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Lipoprotein(a) is strongly associated with coronary artery calcification in type-2 diabetic women

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Abstract

Background—Lp(a), implicated in both atherogenesis and thrombosis pathways, varies significantly by demographic and metabolic factors, providing challenges for its use in Coronary Heart Disease (CHD) risk. The purpose of this study was to investigate whether type-2 diabetic subjects, relative to non-diabetics, might benefit more from Lp(a) measurement in the prediction of CHD risk, as measured by coronary artery calcium (CAC).

Methods—We performed cross sectional analyses in two community-based studies: the Penn Diabetes Heart Study [*N*=1299 with type-2 diabetes] and the Study of Inherited Risk of Coronary Atherosclerosis [*N*=860 without diabetes].

Results—Blacks had 2–3 fold higher Lp(a) levels than whites in diabetic and non-diabetic samples. There was significant difference by gender (interaction $p<0.001$), but not race, in the association of Lp(a) with CAC in type-2 diabetic subjects. In age and race adjusted analysis of diabetic women, Lp(a) was associated with CAC [Tobit regression ratio 2.76 (95% CI 1.73–4.40), $p<0.001$]. Adjustment for exercise, medications, Framingham risk score, metabolic syndrome, BMI, CRP and hemoglobin A1c attenuated this effect, but the association of Lp(a) with CAC remained significant [2.25, (1.34–3.79), $p=0.002$]. This relationship was further maintained in women stratified by race, or by the use of HRT or lipid lowering drugs. In contrast, Lp(a) was not associated with CAC in diabetic men, nor in non-diabetic men and women.

Conclusions—Lp(a) is a strong independent predictor of CAC in type-2 diabetic women, regardless of race, but not in men. Lp(a) does not relate to CAC in men or women without type-2 diabetes.

Keywords

Coronary artery calcium; Lipoprotein(a); Gender; Subclinical atherosclerosis

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7. Disclosures

There are no conflicts of interest for this paper with respect to any of the authors.

1. Introduction

Lipoprotein(a) [Lp(a)], a particle comprised of LDL and covalently bound apolipoprotein(a), [1] is considered a pro-atherogenic, pro-thrombotic risk factor for coronary heart disease (CHD) [2]. Mechanistically, it may be pro-atherogenic because excess Lp(a) preferentially binds proinflammatory oxidized phospholipids and is taken up into the sub-endothelial arterial space [3]. At the same time, it may be prothrombotic because apolipoprotein(a) is similar to plasminogen and may interfere with plasminogen's antithrombotic function [2].

Clinically, both prospective and retrospective studies [2,4] as well as a large meta-analysis [5] have found overall positive associations of Lp(a) levels with CHD. However, many studies show significant heterogeneity in relationships to CHD and CHD risk equivalents, especially with respect to gender and race [6,7], with higher Lp(a) levels but lower Lp(a) related CHD risk in blacks [8,9].

Although Lp(a) is present in atherosclerotic plaque [10], it has variable relationships with measures of subclinical atherosclerosis. There have been conflicting data for coronary artery calcification (CAC) with both positive [11,12] and negative [13,14] findings. Furthermore, none of these studies had large numbers of type-2 diabetic individuals. It is known that Lp(a) function and atherogenicity may be modified by glycation in the milieu of overt diabetes [15]. We therefore investigated the relationship of Lp(a) with CAC, across race, gender and diabetes status using two large cross sectional studies of individuals without known CHD—one recruited on the basis of family history of CHD and the other on the basis of type-2-diabetes. We hypothesized that Lp(a) would have stronger association with CAC in diabetic individuals, and that this relationship would be modified in race and gender subgroups.

2. Materials and methods

2.1. Study participants

Details of the Study of Inherited Risk of Coronary Atherosclerosis (SIRCA) (*N*=860) and the Penn Diabetes Heart Study (PDHS) (*N*=1299) have be reported in detail previously [16,17,18,19]. Both are single center, cross-sectional studies of subjects without clinical evidence of CHD (defined as myocardial infarction, coronary revascularization, angiographic CHD, or positive stress test). Subjects for SIRCA were eligible if they were free of clinical CHD, were men aged 30 to 65 or women aged 35 to 70, and had a family history of premature CHD. Exclusion criteria include presence of traditional CHD risk factors such as known diabetes, total cholesterol >300 mg/dl, cigarette smoking >1 pack per day, or blood pressure >160/100 mm Hg. PDHS is an ongoing, cross-sectional community-based study of type-2 diabetic subjects without clinical evidence of CHD or overt chronic kidney disease. Inclusion criteria are age 35 to 75 years, clinical diagnosis of type-2 diabetes (defined as fasting blood glucose ≥126 mg/dl, 2-h postprandial glucose ≥200 mg/dl, or use of oral hypoglycemic agents/insulin in a subject greater than age 40 yr), and negative pregnancy test if female. Exclusion criteria are presence of clinical CHD, clinical diagnosis of type 1 diabetes (insulin use prior to age 35), serum creatinine >2.5 mg/dl and weight>300 Lb. The SIRCA and PDHS studies are single center studies using the same clinical research center, nursing staff, CT scanner and research laboratories.

2.2. Evaluated parameters

Participants were evaluated at the General Clinical Research Center at the University of Pennsylvania Medical Center after a 12-hour overnight fast. Standard lipid panels and Lp(a) were measured in real-time in Penn's Centers for Disease Control-certified lipid laboratory using enzymatic assays (Hitachi 912, Roche Diagnostic Systems Inc., NJ, USA) in

lipoprotein fractions after ultracentrifugation (β-quantification technique) in PDHS and in whole serum in SIRCA. Lp(a) was measured using a Diasorin Immunoturbidimetric assay [20,21]. LDL cholesterol (LDL-C) was measured directly in PDHS and calculated using the Friedewald formula in SIRCA. C-Reactive Protein (CRP) levels were batch-assayed using a high-sensitivity latex turbidimetric immunoassay (Wako Ltd., Osaka Japan) [16]. Laboratory test results were generated by personnel blinded to the clinical characteristics and CAC scores of research subjects.

Framingham risk scores (FRS), using total cholesterol, were calculated as described previously [16]. Participants were classified as having the metabolic syndrome using the revised National Cholesterol Education Program (NCEP) definition (glucose cut-point 100 mg/dl). Global Agatston CAC scores were measured at electron beam tomography (Imatron, San Francisco, CA).

2.3. Statistical analysis

Data are reported as median and interquartile range (IQR) or mean±standard deviation for continuous variables and as proportions for categorical variables. The relationship of Lp(a) with lipid, metabolic and inflammatory parameters was examined by Spearman correlation. Multivariable analysis of CAC scores was performed using Tobit conditional regression of natural log (CAC+1) as CAC data has many zero scores but also a marked right skew [16]. Tobit regression models a dichotomous outcome of zero versus non-zero and then assumes normality conditional on the presence of nonzero score data. The association of natural log-Lp(a) with CAC was assessed in incremental Tobit models with increasing numbers of confounding CHD risk factors: Model 1: age and race; Model 2: age, race, medications, exercise, Framingham Risk Score(FRS), presence of the metabolic syndrome and CRP; and in diabetic individuals; Model 3 which included Body Mass Index (BMI) and Hemoglobin A1c in addition to Model 2 variables. Interaction of Lp(a) with gender, race, and diabetes was tested by likelihood ratio testing (LRT) and stratified results are presented when appropriate. Subgroup analysis was thereafter performed to assess whether differences by use of hormone replacement therapy (HRT), use of statins and estimated glomerular filtration rate (eGFR) – all factors known to potentially affect Lp(a) levels – could have influenced our findings.

Statistical analyses were performed using Stata 10.0 software (Stata Corp, College Station, TX).

3. Results

3.1. Characteristics of the study sample

Table 1 summarizes study sample characteristics stratified by diabetes and gender. Compared to non-diabetic subjects, those with diabetes were older, included more blacks and had greater obesity and metabolic syndrome. Total cholesterol and LDL-C profiles varied by diabetes status likely due to differences in gender, race, and particularly the use of lipid lowering medications. As expected, FRS and coronary calcification were higher in those with diabetes and in men. Consistent with previous studies, Lp(a) was 2–3 fold higher in blacks, and diabetic black women (81% postmenopausal) had higher median Lp(a) values than diabetic black men (65 vs. 43.5 mg/dl, $p<0.001$). Median Lp(a) levels were higher in diabetic women (30 mg/dl) compared to non-diabetic women (21 mg/dl, $p<0.001$) and diabetic men (17 mg/dl, $p<0.001$). A larger number of women in the diabetic sample were on HRT (37% vs. 27%) and diabetic women on HRT had lower Lp(a) values compared to those not on therapy [25 mg/dl (IQR 11–69) vs. 34 mg/dl (IQR 14–73)].

3.2. Association with lipid, metabolic and inflammatory parameters

Spearman correlations revealed modest associations between Lp(a) and lipid and metabolic parameters. These were broadly similar across gender and diabetes status. In diabetic women only, there was a modest positive association of Lp(a) with inflammatory markers (Table 2).

3.3. Association with CAC

There was significant interaction between gender and Lp(a) in the association with CAC (interaction $p<0.01$ in adjusted Tobit models) in those with diabetes but not in those without diabetes (interaction $p=0.6$). Therefore, for diabetic subjects, results are presented for each gender separately. There was no interaction by race within diabetic (interaction $p=0.59$) nor non-diabetic samples ($p=0.56$). Lp(a) was not associated with CAC in non-diabetic subjects (Table 3). Similarly, there was no association with CAC in diabetic men. In contrast, Lp(a) was strongly associated with CAC in diabetic women [age and race adjusted Tobit ratio for a one unit change in the natural log value of Lp(a); 2.76, 95% CI (1.73–4.40), $p<0.001$], with consistent findings in black women [3.67 (1.45–9.32), $p=0.006$] and white women [2.25 (1.31–3.87), $p=0.003$] (race interaction $p=0.5$). In full models, additionally controlling for Framingham risk score, C-Reactive Protein, BMI, hemoglobin A1c, medications, and exercise, Lp(a) in diabetic women continued to have a strong relationship with CAC [2.25, (1.34–3.79), $p=0.002$] (Table 3).

Findings were also similar in diabetic women when further adjusted for menopausal status and use of HRT [2.26, 95% CI (1.34–3.81), $p=0.002$]. In fact, when stratified by use of HRT in full models, women on HRT had a similar Tobit ratio [2.12, 95% CI (0.89–5.04)] compared to those not on HRT [2.62, 95% CI (1.28–5.36)] (interaction $p=0.51$ for HRT). Similarly, in fully adjusted models there was a similar association with CAC in diabetic women stratified by menopausal status (data not shown). In contrast, Lp(a) was not associated with CAC in non-diabetic women on HRT [1.34, 95% CI (0.81–2.20)] or in those not on HRT [1.12, 95% CI (0.82–1.53)]; further, there was no association in non-diabetic women stratified by menopausal status (data not shown). Similar estimates were observed in diabetic women statin users [2.11, 95% CI (1.07–4.15)] and non–statin users [2.30, 95% CI (1.01–5.24)]. This suggests that the differential use of statins (Table 1) did not account for differences in Lp(a) association with CAC in women with diabetes. Given that nephropathy is known to affect Lp(a) levels, we further adjusted for eGFR in the final model in diabetics. Overall, the findings were similar [Tobit ratio 2.28 (1.36–3.83), $p=0.002$]. This is not surprising in our diabetic sample where <5% had an eGFR less than 60 mL/min.

4. Discussion

The relationship of plasma Lp(a) levels with CHD varies by demographic factors and may be conditional on the burden of other background risk in the population under study. In this large examination of community-based asymptomatic subjects, we found that there was a strong independent association of Lp(a) levels with CAC in diabetic women. In contrast, we found no relationship between CAC and Lp(a) levels in diabetic men or in non-diabetic subjects. Within women, differences in menopausal status, use of either HRT or statins did not contribute to the differential association of Lp(a) with CAC in diabetic vs. non-diabetic individuals. This is the first large study to our knowledge to demonstrate an association of Lp(a) with subclinical atherosclerosis in diabetic women without known CHD.

Several mechanisms have been proposed to explain the atherogenicity of Lp(a) beyond its established role in thrombosis. Lp(a) may have atheroprotective properties through transfer and degradation of oxidized phospholipids from tissues and lipoproteins [22]. However, in

excess, Lp(a) can promote atherogenesis, as it can transport cholesterol and oxidized phospholipids into the sub-endothelial arterial space [22]. Indeed, Lp(a) has been found in atherosclerotic plaques [10] and has been implicated in vascular smooth muscle proliferation and endothelial damage. Thus, plasma Lp(a) levels may relate not just to clinical CHD events, but also to the underlying burden of atherosclerosis.

4.1. Lp(a)'s association with CAD

Numerous studies over the last 20 years have established a link between Lp(a) and clinical CHD events. Danesh et al. performed a meta-analysis of 27 prospective studies that included 5436 CHD cases and found that Lp(a) was an independent risk for CHD events with a risk ratio of [1.7, 95% CI (1.4 to 1.9), $p<0.00001$] in the 18 general population studies reviewed [5]. This relationship between Lp(a) and vascular disease was further underscored in a more recent meta-analysis of 36 prospective studies also showing independent modest association of Lp(a) and CHD and stroke risk [23]. More recent large scale studies of diverse atherosclerotic vascular diseases have shown similar results. For example, Bennet et al. looked at 2047 patients with nonfatal MI or who died of CHD compared to 3921 control patients. The odds ratio for Lp(a)'s association with CHD, after adjustment for many established risk factors was 1.60, 95% CI (1.38 to 1.85) [24].

Increasingly, however, Lp(a) has been considered more of a "conditional risk factor" whereby its utility in risk prediction depends on an individual's background risk based on age, race, gender and coexisting conditions such as diabetes. Several studies suggest such context specific risk [6,7,25]. Shai and colleagues found in the Nurses' Health Study that diabetic women ($N=921$) with increased Lp(a) levels had increased risk of CHD [7]. Frohlich et al. reported that women with positive CAD at angiography had Lp(a) levels almost twice as high as men [25]. Sharrett and colleagues looked at 725 CHD events in the ARIC study and found that Lp(a) was associated with CHD in women but not men [6].

4.2. Lp(a) and gender specific risk

Causes for the gender differences in risk are uncertain. There is, however, well documented evidence that estrogen lowers Lp(a). Lp(a) levels increase by about 25% after onset of menopause, but levels are decreased by HRT [26]. Consistent with these data, we found lower levels of Lp(a) in diabetic women on HRT. The HERS trial of postmenopausal women found that baseline Lp(a) levels modified the effect of estrogen and progestin treatment on the risk of CHD, and that those who had the greatest reduction in Lp(a) appeared to have the lowest risk of events [27]. More recently Suk Danik and colleagues looked at Lp(a), HRT, and risk of future cardiovascular events in over 27,736 individuals, of whom, 12,075 were active HRT users. They found that Lp(a) was associated with increased CHD in women not taking HRT, but there was no such relationship in those on HRT [28].

4.3. Lp(a) and coronary artery calcium

Ours is the largest study of Lp(a) and CAC to date and is unique in its focus on type-2 diabetes and its comparison with non-diabetic individuals. Previous work has focused mostly on healthy populations and results are conflicting. Cassidy et al. examined 616 asymptomatic Caucasians (54% women) as part of the community based Rochester Family Heart Study and found that Lp(a) was a significant predictor of CAC only in women ($P=0.04$) [11]. In the GENOA study of 756 Caucasians recruited on the basis of hypertension (59% women of whom 14% were diabetic), no relationship was demonstrated between Lp(a) and CAC [13]. In this cohort, 48% of the women were on estrogen which might have attenuated the CAC associations. Similarly, in the multiethnic Dallas Heart Study of 761 Blacks and 527 whites (8% diabetic, half women), there was no clear relationship of Lp(a) with CAC [14]. Lee et al. examined 1000 young (age 40–45, 19.4%

Black) healthy subjects and found a positive association [12] as did Raggi et al. in 245 Caucasian subjects self-referred for EBCT screening [29]. However studies by Taylor et al. in 630 active duty US army personnel and Mahoney et al. in young adults (197 men and 187 women) were both negative for an association [30,31]. In our study, Lp(a) was associated with CAC in diabetic women, but not in diabetic men or non-diabetic subjects. Our findings, and suggestive data from prior studies [6,7,25], are consistent with Lp(a) as a risk factor for atherosclerotic CHD conditional on gender and type-2 diabetes.

Compared to non-diabetic women, our diabetic sample of women was older and a greater proportion was post-menopausal. One possible explanation for our finding is that an association with CAC emerges following the menopausal increase in Lp(a) and is not observed in younger pre-menopausal women with both lower Lp(a) and atherosclerotic burden. However, controlling for menopausal status or use of HRT did not account for the apparent differential association with CAC in diabetic compared to non-diabetic women. Indeed, in the subgroup of older non-diabetic women who were postmenopausal, we did not find any association of Lp(a) with CAC. These analyses suggest that mechanisms other than menopause and age, perhaps related to insulin resistance, inflammation-oxidation or glycemia, may enhance the atherogenicity of Lp(a) in type-2 diabetes in a gender specific fashion.

4.4. Lp(a) and diabetes

Lp(a)'s function and atherogenicity may be modified by glycation in the milieu of overt diabetes. In fact, glycation of Lp(a) is increased in diabetic subjects compared to controls and is correlated with HbA1c [15]. Further, Galle and colleagues found that glycation of oxidized Lp(a) potentiates its impairment of endothelial function [32]. Rasouli and colleagues also found in a study of 264 subjects with stable angiographic CHD that Lp(a) may act synergistically with the presence of diabetes in predicting severity of CHD [33]. Notably, in a small study of type-1 diabetes (N =101), Starkman and colleagues found that Lp(a) levels were associated with CAC [34], supporting the concept that diabetes-specific modification may alter Lp(a) atherogenicity. Whether and how gender modifies the influence of glycation and diabetes on Lp(a) remains to be determined.

5. Limitations

Our study has several limitations. Because our analyses were cross-sectional, causal and longitudinal relationships were not addressed. We also evaluated two study populations whose demographics differed somewhat, although they were contemporary and derived from the same community, using similar lab assays and protocols. In addition, our results may not be generalizable to all non-diabetic populations given that SIRCA was derived from those with a family history of coronary artery disease. Finally, we used the surrogate, non-clinical endpoint of CAC, which is an estimate, and not a direct measure of coronary atherosclerosis. While CAC scores do not detect all types of coronary atherosclerotic plaques, they are clinically relevant because they are strong, independent predictors of CHD including in diabetic subjects [35].

6. Conclusions

In conclusion, we report that Lp(a) is an independent predictor of CAC in type-2 diabetic women, but not in diabetic men and is not associated with CAC in non-diabetic men or women. Further investigation is needed to also examine gender differences in the relationship to clinical CHD in diabetes and to explore potential gender-related mechanisms. Finally, our data support the concept that Lp(a) may be a particularly useful as a risk

predictor in high risk type-2 diabetic women. Large clinical outcome studies in type-2 diabetes are required to confirm and extend our findings.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [36].

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Table 1

Characteristics of the study samples.

	Non-diabetic Men (*n*=457)	Non-diabetic Women (*n*=403)	Type-2 diabetic Men (*n*=819)	Type-2 diabetic Women (*n*=480)
Age, years	46 (40–51)	50 (44–57)	60 (54–68)	57 (52–64)
Race: White, %	95	95	69.0	51.7
Black, %	2	3.5	25.1	44.1
Total cholesterol, mg/dl	199 (184–224)	211 (183–234)	171 (148–196)	180 (158–206)
HDL-cholesterol, mg/dl	42 (36–49)	58 (47–68)	42 (36–50)	53 (45–64)
Triglycerides, mg/dl	126 (91–177)	112 (80–147)	124 (87–188)	106 (77–150)
LDL-cholesterol, mg/dl	127 (103.7–149.9)	125.7 (103–146.6)	96 (78–117)	99 (81–120)
Glucose, mg/dl	95 (88–103)	91 (86–98)	120 (101–146)	112 (93–140)
Hemoglobin A1c, %	N/A	N/A	6.7(6.2–7.7)	6.8 (6.2–7.8)
Blood pressure, mm Hg				
Systolic	127 (119.5–136.5)	123.5 (113–134.5)	131 (122–141.5)	130 (120.5–143)
Diastolic	79 (74.5–84.5)	75 (68–82)	77 (72–82.5)	74 (70–80)
Metabolic syndrome, %	34.4	24.9	73.7	80.1
Body Mass Index	27.5 (25.2–30.3)	25.6 (22.8–30.2)	31.2 (28.1–34.6)	33.8 (29.4–38.4)
Waist circumference, in	37.5 (35–41)	32 (29–36)	42 (39–46)	41 (37–46)
Current tobacco use, %	12.1	10.8	11.5	10.1
Framingham risk score	7 (4–8)	4 (2–6)	13 (8–20)	10 (7–13)
Hs-CRP, mg/dl	1.1 (0.5–2.1)	1.4 (0.6–3.7)	1.4 (0.7–2.9)	2.8 (1.4–6.6)
Lipoprotein(a), mg/dl	18.5 (8.4–40.7)	21 (9.2–46.7)	17 (7–44.5)	30 (12–72.5)
Whites	18 (8–40.1)	19.8 (9–44.4)	12 (7–28)	16 (8–38)
Blacks	44.8 (27.6–65.3)	72.5 (44.6–123)	43.5 (21–78)	65 (30–94)
HRT use, %	-	27	–	37
Statin use, %	17.5	10.2	58.7	52.2
Niacin use, %	2.9	2.7	5.8	1
Fibrate use, %	2	1	9.4	2
ACE inhibitor use, %	6.5	5	65.7	60.3
Aspirin use, %	18.2	11.2	48.4	42.1
Metformin use, %	N/A	N/A	62.9	65.5

	Non-diabetic Men (*n*=457)	Non-diabetic Women (*n*=403)	Type-2 diabetic Men (*n*=819)	Type-2 diabetic Women (*n*=480)
Thiazolidinedione use, %	N/A	N/A	29.0	27.0
Sulfonylurea use, %	N/A	N/A	45.5	31.7
Insulin use, %	N/A	N/A	16.8	22.6
Mean CAC (± SD)	123.5±329	41.1 ± 133.1	418.5±751	96.1 ± 261.7
Median CAC	7 (1–82)	1 (0–14)	107.5 (0–467)	0 (0–57)

Data presented as median and inter-quartile range or percentage. HDL=high density lipoprotein. LDL=low density lipoprotein. Hs-CRP=high sensitivity C-reactive protein. HRT=hormone replacement therapy. ACE=Angiotensin converting enzyme. CAC=coronary artery calcium. N/A – not applicable.

Table 2

Spearman correlations of lipid, metabolic and inflammatory variables with plasma lipoprotein(a) levels.

	Non-diabetic Men (*n*=457)	Non-diabetic Women (*n*=403)	Type-2 diabetic Men (*n*=819)	Type-2 diabetic Women (*n*=480)
Total cholesterol	0.15**	0.048	0.083*	0.15**
HDL-cholesterol	0.19***	0.04	0.12***	0.16***
Triglycerides	−0.096*	−0.071	−0.15***	−0.24***
LDL-cholesterol	0.16***	0.06	0.11**	0.21***
Glucose	0.04	−0.001	−0.03	−0.02
Waist circumference	−0.085	−0.004	−0.1*	−0.006
Framingham risk	0.029	−0.065	0.04	0.02
Blood pressure				
Systolic	−0.008	−0.068	0.007	−0.024
Diastolic	−0.12	−0.03	0.044	−0.021
Hs-C reactive protein	0.001	0.03	0.059	0.14**
Interleukin-6	−0.02	−0.02	0.04	0.22**

* $p<0.05$.

** $p<0.01$.

*** $p<0.001$.

Table 3

Adjusted associations of lipoprotein(a) with coronary calcification in (A) non-diabetic and (B) diabetic subjects.

Model adjusted for	Men	Women
	Tobit Ratio (95% CI)	Tobit Ratio (95% CI)
(A) Non-diabetic subjects		
Age and race	1.02 (0.85–1.23), p=0.85	1.12 (0.86–1.45), p=0.41
Age, race, meds, exercise, FRS, Metsyn, and CRP	1.10 (0.91–1.32), p=0.33	1.11 (0.87–1.43), p=0.40
(B) Type-2 diabetic subjects		
Age and race	0.97 (0.78–1.21), p=0.77	2.76 (1.73–4.40), p<0.001
Age, race, meds, exercise, FRS, Metsyn, and CRP	0.88 (0.67–1.14), p=0.32	2.40 (1.41–4.07), p<0.001
Age, race, meds, exercise, FRS, Metsyn, CRP, BMI, and HbA1c	0.90 (0.69–1.17), p=0.42	2.25 (1.34–3.79), p=0.002

Results of Tobit regression are presented as the ratio of increase in coronary artery calcification score for a natural log fold increase in Lp(a) levels. Metsyn=Metabolic Syndrome, Meds include aspirin, statin, niacin and ace inhibitor use, FRS=Framingham Risk Score, BMI=body mass index.