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Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: The Atherosclerosis Risk in Communities Study

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Abstract

Background and aims: Diabetes increases risk for atherosclerotic cardiovascular disease (ASCVD). Current guidelines do not recommend measuring lipoprotein(a), another ASCVD risk factor, in these individuals. We examined the association of lipoprotein(a) levels with incident ASCVD events in persons with and without diabetes or prediabetes.

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Conflict of Interest

Dr. Hoogeveen has received grant support from Denka Seiken Co., Ltd. Denka Seiken Co., Ltd. played no role in design, data analysis, or data interpretation for this study. The other authors have nothing to disclose.

Methods: Lipoprotein(a) and other ASCVD risk factors were measured at baseline (1996–1998) in the biracial Atherosclerosis Risk in Communities study; participants without prevalent ASCVD (coronary heart disease or stroke) were monitored ~15 years for incident ASCVD events.

Results: Of 9871 eligible participants (mean age 63 years; 5816 women; 2155 African Americans), 1543 had diabetes and 3615 had prediabetes. Cumulative ASCVD incidence rates (event/1,000-person years) were higher in participants with diabetes (26%) or prediabetes (13%) than in nondiabetic individuals (10%, $p<0.001$). When comparing highest to lowest lipoprotein(a) categories (>50 mg/dL vs. <10 mg/dL), increasing lipoprotein(a) levels were significantly associated with increasing incident ASCVD events in Caucasian participants with prediabetes (hazard ratio [HR]=1.35; 95% confidence interval [CI] 1.07–1.69; $p=0.03$) and diabetes (HR=1.42; 95% CI 1.10–1.84; $p<0.01$), but not those with normal fasting blood glucose. Adding lipoprotein(a) to Pooled Cohort Equation variables improved risk prediction in persons with diabetes (in area under the receiver operating characteristic curve [AUC] 0.0087, net reclassification index [NRI] 0.1761) and prediabetes (AUC 0.0025, NRI 0.0938). **Conclusions:** In this biracial cohort, elevated lipoprotein(a) levels in Caucasian individuals with diabetes or prediabetes were associated with further increased ASCVD risk. Adding lipoprotein(a) to traditional risk factors improved ASCVD risk prediction.

Keywords

lipoprotein(a); diabetes; prediabetes; cardiovascular risk; prevention

Introduction

Prospective studies and Mendelian randomization data have shown that lipoprotein(a) [Lp(a)] is associated with incidence of atherosclerotic cardiovascular disease (ASCVD) (1–4). Individuals with diabetes mellitus also have high risk for incident ASCVD events (5). The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol management guidelines recommend moderate- or high-intensity statin therapy based on 10-year ASCVD risk in patients with diabetes aged 40–75 years for primary prevention (6). A recent meta-analysis by Waldeyer et al. showed a robust association of elevated Lp(a) and ASCVD events in a European cohort, particularly among those with diabetes (7). The ACC/AHA guidelines do not recommend measurement of Lp(a) for high-risk individuals such as those with diabetes or prediabetes for ASCVD risk stratification (6). Lp(a) measurement may be of particular interest in African Americans, who have higher risk for prediabetes and diabetes as well as higher Lp(a) levels compared with Caucasians (8).

We evaluated the association between Lp(a) and ASCVD events by diabetes status (no diabetes, prediabetes, or diabetes) in African American and Caucasian adults in the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized that measurement of Lp(a) would improve risk prediction of ASCVD events, particularly in those with prediabetes or diabetes.

Participants and methods

Study population

The ARIC study is a prospective study of cardiovascular disease incidence in 15,792 men and women recruited from four US communities (9). The current analyses included 9871 individuals who had Lp(a) measured at ARIC visit 4 (1996–1998) and did not have prevalent ASCVD at that time (Supplemental Figure 1). Participants were categorized by glycemic status. Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL, a nonfasting plasma glucose level ≥ 200 mg/dL, or a self-reported history of physician-diagnosed diabetes or the use of diabetes medication. Prediabetes was defined by fasting blood glucose (FBG) 100 mg/dL to <126 mg/dL.

Lipids and lipoproteins

Plasma total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using enzymatic measures. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Lp(a) was measured using a commercially available automated immunoturbidimetric assay (Denka Seiken Co. Ltd., Tokyo, Japan) insensitive to apo(a) isoform variations (10).

Outcomes

Incident ASCVD events were defined as a composite of incident coronary heart disease and ischemic stroke events. The ARIC study methods for incident event assessment are described elsewhere (11). Briefly, incident ASCVD events included fatal coronary heart disease, definite/probable myocardial infarction, coronary revascularization, and validated definite/probable embolic or thrombotic strokes.

Statistical analysis

Lp(a) concentrations were assessed as continuous (per log unit increase) and categorical (<10 , >10 – 20 , >20 – 30 , >30 – <50 , ≥ 50 mg/dL) variables for association with risk of incident ASCVD events, stratified by glycemic status. Incidence rates (per 1000 person-years) and 10-year absolute risk for ASCVD events were also calculated. *P*-value for linear trend of risk across the Lp(a) categories was calculated.

Using Cox proportional-hazards regression, the hazard ratios (HRs) for incident CVD events were calculated for Lp(a) categories with the lowest category as reference. Data were adjusted for age, gender, race, smoking status, blood pressure, blood pressure medications, total cholesterol, and high-density lipoprotein cholesterol (Pooled Cohort Equation [PCE] variables).

To assess the utility of Lp(a) in risk prediction, we calculated area under the receiver operating characteristic curve (AUC), net reclassification index (NRI), and integrated discrimination index (IDI) for adding Lp(a) to PCE variables in each glycemic subgroup.

Results

Over a median (25th, 75th percentile) follow-up of 15.6 (11.3, 16.6) years, the 10-year absolute risk for ASCVD events was 23% in persons with diabetes, 13% in persons with prediabetes, and 9% in persons with normal FBG (Table 1). Approximately 34% (n=520) of diabetic persons and 29% (n=1049) of prediabetic persons had an Lp(a) level >30 mg/dL; of these, 15% (n=76) of diabetic persons and 11% (n=115) of prediabetic persons were on statins, and 60% (n=310) of diabetic persons and 53% (n=559) of prediabetic persons were on aspirin.

Although a test for interaction by race was not statistically significant ($p=0.23$), we decided to perform race-stratified analyses to investigate the association of Lp(a) with risk for ASCVD because Lp(a) levels and the prevalence of cardiovascular risk factors differ substantially between African Americans and Caucasians. Lp(a) levels analyzed as continuous variables were associated with risk for ASCVD events in Caucasian individuals with diabetes (HR=1.10; 95% confidence interval [CI] 1.01–1.19; $p=0.02$) or prediabetes (HR=1.13; 95% CI 1.05–1.20; $p=0.001$) but not in those with normal FBG (HR=1.02; 95% CI 0.95–1.08; $p=0.65$) (Table 2). No significant associations between Lp(a) levels and incident ASCVD events were found in African American participants regardless of diabetes status.

Similarly, in categorical race-specific analyses, increasing Lp(a) levels were significantly associated with increasing incident ASCVD events only in Caucasian participants with prediabetes and diabetes but not those with normal FBG (Table 3). Compared with the lowest Lp(a) category (corresponding to the 52nd percentile), increasing Lp(a) level was associated with increasing ASCVD risk in Caucasian diabetic and prediabetic individuals (p -trend=0.03 and 0.05, respectively) in models fully adjusted for traditional ASCVD risk factors (Table 3a). Very high levels of Lp(a) (> 50 mg/dL) were associated with a significant increase in ASCVD risk in Caucasian individuals with diabetes (HR=1.59; 95% CI 1.18–2.15) or prediabetes (HR=1.40; 95% CI 1.09–1.81). However, we did not find a significant association of Lp(a) concentration with incident ASCVD events by diabetes status among African American participants (Table 3b).

AUCs showed a significant, albeit modest, improvement with addition of Lp(a) to the PCE variables in the risk prediction model for all glycemic subgroups, whereas the continuous NRI showed significant improvement for persons with diabetes (NRI 0.176; 95% CI 0.028–0.293) or prediabetes (NRI 0.094; 95% CI 0.019–0.215) but not for those with normal FBG (Table 4).

Discussion

Our results show that diabetic and prediabetic individuals with higher Lp(a) levels had higher rates of incident ASCVD events in this biracial cohort of Americans. When stratified by race, this association was significant only in Caucasian and not in African American participants. In the overall cohort, the addition of Lp(a) to the PCE variables improved ASCVD risk prediction.

Similar findings were shown in an analysis of European individuals with diabetes from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium. Lp(a)-associated risk for major coronary events was higher in individuals with diabetes (HR=1.31; 95% CI 1.15–1.50) compared with individuals without diabetes (HR=1.15; 95% CI 1.08–1.21) (7).

In the ACC/AHA guidelines (6), statins are indicated for persons with diabetes and those with a 10-year ASCVD risk $\geq 7.5\%$, and the US Preventive Services Task Force recommends aspirin for individuals with 10-year ASCVD risk $\geq 10\%$ in primary prevention (12). In our study, approximately 38% (n=399) of prediabetic participants with Lp(a) >30 mg/dL had a 10-year ASCVD risk $<7.5\%$ and hence were not indicated for statin therapy, and 12% (n=60) of diabetic and 53% (n=559) of prediabetic participants with Lp(a) >30 mg/dL had a 10-year ASCVD risk $<10\%$ and hence were not candidates for aspirin therapy. Diabetic and prediabetic individuals were at higher absolute risk for incident ASCVD events in this cohort than individuals without diabetes, with absolute risk (95% CI) 23.4 (21–26), 12.5 (11–13), and 9 (8.5–10) in the respective subgroups (Table 1). Caucasian diabetic and prediabetic participants with elevated Lp(a) were noted to have higher than calculated risk for incident ASCVD events (Table 3a).

Currently, the European Society of Cardiology/European Atherosclerosis Society recommend measuring Lp(a) in individuals with premature CVD or family history of premature CVD, familial hypercholesterolemia, family history of elevated Lp(a), recurrent CVD events with optimal lipid-lowering therapy and $\geq 5\%$ 10-year fatal CVD risk (as per the SCORE algorithm) (13). The European guidelines suggest an elevated risk of CVD with Lp(a) levels >80 th percentile (> 50 mg/dL or ~ 100 – 125 nmol/L). The National Lipid Association and the Canadian Cardiovascular Society guidelines for CVD prevention have similar recommendations but identify the “elevated” cut point of Lp(a) as > 30 mg/dL (14). The ACC/AHA guidelines do not make any definitive recommendation for Lp(a) measurement. The NHLBI recently released a set of recommendations to increase research efforts to understand the pathophysiology of Lp(a) and facilitate advances in clinical diagnosis and treatment of elevated Lp(a) and associated CVD (15).

Measurement of Lp(a) has previously been shown to improve ASCVD risk reclassification and prediction (16). Given the increased risk for subclinical and clinical ASCVD events in individuals with diabetes and prediabetes (17,18), our results suggest that Lp(a) quantification may be helpful in further risk stratification to determine which individuals may need more aggressive lifestyle changes and pharmacotherapy for primary prevention. Currently, no direct Lp(a)-lowering pharmacotherapies with favorable clinical event reduction are available. However, data support that genetically lowered Lp(a) levels and use of statins and low-dose aspirin for primary prevention in individuals with elevated Lp(a) levels may lead to lower ASCVD event rates. Emdin et al. studied the phenotypic impact of *LPA* gene variation and genetically altered Lp(a) levels with ASCVD (coronary heart disease, peripheral arterial disease, and stroke) in a large genomic panel including the ARIC study (19). A 29% lower risk of coronary heart disease (odds ratio [OR]=0.71; 95% CI 0.69–0.73), a 31% lower risk of peripheral arterial disease (OR=0.69; 95% CI 0.59–0.80), and a 13% lower risk of stroke (OR=0.87; 95% CI 0.79–0.96), was shown with each 1-SD

genetically mediated lowering of Lp(a) (19). In Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), rosuvastatin significantly reduced ASCVD events in participants with baseline Lp(a) greater than or equal to the median (HR=0.62; 95 CI 0.430.90) (20). Aggressive lifestyle risk factor management (21) and use of aspirin (22) in individuals with elevated Lp(a) have been shown to reduce ASCVD risk.

Given the substantially lower number of African American study participants compared with Caucasians, it is possible that our analysis was underpowered to find significant differences by glycemic subgroups in African Americans. Future studies are needed to examine whether Lp(a) level is associated with incident ASCVD events among glycemic categories in other ethnicities.

In conclusion, measuring Lp(a) levels in high-risk Caucasian individuals with diabetes and prediabetes may be beneficial for patient–physician discussions on more aggressive lifestyle modifications and pharmacotherapy initiation in primary prevention of ASCVD events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline characteristics and incident atherosclerotic cardiovascular disease events across glycemic subgroups

	Diabetes (N=1543)	Prediabetes (N=3615)	Normal fasting glucose (N=4713)	p-trend
Lp(a), mg/dL	14.3 (4.7, 40.7)	12.4 (5.0, 35.6)	13.0 (5.3, 39.6)	0.765
African Americans	31.2 (17.8, 53.2) (n=562)	32.4 (17.5, 53.1) (n=815)	33.1 (16.9, 54.4) (n=778)	0.674
Caucasians	7.5 (3.0, 24.5) (n=981)	9.3 (3.9, 24.8) (n=2800)	10.3 (4.4, 30.6) (n=3935)	<0.001
Age, years	63.1±5.60	62.7±5.66	62.4±5.65	<0.001
Female, %	56.51	49.68	66.79	<0.001
African Americans, %	36.42	22.54	16.51	<0.001
Total cholesterol, mg/dL	199.5±39.19	202.9±36.83	201.8±35.52	0.021
HDL-C, mg/dL	44.6±14.29	48.0±15.16	55.0±17.44	<0.001
Triglycerides, mg/dL	147 (104, 215)	126 (93, 174)	111 (81, 156)	<0.001
LDL-C, mg/dL	121.1±34.33	126.2±33.12	121.4±33.05	0.062
BMI, kg/m ²	31.8±5.98	29.7±5.51	27.1±4.96	<0.001
SBP, mmHg	132.7±19.11	128.0±18.26	124.8±18.74	<0.001
DBP, mmHg	70.7±10.51	72.0±10.07	70.5±10.12	0.006
Waist circumference, cm	110.1±14.48	104.4±13.81	97.0±13.37	<0.001
Hypertensive medication use, %	62.73	40.61	31.44	<0.001
Statin use, %	13.82	8.89	7.12	<0.001
Lipid-lowering medication use, %	18.06	11.16	9.42	<0.001
Current smoking, %	12.69	14.58	15.18	0.025
hs-CRP, mg/L	3.95 (1.63, 7.77)	2.38 (1.11, 5.23)	2.06 (0.94, 4.73)	<0.001
ASCVD events, %	30.40 (n=469)	17.81 (n=644)	14.24 (n=671)	<0.001
Incidence rate, events/1,000 person-years	26.0	13.2	10.2	<0.0001
10-year absolute risk, % [95% confidence interval]	23.4 [21–26]	12.5 [11–13]	9 [8.5–10]	<0.0001

Data presented as median (25th, 75th percentile), mean±standard deviation, percentage, or percentage [95% confidence interval]; *p*-trends were calculated by test for trend across ordered groups.

ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; DBP=diastolic blood pressure; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); SBP=systolic blood pressure.

Table 2:

Association of Lp(a) levels with incident ASCVD events, stratified by glycemic subgroups, in Caucasians and African Americans

	Model	Hazard ratio	95% Confidence interval	<i>p</i>
Caucasians (n=7716)				
Diabetes	Model 1	1.10	1.01–1.19	0.021
	Model 2	1.10	1.01–1.19	0.022
Prediabetes	Model 1	1.12	1.05–1.20	0.001
	Model 2	1.13	1.05–1.20	0.001
Normal fasting glucose	Model 1	1.02	0.95–1.08	0.652
	Model 2	1.02	0.95–1.08	0.652
African Americans (n=2155)				
Diabetes	Model 1	1.18	0.98–1.42	0.080
	Model 2	1.17	0.97–1.40	0.103
Prediabetes	Model 1	1.04	0.85–1.27	0.723
	Model 2	1.02	0.84–1.25	0.826
Normal fasting glucose	Model 1	1.18	0.96–1.44	0.122
	Model 2	1.16	0.94–1.42	0.165

Hazard ratios were calculated per natural-log unit of Lp(a) increase; time of follow-up is from date of visit 4 to December 31, 2013; mean follow-up is 13.4±4.75 years, median (25th percentile, 75th percentile) follow-up is 15.6 (11.3, 16.6) years. Model 1: Pooled Cohort Equation (PCE) models were applied for hazard ratio estimation in which the association of Lp(a) level and incident ASCVD was adjusted for age, gender, total cholesterol, HDL-C, SBP, antihypertensive medication use, and current smoking. Model 2: model 1 plus estimated glomerular filtration rate (eGFR).

Table 3A:

Association of Lp(a) levels with risk of incident ASCVD events in Caucasians with diabetes, prediabetes, and normal fasting glucose levels

		Lp(a) categories, mg/dL (percentiles)					<i>p</i> -trend
		10 (0–13)	>10–20 (13–30)	>20–30 (30–47)	>30–<50 (47–71)	50 (71–100)	
Diabetes (n=981)	Model 1	Ref	0.94 (0.66–1.34)	0.91 (0.52–1.60)	1.20 (0.81–1.78)	1.59 (1.18–2.16)	0.028
	Model 2	Ref	0.94 (0.66–1.34)	0.90 (0.51–1.58)	1.21 (0.81–1.80)	1.59 (1.18–2.15)	0.028
	Events/ Popn	175/577 (30.33)	37/133 (27.82)	13/50 (26.00)	29/84 (34.52)	59/137 (43.07)	0.010
Prediabetes (n=2800)	Model 1	Ref	1.06 (0.83–1.34)	1.39 (1.00–1.92)	1.20 (0.88–1.63)	1.40 (1.09–1.80)	0.046
	Model 2	Ref	1.06 (0.83–1.34)	1.37 (0.99–1.90)	1.20 (0.88–1.63)	1.40 (1.09–1.81)	0.048
	Events/ Popn	255/1472 (17.32)	94/523 (17.97)	42/187 (22.46)	49/237 (20.68)	83/381 (21.78)	0.017
Normal fasting glucose (n=3935)	Model 1	Ref	0.95 (0.75–1.20)	1.18 (0.86–1.61)	1.02 (0.74–1.41)	1.20 (0.95–1.51)	0.423
	Model 2	Ref	0.95 (0.75–1.20)	1.18 (0.86–1.61)	1.02 (0.74–1.41)	1.20 (0.95–1.51)	0.420
	Events/ Popn	259/1937 (13.37)	96/720 (13.33)	46/286 (16.08)	43/310 (13.87)	104/682 (15.25)	0.192

Model 1: PCE models were applied for hazard ratio estimation in which the association of Lp(a) level and incident ASCVD was adjusted for age, gender, total cholesterol, HDL-C, SBP, antihypertensive medication use, and current smoking. Model 2: model 1 plus eGFR. ASCVD events included coronary heart disease death, definite or probable myocardial infarction, coronary revascularization, and ischemic stroke. Diabetes was defined as fasting glucose ≥ 126 mg/dL or nonfasting glucose ≥ 200 mg/dL or diabetes medication use; prediabetes was defined as impaired fasting glucose ≥ 100 mg/dL and <126 mg/dL; normal fasting glucose was defined as <100 mg/dL.

Popn=Population in subgroup

Table 3B:

Association of lipoprotein (a) levels with risk of incident CVD events in African Americans with diabetes, prediabetes, and normal fasting glucose levels

		Lp(a) categories, mg/dL (percentiles)					<i>p</i> -trend
		10 (0–13)	>10–20 (13–30)	>20–30 (30–47)	>30–<50 (47–71)	50 (71–100)	
Diabetes (n=562)	Model 1	Ref	0.86 (0.43–1.71)	1.03 (0.54–1.96)	1.48 (0.83–2.64)	1.26 (0.71–2.22)	0.298
	Model 2	Ref	0.87 (0.43–1.72)	1.02 (0.53–1.94)	1.41 (0.79–2.53)	1.24 (0.70–2.20)	0.419
	Events/Popn	17/73 (23.29)	18/91 (19.78)	23/99 (23.23)	47/137 (34.31)	51/162 (31.48)	0.018
Prediabetes (n=815)	Model 1	Ref	1.02 (0.50–2.07)	1.40 (0.72–2.73)	1.13 (0.59–2.15)	1.16 (0.62–2.19)	0.837
	Model 2	Ref	0.97 (0.47–1.98)	1.33 (0.68–2.60)	1.06 (0.55–2.02)	1.11 (0.59–2.10)	0.859
	Events/Popn	14/106 (13.21)	17/135 (12.59)	24/143 (16.78)	31/202 (15.35)	35/229 (15.28)	0.497
Normal fasting glucose (n=778)	Model 1	Ref	1.51 (0.74–3.10)	1.30 (0.62–2.72)	1.58 (0.81–3.07)	1.61 (0.83–3.14)	0.661
	Model 2	Ref	1.48 (0.72–3.03)	1.26 (0.60–2.64)	1.54 (0.79–3.00)	1.52 (0.78–2.97)	0.726
	vents/Popn	12/109 (11.01)	21/126 (16.67)	18/125 (14.40)	34/186 (18.28)	38/232 (16.38)	0.248

Models and definitions as in Table 3A.

Table 4:

Risk prediction for ASCVD events in diabetes, prediabetes, and normal fasting glucose subgroups

	AUC (95% CI) Model 1	AUC (95% CI) Model 2	AUC (95% CI) Model 1 vs Model 2	NRI (95% CI) Model 2	IDI (95% CI) Model 2
Diabetes	0.6478 (0.6284, 0.6793)	0.6565 (0.6374, 0.6925)	0.0087 (0.0024, 0.0236)	0.1761 (0.0279, 0.2928)	0.0068 (0.0020, 0.0200)
Prediabetes	0.7143 (0.6938, 0.7337)	0.7167 (0.6973, 0.7364)	0.0025 (0.0007, 0.0086)	0.0938 (0.0193, 0.2151)	0.0036 (0.0011, 0.0090)
Normal fasting glucose	0.6895 (0.6721, 0.7134)	0.6907 (0.6728, 0.7155)	0.0013 (0.0003, 0.0062)	0.0686 (-0.0305, 0.1638)	0.0011 (0.0003, 0.0045)

Model 1 (PCE variables) includes age, gender, race, total cholesterol, HDL-C, SBP, antihypertensive medication use, and current smoking. Model 2 includes PCE variables plus Lp(a) categories.

AUC=area under the receiver operating characteristic curve; CI=confidence interval; IDI=integrated discrimination index; NRI =category-free net reclassification index.