) and subclinical CAVD was observed in Hispanics or Chinese. Taken together, race/ethnicity may be an important variable in determining whether elevated Lp(a) identifies subclinical CAVD or severity of aortic valve calcification. The present observations may help identify at-risk individuals and inform clinical decisions for disease risk management.

**Table 1**

Characteristics of MESA participants in 4 race/ethnic groups at visit 1.

| | Blacks | Caucasians | Hispanics | Chinese |
|---|---|---|---|---|
| **N** | 1347 | 1708 | 1064 | 559 |
| **Age (years)** | 61 (52–70) | 62 (54–71) | 61 (52–69) | 62 (53–71) |
| **Gender (male)** | 621 (46.1%) | 813 (47.6%) | 517 (48.6%) | 217 (38.8%) |
| **Smoker (former or current)** | 726 (53.9%) | 929 (54.4%) | 504 (47.4%) | 137 (24.5%) |
| **Diabetic or on diabetes meds** | 196 (14.6 %) | 86 (5.0 %) | 171 (16.1%) | 55 (9.8 %) |
| **Hypertensive** | 428 (31.8%) | 325 (19.0%) | 257 (24.2%) | 126 (22.5%) |
| **On hypertension meds** | 613 (45.5%) | 493 (28.8%) | 305 (28.7%) | 138 (24.7%) |
| **Non-Lp(a) LDL-C (mg/dL)** | 113 (92–133) | 115 (97–136) | 116 (97–137) | 114 (96–132) |
| **HDL-C (nmol/L)** | 1.29 (1.06–1.57) | 1.29 (1.06–1.60) | 1.16 (0.98–1.40) * | 1.24 (1.03–1.50) * |
| **Triglycerides (nmol/L)** | 1.00 (0.75–1.38) * | 1.24 (0.85–1.81) * | 1.50 (1.06–2.13) * | 1.37 (0.96–1.91) * |
| **Lp(a) (mg/dL)** | 35.1 (20.4–61.6) * | 13.0 (5.8–29.6) | 13.1 (6.3–28.8) | 12.9 (7.7–23.4) |
| **AVC presence** | 157 (11.7%) | 248 (14.5%) | 140 (13.2%) | 37 (6.6%) |
| **AVC severity (Agatston units)** | | | | |
| **0** | 1190 | 1460 | 924 | 522 |
| **>0–100** | 101 | 155 | 81 | 28 |
| **>100** | 56 | 93 | 59 | 9 |

Data are shown in median (interquartile range) for continuous variable and as count (%) for categorical variable. Definition: smoker (former & current), diabetic (treated & untreated), hypertensive (systolic blood pressure >= 140 mmHg).

* $P<0.05$ indicating significant difference compared to other race/ethnicity groups.

**Table 2**

Association of Lp(a) levels with the presence of subclinical calcific aortic valve disease. Relative risk (RR; 95% confidence interval-CI, p-value) is presented per unit increment in log Lp(a) or categorically (30 or 50 mg/dL). Models were adjusted for age, gender, hypertension (SBP and medication), smoking, education status, diabetes, non-Lp(a)-LDL-C, HDL-C, log(triglycerides), presence of coronary artery calcium, and serum phosphate levels. $P<0.05$ indicates significant associations.

| | Blacks | Caucasians | Hispanics | Chinese Americans | All groups |
|---|---|---|---|---|---|
| N | 1324 | 1677 | 1044 | 548 | 4593 * |
| ***per log unit*** | | | | | |
| Estimated RR | 1.26 | **1.19** | 0.94 | 0.91 | **1.11** |
| 95% CI | 0.97–1.65 | **1.06–1.33** | 0.85–1.03 | 0.23–3.64 | **1.02–1.21** |
| *p* value | 0.088 | **0.0023** | 0.18 | 0.90 | **0.021** |
| ***≥ 30 mg/dL*** | | | | | |
| N (%) † | 774 (57.5) | 423 (24.8) | 258 (24.2) | 108 (19.3) | 1563 (33.4) |
| Estimated RR | 1.55 | **1.56** | 1.09 | 2.18 | **1.38** |
| 95% CI | 0.98–2.44 | **1.24–1.96** | 0.79–1.51 | 0.52–9.21 | **1.18–1.62** |
| *P* value | 0.059 | **<0.001** | 0.61 | 0.29 | **<0.001** |
| ***≥ 50 mg/dL*** | | | | | |
| N (%) ‡ | 445 (33.0) | 255 (14.9) | 140 (13.2) | 54 (9.7) | 894 (19.1) |
| Estimated RR | 1.24 | **1.72** | 1.24 | 2.25 | **1.44** |
| 95% CI | 0.85–1.80 | **1.36–2.17** | 0.82–1.87 | 0.54–9.44 | **1.21–1.72** |
| *P* value | 0.26 | **<0.001** | 0.31 | 0.27 | **<0.001** |

* Excluding individuals with missing covariate data

† number of individuals with Lp(a) ≥ 30 mg/dL;

‡ number of individuals with Lp(a) ≥ 50 mg/dL.

**Table 3**

Association of Lp(a) levels and severity of aortic valve calcification. Lp(a) and severity of AVC (categorized by Agatston scores of 0, 1–100, and >100) are shown below [estimated odds ratio (OR), 95% confidence interval (CI), p-value]. Models were adjusted for age, gender, hypertension (SBP and medication), smoking, education status, diabetes, non-Lp(a)-LDL-C, HDL-C, log(triglycerides), presence of coronary artery calcium, and serum phosphate levels. $P<0.05$ indicates significant associations.

| | Blacks | Caucasians | Hispanics | Chinese Americans | All Groups |
|---|---|---|---|---|---|
| N | 1324 | 1677 | 1044 | 548 | 4593 * |
| ***per log unit*** | | | | | |
| Estimated OR | **1.48** | **1.33** | 1.01 | 0.97 | **1.21** |
| 95% CI | **1.18–1.87** | **1.17–1.51** | 0.87–1.17 | 0.66–1.43 | **1.11–1.31** |
| *P* value | **<0.001** | **<0.001** | 0.91 | 0.87 | **<0.001** |
| ***≥ 30 mg/dL*** | | | | | |
| N (%) † | 774 (57.5) | 423 (24.8) | 258 (24.2) | 108 (19.3) | 1563 (33.4) |
| Estimated OR | **1.93** | **2.22** | 1.37 | 1.14 | **1.80** |
| 95% CI | **1.29–2.91** | **1.59–3.10** | 0.86–2.17 | 0.44–2.91 | **1.46–2.23** |
| *P* value | **0.001** | **<0.001** | 0.19 | 0.79 | **<0.001** |
| ***≥ 50 mg/dL*** | | | | | |
| N (%) ‡ | 445 (33.0) | 255 (14.9) | 140 (13.2) | 54 (9.7) | 894 (19.1) |
| Estimated OR | **1.71** | **2.95** | 3.01 | 1.65 | **2.14** |
| 95% CI | **1.17–2.50** | **2.03–4.29** | 0.94–9.58 | 0.93–2.92 | **1.69–2.71** |
| *P* value | **0.005** | **<0.001** | 0.062 | 0.087 | **<0.001** |

* Excluding individuals with missing covariate data

† number of individuals with Lp(a) ≥ 30 mg/dL;

‡ number of individuals with Lp(a) ≥ 50 mg/dL.