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ORIGINAL RESEARCH ARTICLE

Evaluation of Lipoprotein(a) as a Prognostic Marker of Extracoronary Atherosclerotic Vascular Disease Progression

Tiffany R. Bellomo, MD; Emily E. Bramel, PhD; Jiwoo Lee, MS; Sarah Urbut, MD, PhD; Alyssa Flores, MD; Zhi Yu, PhD; Satoshi Koyama, MD, PhD; Buu Truong, BS; Sara Haidermota, BS; Matthew J. Eagleton, MD; Pradeep Natarajan, MD, MMSc*; Aniruddh P. Patel, MD*

BACKGROUND: Despite current treatment strategies for atherosclerotic vascular disease focusing on lifestyle modification and lowering cholesterol, a significant residual risk of major atherosclerotic complication remains, prompting investigation into lipoprotein(a) (Lp(a)) as a potential predictive biomarker. The objective of this study was to determine the usefulness of Lp(a) in identifying patients at high risk of incident extracoronary atherosclerotic vascular disease and complications.

METHODS: Data from 460 544 participants in the UK Biobank with prospectively measured Lp(a) concentrations were included in this analysis. Cox proportional hazards regressions modeled the associations of Lp(a) concentrations with incident peripheral artery disease (PAD) and incident carotid artery stenosis and progression to the first major adverse limb event and the first stroke, respectively.

RESULTS: Of the study participants, the median [interquartile range] age at study enrollment was 58 [51–64] years, 54.2% were male, 94.4% were European, 5.5% had diabetes, and 10.5% were smokers. Over a median follow-up time of 13.6 [12.9–14.4] years, 6347 (1.4%) and 1972 (0.43%) developed the first incidence of PAD and carotid stenosis, respectively. Among participants with prevalent PAD and carotid stenosis at enrollment, 196 (2.7%) and 67 (1.9%) progressed to the first incidence of major adverse limb event and stroke, respectively. Median Lp(a) concentrations were significantly different in those without atherosclerotic vascular disease at 19.5 nmol/L [7.6–73.5] compared with incident PAD at 25.3 nmol/L [8.3–107.3], progression to major adverse limb event at 33.3 nmol/L [8.7–158.2], incident carotid stenosis at 29.5 nmol/L [8.5–116.3], and carotid stenosis progression to stroke at 37.8 nmol/L [11.1–158.3]. The risk estimate per 75 nmol/L Lp(a) for incident PAD (hazard ratio [HR], 1.18 [95% CI, 1.15–1.20]; $P<0.0001$) was similar to that for incident carotid stenosis (HR, 1.17 [95% CI, 1.13–1.20]; $P<0.0001$). Among participants with PAD, those with high Lp(a) concentrations had 1.57 times the risk of developing major adverse limb event than participants with normal Lp(a) concentrations (95% CI, 1.14–2.16; $P=0.006$). Among participants with carotid stenosis, participants had 1.40 times the risk of developing an ischemic stroke with high Lp(a) concentrations, although this was not significant (95% CI, 0.81–2.40; $P=0.228$).

CONCLUSIONS: High concentrations of Lp(a) are associated with both incident extracoronary atherosclerotic vascular disease and progression to major complications.

Key Words: atherosclerotic disease progression ■ extracoronary atherosclerotic vascular disease ■ lipoprotein(a)

Vascular health beyond the coronary arteries is a worsening global public health issue,[1] affecting over 200 million patients worldwide.[2] Atherosclerotic extracoronary vascular disease often remains indolent for long periods before progressing to morbid complications. Lower-extremity peripheral artery disease

Correspondence to: Aniruddh P. Patel, MD, 185 Cambridge St, CPZN 3.218, Boston, MA 02114, Email apatel32@mgh.harvard.edu, or Pradeep Natarajan, MD, MSc, 185 Cambridge St, CPZN 3.184, Boston, MA 02114, Email pnatarajan@mgh.harvard.edu
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Clinical Perspective

What Is New?

- Building upon previous work linking lipoprotein(a) (Lp(a)) with peripheral artery disease, Lp(a) is now shown to be significantly associated with major adverse limb events and carotid artery stenosis independent of established clinical risk factors.
- Among patients with peripheral artery disease or carotid artery stenosis, elevated Lp(a) concentrations are strongly associated with progression to major adverse limb events or stroke, respectively.

What Are the Clinical Implications?

- Lp(a) may serve as an important biomarker for both the onset and progression of extracoronary atherosclerotic vascular disease.
- Stricter risk factor control and therapies aimed at lowering Lp(a) should be considered for individuals at high risk for extracoronary atherosclerotic vascular disease progression.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CKD	chronic kidney disease
HDL	high-density lipoprotein
HR	hazard ratio
ICD	*International Classification of Diseases*
IQR	interquartile range
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
MALE	major adverse limb event
OPCS	Office of Population Censuses and Surveys
OR	odds ratio
PAD	peripheral artery disease
UKB	UK Biobank

(PAD) and carotid stenosis are often diagnosed at late stages, disproportionately affect minority populations, and have marked differences in patient outcomes.[3] A lack of understanding of the progression of extracoronary atherosclerotic vascular disease despite traditional lipid-lowering therapies has driven research into proatherogenic lipoprotein(a) (Lp(a)), which serves as the primary plasma sink for oxidized phospholipids and can contribute to plaque formation through inflammatory pathways.[4] Lp(a) concentrations remain stable over a person's lifetime and represent an independent causal risk factor for atherosclerosis.

Despite research examining the role of Lp(a) in the development of atherosclerotic disease, key gaps remain in understanding its role in extracoronary vascular outcomes. First, many previous studies have been underpowered to allow continuous risk estimation and query of risk across important subgroups in the general population. Previous studies have reported categorical risk estimates in largely European ancestry data sets[5–8] or cohorts ascertained in procedural settings.[9] Second, lack of uniform risk factor collection or inconsistencies in Lp(a) assays across multiple cohorts have introduced heterogeneity in results. Several studies report units of mass concentration instead of the more biologically meaningful particle quantification.[6–8] Third, although Lp(a) is well established as a risk factor for incident atherosclerosis, its role in disease progression remains undercharacterized. Although a few studies have independently examined Lp(a) associations with major adverse limb events (MALEs) in PAD[6,10,11] or incidence of stroke,[8,12] none have examined progression of carotid disease to stroke. Previous UK Biobank (UKB) analyses have often relied on composite outcomes inclusive of PAD,[13,14] focused on narrow risk factor contexts,[15] or relied on genetically determined Lp(a)[16–18] or did not comprehensively assess for primary and secondary extracoronary vascular disease.

The UKB is a large prospective cohort that enables the analysis of particle-based Lp(a) measurements and the risk of atherosclerotic diseases across vascular beds.[19] With linked electronic health record and standardized baseline data, it supports well-powered analyses of primary and secondary vascular disease end points across diverse groups within the broader context of cardiovascular risk factors. This study aims to leverage UKB data to quantify the risk of incident and secondary vascular disease associated with Lp(a), potentially supporting its use as a screening biomarker and therapeutic target.

METHODS

Design

This cohort study used prospectively collected data where the beginning of the study period was defined as the time of enrollment between 2006 and 2010,[20] which was also the time of sample collection for the Lp(a) assay (Supplemental Figure 1). Participants were prospectively monitored through to the most recent update of the UKB data available as of 2024. UKB analyses were performed under application number 7089, and all participants provided informed consent. The Mass General Brigham human research committee institutional review board approved the secondary analyses of UKB (institutional review board No. 2021P002228). All data and materials are publicly available at the UKB and can be accessed at https://biobank.ndph.ox.ac.uk/showcase/. Code to perform the analyses in this manuscript is available from the authors upon request.

Study Population

The UKB is a prospective cohort study with genetic and clinical data collected from approximately 500 000 individuals

between 40 and 69 years of age at the time of recruitment.[19] Participants underwent baseline assessments between 2006 and 2010 at 22 centers across the United Kingdom, including medical history, lifestyle exposures, and collection of physical and clinical data with subsequent prospective follow-up for health outcomes. These data were linked to the National Health Service records, which permits identification of prevalent clinical conditions and incident events based on the *International Classification of Diseases,* Ninth and Tenth revisions (*ICD-9* and *ICD-10*, respectively), Office of Population Censuses and Surveys versions 3 and 4 (OPCS-3 and OPCS-4, respectively), and United Kingdom death registry data. The inclusion criterion were participants >18 years of age with an Lp(a) metabolite value. Exclusion criteria were related individuals and individuals with an existing diagnosis of our outcomes at the time of enrollment.

Lp(a) Measurement

The UKB is the ideal cohort for primary investigation, given robust follow-up and measurement of Lp(a) in a subset of 460 506 participants as part of the study protocol using samples from the time of enrollment. Serum Lp(a) concentrations were measured as previously described by the UKB.[21] Briefly, the immunoturbidimetric assay (Randox Laboratories; Crumlin, County Antrim, United Kingdom), using a Beckman Coulter AU5800 Platform, uses the Denka Seiken method.[22] Measured values for participants reporting use of lipid-lowering medications to estimate untreated values for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were adjusted as performed previously, and high Lp(a) concentrations were defined as ≥150 nmol/L. Consistent use of niacin can decrease Lp(a) concentrations, but only 0.02% (n=77) of participants included in the analysis reported use.

Outcome Definitions

The definition of lower-extremity PAD was derived from a previous genome-wide association study of PAD[23] and a PAD-specific polygenic risk score.[24] The definition incorporated a self-reported history of "peripheral vascular disease," which included "leg claudication/intermittent claudication" or "arterial embolism" as well as *ICD* codes and cilostazol prescriptions within the UKB (Supplemental Table 1). The definition was subdivided into categories of claudication, atherosclerosis, embolism, revascularization procedures, major amputation, minor amputation, and amputation of unspecified level for sensitivity analysis. Individuals with codes related to trauma preceding or concurrent with amputation codes or those with vasculitis or congenital malformation codes concomitant with PAD codes were excluded (Supplemental Table 1). Prevalent PAD was identified on the basis of the presence of these criteria at the time of enrollment, whereas incident PAD was defined by the first occurrence of these criteria during the follow-up period. MALE was chosen as a clinically relevant end point for PAD progression, as it has been used in multiple clinical trials.[25,26] The progressive atherosclerotic outcome of MALEs was defined as the incident first occurrence of an amputation or a surrogate of acute limb ischemia among those with prevalent PAD, as the specific diagnosis codes for acute limb ischemia were unavailable in the UKB. Specifically, ICD and OPCS Classifications of Interventions and Procedures codes were included for embolism and thrombosis, major amputation, minor amputation, amputation of unspecified level, emergent procedures, and revascularization procedures. Revascularization procedures included angioplasty and stenting, thrombectomy, thrombolysis, and lower-extremity bypass (Supplemental Table 2). In total, there were 7144 participants with incident PAD, 3701 participants with prevalent PAD, and 196 participants with PAD that progressed to MALEs.

Carotid stenosis was defined on the basis of *ICD* codes and OPCS codes for carotid revascularization (Supplemental Table 3). Prevalent carotid stenosis was identified on the basis of the presence of these criteria at the time of enrollment, whereas incident carotid stenosis was defined by the first occurrence of these criteria during the follow-up period. Ischemic stroke was chosen as a clinically relevant end point for carotid stenosis progression, as it has been used in multiple clinical trials.[27,28] The progressive atherosclerotic outcome of ischemic stroke was defined as the first occurrence of an algorithm including *ICD* and OPCS codes (Supplemental Table 4) among those with prevalent carotid stenosis. The algorithm for ischemic stroke was developed by the UKB Stroke Outcomes Group, where expert physicians had individual-level data access for adjudication of outcomes, reporting a positive predictive value of 80% to 90%.[29] In total, there were 3477 participants with incident carotid stenosis, 1226 participants with prevalent carotid stenosis, and 67 participants with carotid stenosis that progressed to ischemic stroke.

Demographics and Comorbidities

Subanalyses were performed using both demographic and common comorbidities related to extracoronary atherosclerotic vascular disease.[1] Specifically, age was defined at the time of enrollment, and sex was self-reported from fixed categories of female and male. Race was determined on the basis of self-identified ethnicity and country of origin and collapsed into African, European, South Asian, and other, with low sample size prohibiting more granular detail (Supplemental Table 5). Ancestry was calculated using a k-nearest neighbors algorithm based on genetic similarities to continental ancestry groups.[30] We have previously shown that Lp(a) expression varies significantly with ethnicity, where substantial differences in concentrations were noted according to race-median values of Lp(a).[31] Current smoking was defined as lifetime smoking of at least 100 cigarettes and currently without cessation.

Relevant comorbidities included obesity, diabetes, hypertension, hyperlipidemia, coronary artery disease (CAD), chronic kidney disease (CKD), and lipid levels ascertained at the time of enrollment.[32] Obesity was categorized using a body mass index cutoff of 30 kg/m^2. Diabetes was defined as glycated A1c ≥6.5% or previous physician diagnosis. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or prescription of an antihypertensive medication. Hyperlipidemia was defined as total cholesterol ≥200 mg/dL or statin prescription. CAD was defined as a diagnosis of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or death register indicating myocardial infarction and related sequelae as either a primary or secondary cause of death. CKD status was determined on the basis of estimated glomerular filtration rate calculated using the CKD epidemiology collaboration equation. LDL cholesterol was classified into 3 groups: low (<100 mg/

dL), medium (100–160 mg/dL), and high (>160 mg/dL). HDL cholesterol was categorized as low or normal, using a cutoff of <40 mg/dL to define low HDL in men and <50 mg/dL to define low HDL in women. Triglycerides were classified as normal (≤150 mg/dL) or high (>150 mg/dL).

Statistical Analysis

Descriptive statistics were used to calculate the distribution of all covariates stratified by dichotomous Lp(a) >150 nmol/L and compared using Mann-Whitney *U* tests (Table). The relationship between Lp(a) and incident extracoronary atherosclerotic vascular diseases were initially modeled using natural cubic splines, given previous literature demonstrating nonlinear relationship between Lp(a) and recurrent CAD events.[33] The reference values were median Lp(a) concentrations, and the covariates were enrollment age, sex, and ancestry. Akaike's information criterion score was used to determine the degrees of freedom for the natural cubic splines of the best-fitting model. Models were also generated using common risk factors for extracoronary atherosclerotic vascular disease to ensure that effect estimates did not vary. A sensitivity analysis within racial subgroups with high Lp(a) concentrations was conducted by 25 nmol/L increments to determine the concentration of Lp(a) lowering at which a 20% risk reduction for PAD would be achieved. Subsequent analyses used this increment.

Cox proportional hazards regression models within demographic and comorbid subgroups were used to quantify the relationship between Lp(a) per 75 nmol/L increase and time to incident atherosclerotic disease of PAD and carotid stenosis, adjusting for covariates of age at enrollment, ancestry, and sex. The prognostic importance of Lp(a) threshold >150 nmol/L in determining atherosclerotic vascular disease complications was modeled using Cox proportional hazards regression to MALEs within a subgroup of PAD and stroke within a subgroup of carotid stenosis, adjusted for age at enrollment, ancestry, and sex. Significance was defined as $P<0.05$. Figure legends indicate the *P* values and statistical tests used. Statistical analysis was performed using R (version 4.4.1).

RESULTS

Cohort

A total of 460 544 participants with measured Lp(a) concentrations (median, 19.6 [interquartile range, 7.6–73.8]) were included in this analysis. These participants were an average of 57 years of age at enrollment, 94.9% of participants were European, and 54.2% were male; they were followed over a median period of 13.6 [12.9–14.4] years (Table). Some demographics significantly

Table. Summary of Baseline Characteristics of Individuals Studied from the UK Biobank by Lipoprotein(a) Level

Variable	Lipoprotein(a) <150 nmol/L (n=403 180)	Lipoprotein(a) >150 nmol/L (n=57 374)	*P* value
Age, mean (SD)	56.92 (8.12)	57.88 (7.77)	<0.001
Male sex, no. (%)	215 382 (53.4)	340 78 (59.4)	<0.001
Ancestry, %			<0.001
African, No. (%)	6866 (1.7)	1821 (3.2)	…
South Asian, No. (%)	9040 (2.3)	862 (1.5)	…
European (%)	379 147 (94.9)	53 781 (94.7)	…
Admixed American, No. (%)	2050 (0.5)	227 (0.4)	…
Eastern Asian, No. (%)	2307 (0.6)	123 (0.2)	…
Current smoker, No. (%)	42 227 (10.5)	6057 (10.6)	0.535
Statin at enrollment, No. (%)	61 364 (15.2)	13 780 (24.0)	<0.001
Obesity, No. (%)	97 631 (24.3)	14 107 (24.7)	0.049
Hyperlipidemia, No. (%)	94 322 (23.4)	19 575 (34.1)	<0.001
Hypertension, No. (%)	116 108 (28.8)	18 883 (32.9)	<0.001
Diabetes, No. (%)	22 187 (5.5)	3183 (5.5)	0.667
Atrial fibrillation, No. (%)	28 182 (7.0)	4402 (7.7)	<0.001
Coronary artery disease, No. (%)	45 662 (11.3)	9439 (16.5)	<0.001
Chronic kidney disease, No. (%)	19 611 (4.9)	3292 (5.7)	<0.001
Lipoprotein(a), median [IQR]	15.20 [6.64–43.46]	204.76 [173.10–252.80]	<0.001, non-norm
Incident PAD, No. (%)	5863 (1.5)	1281 (2.2)	<0.001
Incident carotid stenosis, No. (%)	2855 (0.7)	622 (1.1)	<0.001
Prevalent PAD and incident MALE, No. (%)	144 (0.0)	52 (0.1)	<0.001
Prevalent carotid stenosis and incident stroke, No. (%)	49 (0.0)	18 (0.0)	0.001

P values are reported on the basis of χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. IQR indicates interquartile range; MALE, major adverse limb event; and PAD, peripheral artery disease.

differed between normal and high Lp(a) concentrations (≥150 nmol/L), with the high-Lp(a) group being older and having a greater proportion of males. There was a higher prevalence of cardiovascular comorbidities in participants with high Lp(a), including hypertension (32.9% versus 28.8%, $P<0.001$), CAD (16.5% versus 11.3%, $P<0.001$), and CKD (5.7% versus 4.9%, $P<0.001$). There were no differences among current smoking, diabetes, and obesity between high and normal concentrations of Lp(a) (Table). There was a similar trend observed in both the population with extracoronary incident atherosclerotic vascular disease (Supplemental Table 6) and those with progressive vascular disease (Supplemental Table 7).

Median Lp(a) concentrations in those without extracoronary atherosclerotic vascular disease were significantly lower than in those with incident atherosclerotic disease and with major atherosclerotic complications (Figure 1). The median [interquartile range] Lp(a) concentration in those without extracoronary atherosclerotic vascular disease was 19.5 nmol/L [7.6–73.5] compared with incident PAD at 25.3 nmol/L [8.3–107.3], PAD progression to MALEs at 33.3 nmol/L [8.7–158.2], incident carotid stenosis at 29.5 nmol/L [8.5–116.3], and carotid stenosis progression to stroke at 37.8 nmol/L [11.1–158.3]. The incidence rate of extracoronary atherosclerotic vascular disease was higher among participants with higher Lp(a) concentrations (Figure 2A and 2C). A similar trend of increased incidence rates across Lp(a) concentrations was observed in participants with extracoronary atherosclerotic vascular disease progressing to major complications (Figure 2B and 2D).

The cumulative incidence of incident extracoronary atherosclerotic vascular disease displayed a stepwise relationship with increasing Lp(a) concentrations (Figure 3A and 3B). The dose-response relationship became even more pronounced in participants with progressive major atherosclerotic complications (Figure 3C and 3D). The shape of the relationship between Lp(a) and atherosclerotic events was modeled using smoothed adjusted hazard ratios (HRs) and generally showed a linear gradient increase in risk across incident atherosclerotic events (Figure 4). The slope of the spline curve remained steep for both incident PAD with 1 knot (Figure 4A) and incident carotid stenosis with 4 knots (Figure 4C). The linear gradient increase in risk was minimally attenuated after adjustment of cardiovascular risk factors (Figure 4C) and incident carotid stenosis (Figure 4D). Whereas the slope of the spline curve with 3 knots remained steep for progressive MALEs, the slope of the spline curve for stroke with one knot showed a slightly more shallow rise in HR (Supplemental Figure 2). There was no significant heterogeneity (P heterogeneity >0.1) across lipid subgroups in the association between Lp(a) levels and incident atherosclerotic disease (Supplemental Figure 3). We then performed a time-varying analysis, which showed

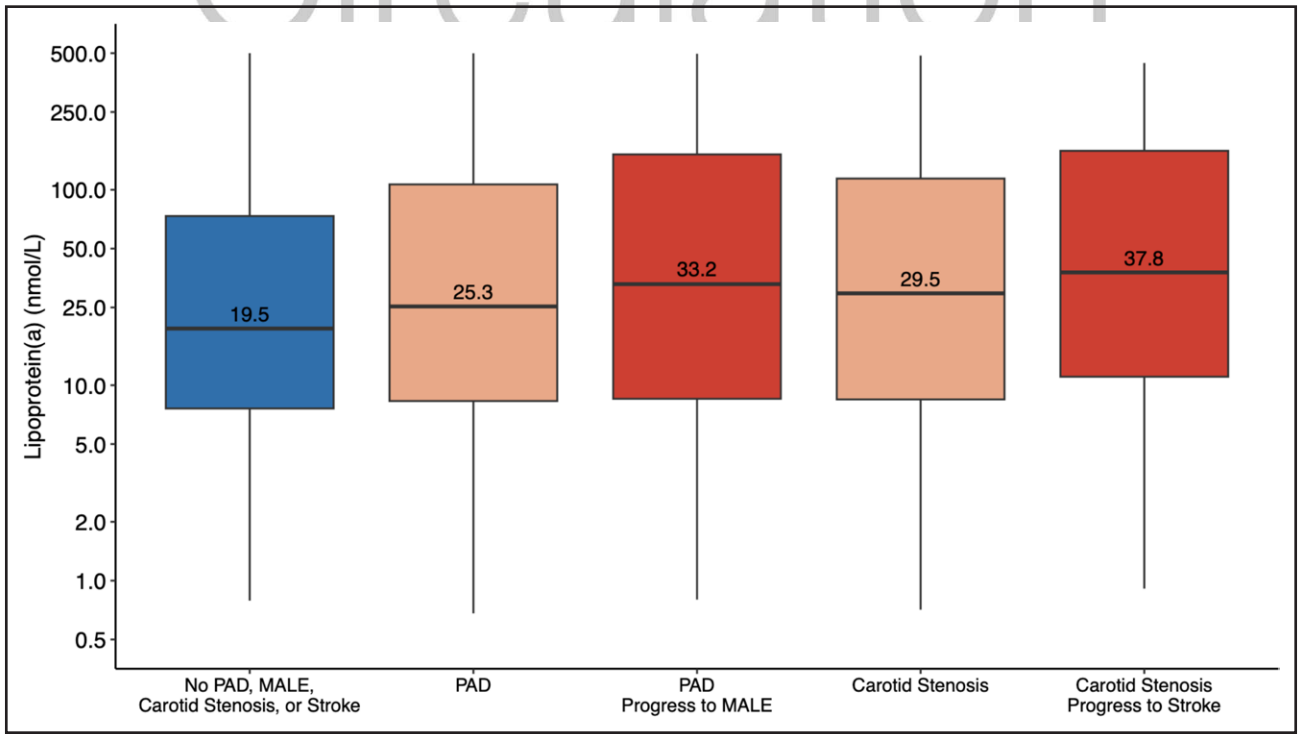

Figure 1. Lipoprotein(a) concentrations according to disease status at time of enrollment.
Mann-Whitney *U* test comparing all diseases states with the blue bar representing no peripheral artery disease, major adverse limb event, carotid artery stenosis, or stroke showed $P<0.0001$. Dimensions of the box capture the 25th to 75th percentiles, and whiskers capture one additional interquartile range. MALE indicates major adverse limb event; and PAD, peripheral artery disease.

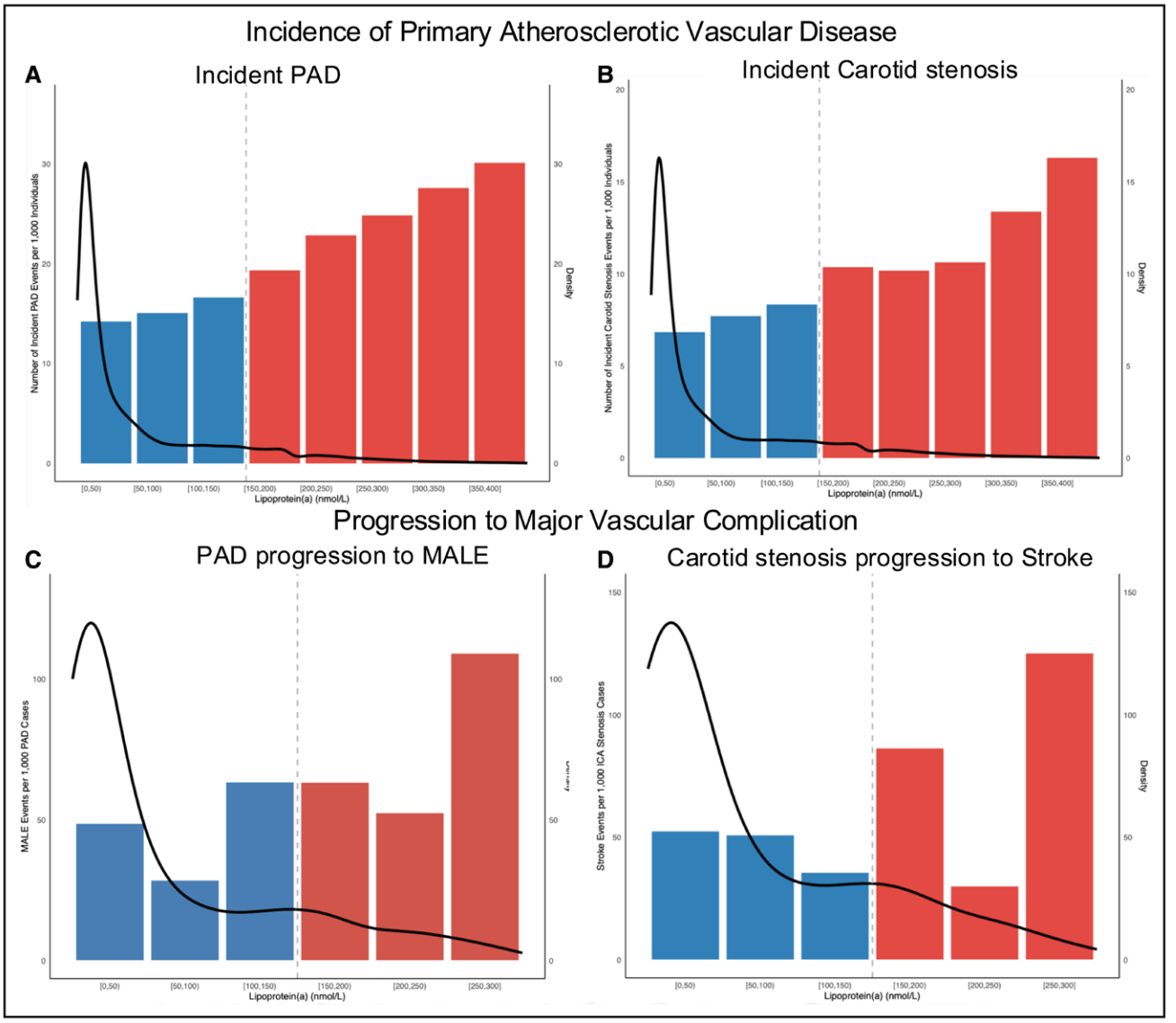

Figure 2. Distribution of incident and progressive atherosclerotic vascular disease.
Bar plots represent those without incident vascular disease progressing to PAD (**A**) and carotid stenosis (**B**) and those with incident vascular disease progressing to MALE (**C**) and ischemic stroke (**D**). Events per 1000 individuals were stratified by lipoprotein(a) concentration with the overlaid density plot (black line), where red indicates Lp(a) values >150 nmol/L. MALE indicates major adverse limb event; and PAD, peripheral artery disease.

that the importance of Lp(a) in incident PAD risk was not impacted by the life years considered (Supplemental Figure 4). The proportional hazards assumption tested by Schoenfeld residuals was met by clinical covariates assessed in this study (Supplemental Figure 5).

Ancestry subgroups based on genetic similarity had widely varying concentrations of median [interquartile range] Lp(a) (detailed in Supplemental Results). Initial sensitivity analysis of gradient of Lp(a) concentrations to incident PAD showed similar effects for different ancestries (Supplemental Figure 6). Given that median values of Lp(a) were below 75 nmol/L for all ancestries and that our clinical interest focused on participants with high Lp(a) concentrations to understand the potential effects of lowering concentrations, we restricted our sensitivity analysis to participants with Lp(a) above 75 and 150 nmol/L (Supplemental Figure 3). This analysis showed that lowering Lp(a) concentrations by 75 nmol/L would achieve approximately a 20% risk reduction in Europeans, and the resolution in non-European ancestry was limited by sample size. A similar phenomenon was observed for carotid stenosis, where lowering Lp(a) concentrations by 75 nmol/L would achieve around a 16% risk reduction, and there were no major differences between self-reported race or genetically determined ancestry (Supplemental Figure 7). When observing the slope of the spline curves for PAD stratified by racial group, there were no significant differences between the slope for the African self-reported race or ancestry groups compared with the European and South Asian ancestry, given

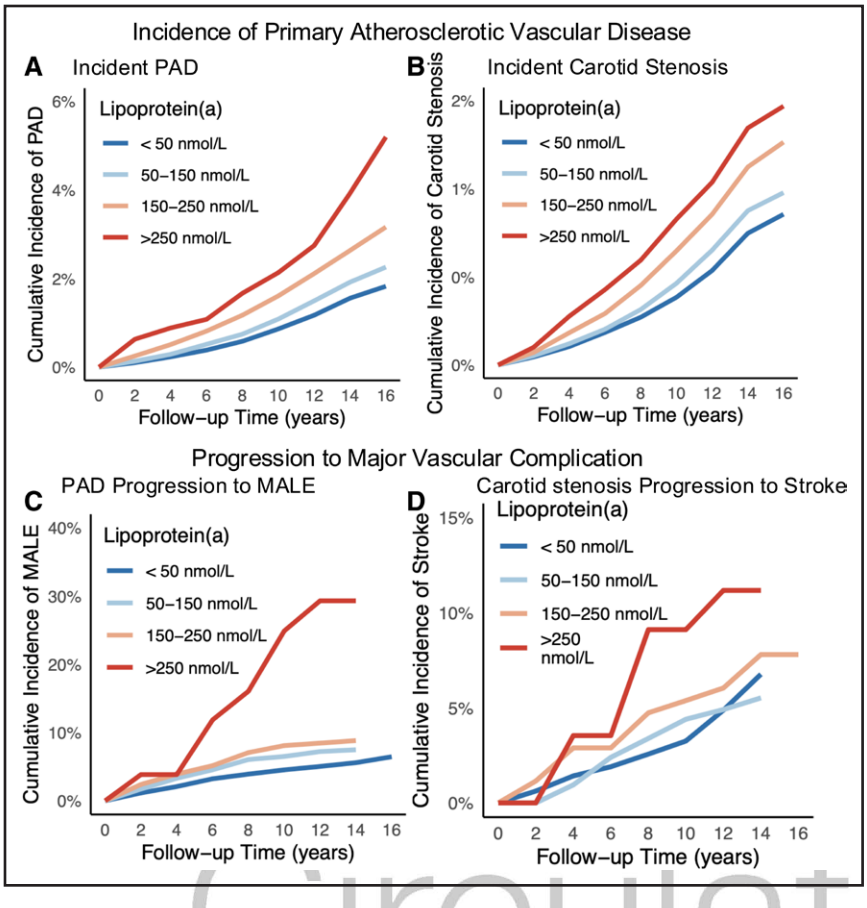

Figure 3. Kaplan-Meier curves of incident vascular disease and major atherosclerotic complications. Shown are Kaplan-Meier curves of incident PAD (**A**) and incident carotid stenosis (**B**) to MALE (**C**) and ischemic stroke (**D**). Curves were stratified by a gradient of Lp(a) concentrations of <50, 50 to 150, 150 to 250, and >250 nmol/L. MALE indicates major adverse limb event; and PAD, peripheral artery disease.

the wide confidence intervals (Supplemental Figure 8). Spline curves for carotid stenosis showed the same consistent slope across European self-reported and genetically determined ancestries (Supplemental Figure 9).

Incident Vascular Disease

The risk estimate per 75 nmol/L Lp(a) for incident PAD in the total population at HR 1.18 (95% CI, 1.15–1.20; $P<0.0001$) was similar to the risk estimate for incident carotid stenosis in the total population at HR 1.17 (95% CI, 1.13–1.20; $P<0.0001$; Figure 5). The risk of incident PAD per 75 nmol/L Lp(a) was not significantly different among age groups, sex, or ancestry (Figure 5). However, we cannot exclude the possibility of reduced power to detect differences across groups. There were significant differences among subgroups of PAD (P heterogeneity<0.0001), where the risk estimate per 75 nmol/L Lp(a) was highest for PAD requiring a revascularization procedure (HR, 1.27 [95% CI, 1.23–1.31]; $P<0.0001$; Supplemental Figure 10). The risk of incident carotid stenosis per 75 nmol/L Lp(a) was not significantly different among age groups or ancestry. There was a significant difference in sex, where men had a significantly higher HR compared with women (P heterogeneity=0.045; Supplemental Results).

We performed regression analyses within other clinically relevant populations to ensure that the effect of Lp(a) on incident extracoronary atherosclerotic vascular disease was robust to these subgroups (Figure 6). Regression analysis adjusting for age of enrollment, sex, and ancestry revealed a significantly increased risk estimate for incident PAD in participants who were not on a statin compared with those who were on a statin (P interaction=0.003), those who were not obese compared with those who were obese (P interaction=0.017), and those who were smokers compared with those who were nonsmokers (P interaction=0.014). However, there were no significant differences attributable to hyperlipidemia, hypertension, diabetes, CAD, and CKD. There were also no significant differences in subgroups tested for incident carotid stenosis (Supplemental Results).

Progressive Vascular Disease

We then sought to examine the association of Lp(a) and major atherosclerotic complications in individuals with atherosclerotic vascular disease. Restricting the population to those with prevalent extracoronary vascular disease facilitated comparative analysis of Lp(a) and other risk factors assessed at enrollment. Given the smaller sample size, we conducted the analysis using

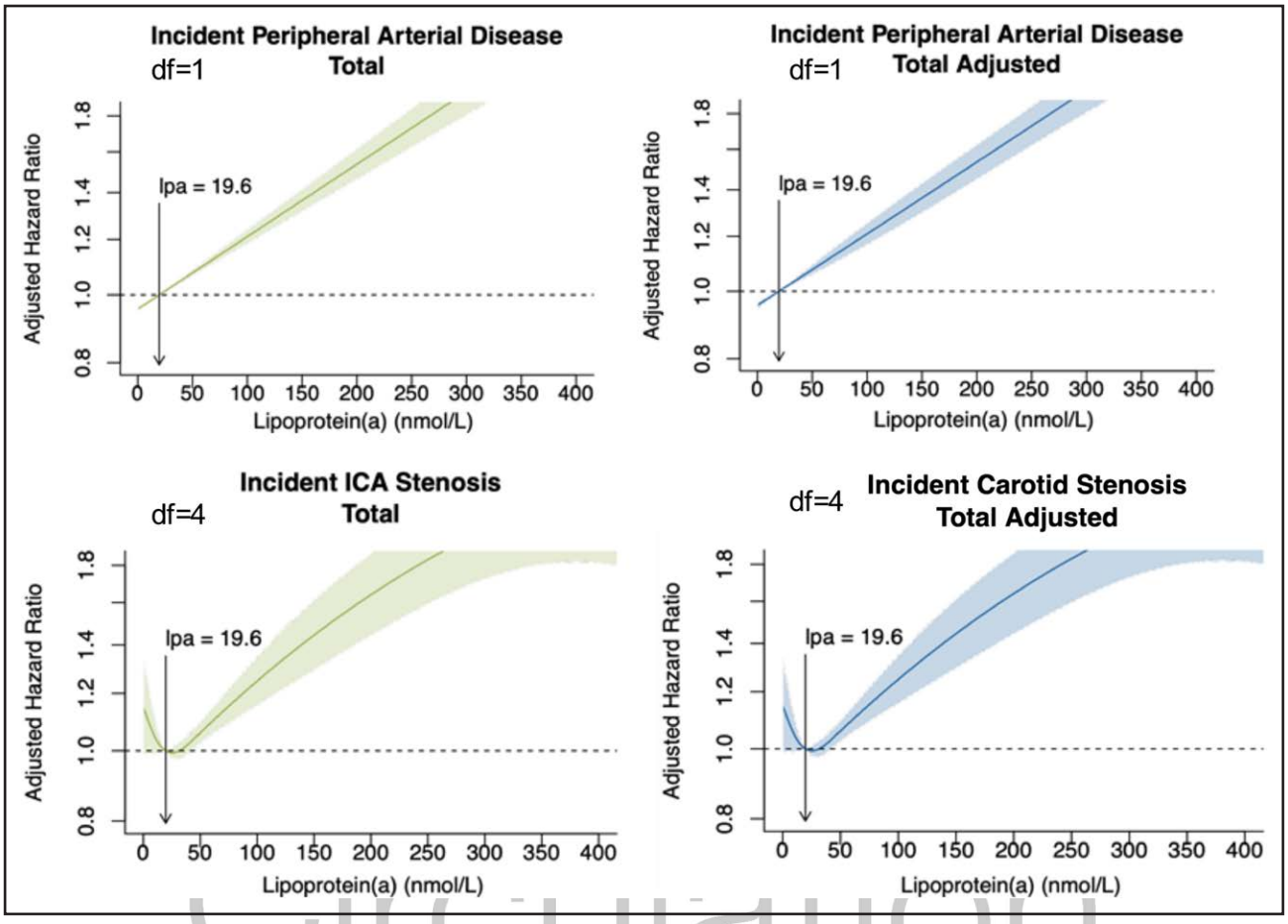

Figure 4. Smoothed adjusted hazard ratio and 95% CI of individuals with a given lipoprotein(a) concentration, estimated using a Cox proportional hazards regression model.

Incident peripheral artery disease (**A**) and carotid stenosis (**C**) with covariates included enrollment age, sex, and ancestry, modeled using cubic natural splines. Incident peripheral artery disease (**B**) and carotid stenosis (**D**) with covariates included enrollment age, sex, ancestry, systolic blood pressure, high-density cholesterol, low-density cholesterol, triglycerides, diabetes, and smoking, modeled using cubic natural splines. Lp(a) indicates lipoprotein(a).

a dichotomous threshold of high Lp(a) at 150 nmol/L (Figure 7), which reflected the standard clinical threshold. Among participants with PAD, those with high Lp(a) concentrations had 1.60 times the risk of developing MALEs than participants with normal Lp(a) concentrations (95% CI, 1.17–2.20; *P*=0.004). There were significant differences among subgroups of MALEs (*P* heterogeneity=0.028), where the risk estimate per 75 nmol/L Lp(a) was highest for MALEs requiring an emergent procedure (HR, 3.63 [95% CI, 1.11–11.90]; *P*=0.033; Supplemental Figure 11). The risk estimate for incident MALEs per 75 nmol/L Lp(a) among all individuals was also elevated at 1.64 (95% CI, 1.45–1.86; *P*<0.0001; Supplemental Figure 12). The risk of PAD progression to incident MALEs among participants with high Lp(a) concentrations was not significantly different among age groups, sex, or ancestry (Figure 7). Associations between Lp(a) and major complications of PAD were robust in subgroups with larger sample sizes. The previously significant risk estimates were attenuated for PAD progression to MALEs compared with incident PAD alone in participants who were not on a statin, not obese, and not smokers (Supplemental Results).

Among participants with carotid stenosis, participants had 1.40 times the risk of developing an ischemic stroke with high compared with normal Lp(a) concentrations, although this was not significant (95% CI, 0.81–2.40; *P*=0.228; Figure 7). The risk estimate for incident stroke per 75 nmol/L Lp(a) among all individuals was also elevated at 1.17 (95% CI, 1.10–1.24; *P*<0.0001; Supplemental Figure 12). The risk of carotid stenosis progression to incident stroke among participants with high Lp(a) concentrations was not significantly different among age groups, sex, or ancestry (Supplemental Results). Similarly, no significant differences were observed across the clinical subgroups tested.

DISCUSSION

In this study, using a large prospective biobank, we demonstrate a stepwise relationship between Lp(a) concentrations and incident extracoronary atherosclerotic vascular

Disease	Demographic	Affected/Total (%)	Incidence (1000 p-y)	p-value	HR (95% CI)	p-het
PAD	Total	7144 / 460554 (1.6 %)	1.18	<0.0001	1.18 (1.15 to 1.20)	
	Age<50	430 / 107811 (0.4 %)	0.29	<0.0001	1.26 (1.16 to 1.37)	0.07
	Age 50-60	1573 / 153203 (1 %)	0.77	<0.0001	1.21 (1.16 to 1.26)	
	Age >60	5141 / 199540 (2.6 %)	2.03	<0.0001	1.16 (1.13 to 1.19)	
	Women	2504 / 249460 (1 %)	0.76	<0.0001	1.17 (1.14 to 1.21)	0.712
	Men	4640 / 211094 (2.2 %)	1.71	<0.0001	1.18 (1.15 to 1.21)	
	African	93 / 8687 (1.1 %)	0.83	0.979	1.00 (0.83 to 1.20)	0.17
	European	6802 / 432928 (1.6 %)	1.20	<0.0001	1.18 (1.16 to 1.20)	
	South Asian	154 / 9902 (1.6 %)	1.21	0.183	1.12 (0.95 to 1.31)	
Carotid Stenosis	Total	3477 / 460554 (0.8 %)	0.57	<0.0001	1.17 (1.13 to 1.20)	
	Age<50	222 / 107811 (0.2 %)	0.15	0.216	1.09 (0.95 to 1.25)	0.183
	Age 50-60	704 / 153203 (0.5 %)	0.34	<0.0001	1.22 (1.15 to 1.30)	
	Age >60	2551 / 199540 (1.3 %)	0.99	<0.0001	1.16 (1.12 to 1.19)	
	Women	1270 / 249460 (0.5 %)	0.38	<0.0001	1.13 (1.08 to 1.18)	0.045
	Men	2207 / 211094 (1 %)	0.80	<0.0001	1.19 (1.15 to 1.24)	
	African	93 / 8687 (1.1 %)	0.83	0.979	1.00 (0.83 to 1.20)	0.17
	European	6802 / 432928 (1.6 %)	1.20	<0.0001	1.18 (1.16 to 1.20)	
	South Asian	154 / 9902 (1.6 %)	1.21	0.183	1.12 (0.95 to 1.31)	

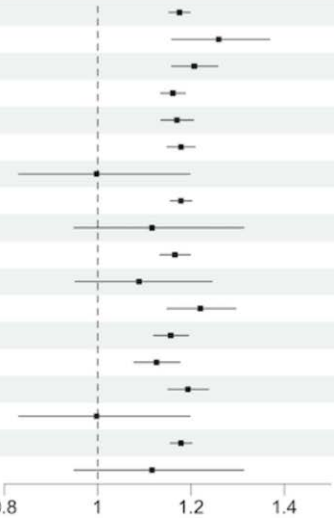

Figure 5. Demographic subgroups exhibit varying risks of incident peripheral artery disease and carotid stenosis events per 75 nmol/L increase in lipoprotein(a).

Cox proportional hazards regression models were performed by subgroups of demographics. A heterogeneity *P* value was calculated to examine the significance of effect modification within demographic subgroups in influencing incident atherosclerotic peripheral artery disease and carotid stenosis risk. HR indicates hazard ratio; PAD, peripheral artery disease; and *P*-het, heterogeneity *P* value.

disease that was not attenuated after adjusting for common risk factors related to extracoronary atherosclerotic vascular disease. Sensitivity analysis showed that lowering Lp(a) concentrations by 75 nmol/L would achieve around an 18% risk reduction for incident PAD and a 17% risk reduction for incident carotid stenosis. We also show that, among participants with prevalent PAD, high Lp(a) concentrations were associated with progression to MALEs that remained robust to the analyzed clinical subgroups. Among participants with carotid stenosis, high Lp(a) concentrations were significantly associated with progression to incident stroke in nonsmokers. On the basis of these data, we believe that Lp(a) has the potential to serve as both a biomarker and a therapeutic target for extracoronary atherosclerotic vascular disease and its progression to major complications.

Risk of Incident Disease Associated With Lp(a) Is Similar Across Vascular Beds

Individuals with clinically measured elevated Lp(a) concentrations have a consistently high risk of developing extracoronary atherosclerotic vascular disease across multiple vascular beds. Additionally, Lp(a) has been consistently associated with other cardiovascular diseases across both US and non-US cohorts.[34] The risk of incident PAD has been studied in a prospective cohort of 1162 participants with PAD from the Copenhagen General Population Study, in which the risk of PAD was estimated to be 1.39 (95% CI, 1.24–1.56) per 50 mg/dL of genetically elevated Lp(a).[5] Another study focusing on genetics used the technique of Mendelian randomization to establish a causal relationship between genetically determined Lp(a) and PAD (HR, 1.38 [95% CI, 1.30–1.46]) in the UKB.[18] Our group identified a similar risk profile between the risk of *LPA* gene variants and peripheral vascular disease, where 1 SD of genetically lowered Lp(a) concentration was associated with a 31% lower risk of peripheral vascular disease (odds ratio [OR], 0.69 [95% CI, 0.59–0.80]).[17] These results are concordant with our observational findings with clinically collected Lp(a) concentrations, where every 75 nmol/L Lp(a) increase resulted in an 18% (95% CI, 1.15–1.20) increased risk for incident PAD and 17% (95% CI, 1.13–1.20) increased risk for incident carotid stenosis. Participants not on statins at enrollment had a higher risk of incident PAD, potentially because of confounding by indication. Those prescribed statins may have received closer cardiovascular risk management, whereas those not on statins might have had statin intolerance or required more intensive lipid-lowering therapy. Similarly, stronger associations of Lp(a) outcome were observed among nonobese individuals versus obese individuals, potentially in a setting of confounding related to a PAD-related decrease in mobility. Separately, individuals who smoked had an increased risk of Lp(a)-associated vascular events, potentially suggesting a synergistic effect between the two risk factors.

Risk Associated With Lp(a) Increases for Secondary Disease Events

Participants with established extracoronary atherosclerotic vascular disease and elevated Lp(a) concentrations

Diesease	Group	Status	Affected/Total (%)	Median (Lpa (nmol/L)	HR (95% CI)	p-interaction
PAD	Current Smoker	Yes	1929 / 48284 (4 %)	19.50	1.22 (1.18 to 1.26)	0.014
	Current Smoker	No	5152 / 410027 (1.3 %)	19.60	1.16 (1.13 to 1.19)	
	Statin	Yes	3053 / 75144 (4.1 %)	24.00	1.10 (1.07 to 1.13)	0.003
	Statin	No	4091 / 385410 (1.1 %)	19.00	1.17 (1.13 to 1.20)	
	Obesity	Yes	2490 / 111738 (2.2 %)	19.00	1.15 (1.11 to 1.18)	0.017
	Obesity	No	4598 / 347044 (1.3 %)	19.80	1.20 (1.17 to 1.23)	
	Hyperlipidemia	Yes	4348 / 113897 (3.8 %)	24.80	1.13 (1.10 to 1.15)	0.066
	Hyperlipidemia	No	2796 / 346602 (0.8 %)	18.40	1.08 (1.04 to 1.12)	
	Hypertension	Yes	4035 / 134991 (3 %)	20.50	1.17 (1.14 to 1.20)	0.476
	Hypertenson	No	3109 / 325563 (1 %)	19.30	1.15 (1.12 to 1.19)	
	Diabetes	Yes	1447 / 25307 (5.7 %)	16.86	1.14 (1.09 to 1.19)	0.076
	Diabetes	No	5697 / 435247 (1.3 %)	19.80	1.19 (1.16 to 1.21)	
	Coronary Artery Disease	Yes	3704 / 55101 (6.7 %)	25.00	1.09 (1.07 to 1.12)	0.386
	Coronary Artery Disease	No	3440 / 405398 (0.8 %)	19.10	1.12 (1.08 to 1.15)	
	Chronic Kidney Disease	Yes	1722 / 22903 (7.5 %)	22.20	1.14 (1.10 to 1.18)	0.13
	Chronic Kidney Disease	No	5422 / 437596 (1.2 %)	19.50	1.18 (1.15 to 1.20)	
Carotid Stenosis	Current Smoker	Yes	622 / 48284 (1.3 %)	19.50	1.18 (1.10 to 1.26)	0.775
	Current Smoker	No	2826 / 410027 (0.7 %)	19.60	1.16 (1.13 to 1.20)	
	Statin	Yes	1329 / 75144 (1.8 %)	24.00	1.10 (1.06 to 1.15)	0.198
	Statin	No	2148 / 385410 (0.6 %)	19.00	1.16 (1.11 to 1.20)	
	Obesity	Yes	1045 / 111738 (0.9 %)	19.00	1.16 (1.10 to 1.22)	0.763
	Obesity	No	2417 / 347044 (0.7 %)	19.80	1.17 (1.13 to 1.21)	
	Hyperlipidemia	Yes	2121 / 113897 (1.9 %)	24.80	1.11 (1.07 to 1.14)	0.715
	Hyperlipidemia	No	1356 / 346602 (0.4 %)	18.40	1.10 (1.04 to 1.16)	
	Hypertension	Yes	1894 / 134991 (1.4 %)	20.50	1.15 (1.11 to 1.19)	0.953
	Hypertenson	No	1583 / 325563 (0.5 %)	19.30	1.16 (1.11 to 1.21)	
	Diabetes	Yes	498 / 25307 (2 %)	16.86	1.12 (1.04 to 1.20)	0.398
	Diabetes	No	2979 / 435247 (0.7 %)	19.80	1.17 (1.14 to 1.21)	
	Coronary Artery Disease	Yes	1432 / 55101 (2.6 %)	25.00	1.11 (1.06 to 1.15)	0.847
	Coronary Artery Disease	No	2045 / 405398 (0.5 %)	19.10	1.12 (1.08 to 1.17)	
	Chronic Kidney Disease	Yes	621 / 22903 (2.7 %)	22.20	1.15 (1.08 to 1.22)	0.83
	Chronic Kidney Disease	No	2856 / 437596 (0.7 %)	19.50	1.16 (1.13 to 1.20)	

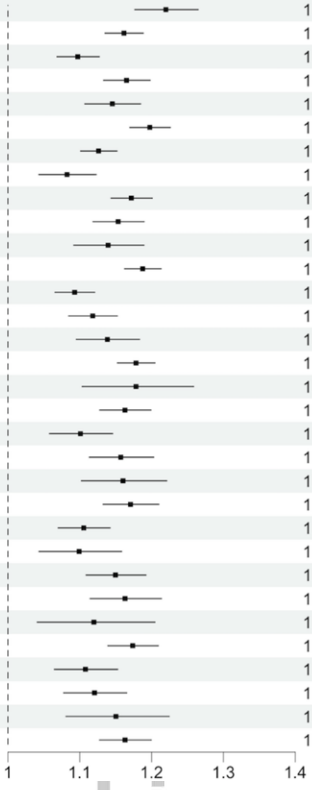

Figure 6. Risk of incident peripheral artery disease and carotid artery stenosis events per 75 nmol/L increase in lipoprotein(a) by clinical subgroups.

Hazard ratios with corresponding 95% CI were reported on the basis of Cox proportional hazards regression models with covariates of enrollment age, sex, and ancestry. Subgroup analyses were performed by splitting cohorts on the basis of presence or absence of clinical grouping. All $P<0.0001$. An interaction P value was calculated to identify significant interactions between clinical subgroups and lipoprotein(a) concentrations influencing incident atherosclerotic disease risk. HR indicates hazard ratio; Lp(a), lipoprotein(a); and PAD, peripheral artery disease.

are at high risk of progression to major atherosclerotic complications. Genetic studies have linked Lp(a) to atherosclerotic vascular complications of both progressive MALEs and incident stroke. The prospective Copenhagen General Population Study also investigated lower-extremity amputation and found an HR of 1.69 (95% CI, 1.11–2.56) for lower-extremity amputation per 50 mg/dL (105 nmol/L) genetically elevated Lp(a).[5] Within the UKB, our group found that 1 SD in genetically lowered Lp(a) concentration was associated with a 13% lower risk of stroke (OR, 0.87 [95% CI, 0.79–0.96]).[17] Aside from genetic studies, there is growing evidence that clinical measurements of Lp(a) in smaller populations are associated with MALEs and stroke.[12] However, most of the current literature focuses on the link between poor procedural outcomes and increased Lp(a) concentrations, including femoral endarterectomy,[35] peripheral revascularization,[11] and carotid endarterectomy.[36] In our study, the risk estimated for PAD progression to MALEs (HR, 1.60 [95% CI, 1.17–2.20]) or stroke (HR, 1.38 [95% CI, 0.80–2.37]) among those with prevalent PAD or ICA, respectively, may exceed that of secondary cardiovascular events in those with previous myocardial infarction or stroke (HR, 1.50 [95% CI, 1.44–1.56]).[31]

Screening for Incident Disease and Prevention of Progressive Complications

Lp(a) has the potential to become a screening tool for atherosclerotic disease across vascular beds. Current detection of atherosclerotic vascular disease outside of the coronary arteries relies mainly on symptoms to prompt testing for diagnosis, and there is generally a lack of consensus on screening recommendations from major health organizations.[37] PAD is screened and diagnosed through ankle-brachial indices, whereas carotid stenosis is similarly screened and diagnosed using carotid duplex ultrasound. Currently, no serum biomarker is clinically used to predict incidence of either condition.[38,39] There is evidence that advanced atheroma regions contain high levels of Lp(a), which potentially contribute to carotid plaque instability and subsequent stroke.[40] Lp(a) may have potential use as a biomarker for vascular atherosclerosis; however, further

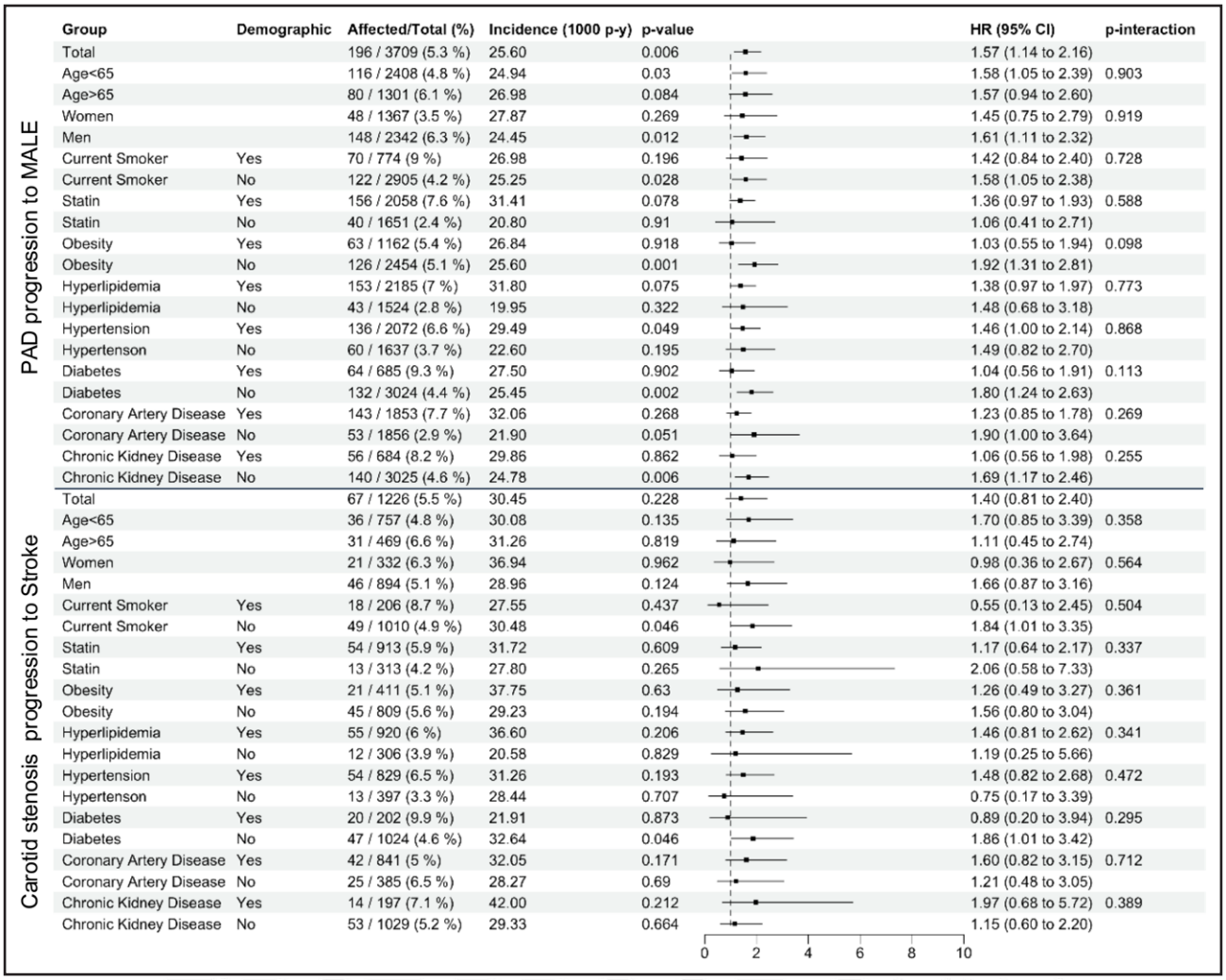

Figure 7. Risk of extracoronary disease progression to major complication stratified by lipoprotein(a) concentrations >150 nmol/L by clinical subgroups.

Hazard ratios with corresponding 95% CI were reported on the basis of Cox proportional hazards regression models with covariates of enrollment age, sex, and ancestry. Subgroup analyses were performed by splitting cohorts on the basis of presence or absence of clinical grouping. An interaction *P* value was calculated to identify significant interactions between clinical subgroups and lipoprotein(a) concentrations influencing incident atherosclerotic disease risk. HR indicates hazard ratio; and MALE, major adverse limb event.

studies are needed before readily available clinical assays can be used to inform treatment decisions.[41] A new policy by the National Lipid Association recommends measurement of Lp(a) concentrations once in an adult's lifetime,[42] and these available concentrations can potentially guide clinicians in detecting atherosclerotic vascular disease across multiple vascular beds by prompting potential screening tests in patients with significantly elevated Lp(a).

Participants with established atherosclerotic vascular disease and elevated Lp(a) concentrations may represent the ideal group to benefit from targeted preventive interventions. Both PAD and carotid stenosis can be indolent diseases with very morbid consequences of disease progression. The progression of PAD to MALEs confers an increased risk of mortality, with up to 50% of patients dying within 1 year of amputation related to PAD.[43] A large body of evidence has been generated surrounding procedural treatment of PAD,[37,44,45] but the limited research on prevention is focused on traditional risk factors of smoking prevention, lipid-lowering therapies, and increased exercise to decrease inflammation and thrombosis.[46] Early detection of PAD would enable timely initiation of a supervised walking program, the evidence-based first-line treatment recommendation for managing this condition in the United States and elsewhere.[45,46] In a similar fashion, the progression of carotid stenosis to ischemic stroke has an evidence-based approach in both the United States and United Kingdom for prevention through surgical revascularization.[28,47] However, clinicians cannot predict which patients will progress from asymptomatic carotid stenosis to stroke, making it difficult to accurately identify the patient populations

who would benefit most from preventative surgical intervention.[48,49] There is an opportunity to both detect and treat patients at high risk of progression by using Lp(a)-specific therapeutics that are currently being tested in participants with CAD.[50]

Limitations

There are inherent limitations of the present study with respect to the cohort, Lp(a) measurement, outcome definitions, and analysis. The UKB is a volunteer-based prospective cohort that relies on diagnosis and procedure codes from existing health records, mostly without physician adjudication of outcomes or distinction between events attributable to screening versus symptom-driven assessments. Lp(a) measurement with the immunoassay is not fully isoform insensitive and can lead to errors in measurement among individuals with large Lp(a) isoforms. Our outcome definitions have inherent limitations. There were no ankle-brachial index measurements in the UKB that could be used to define PAD, and thus we relied on self-reports, diagnosis codes, and procedure codes. However, this likely prioritizes clinically relevant PAD. Although we attempted to restrict the definition of MALE to amputation resulting from atherosclerosis, other indications for amputation include diabetes, cancer, and traumatic injury not captured by our exclusion codes. However, we found no significant interactions between diabetes and PAD or between diabetes and progression to MALE in association with Lp(a). Although there was carotid ultrasound performed for a subset of UKB participants, percent stenosis was not reported and therefore could not be used to define carotid stenosis. Our outcome of ischemic stroke may not be a direct result of carotid stenosis, potentially leading to an overestimation of our HR. The wide confidence intervals for effect estimates of carotid stenosis progression to stroke suggest that we had reduced power to detect potential subgroup heterogeneity. In terms of our analysis, we may not be adjusting for all known and unknown confounders. It is possible that the second assumption of the Cox proportional hazards regression model is violated by very sick participants transferring to a different health system, but the UKB is a national prospective cohort that may still be able to capture these participants.

Conclusions

Despite current treatment strategies of atherosclerotic vascular disease focusing on lifestyle modification and lowering cholesterol, a significant residual risk of major atherosclerotic complication remains, prompting investigation of Lp(a) as a potential predictive biomarker. In this study, we investigated the association between elevated Lp(a) concentrations and incident extracoronary atherosclerotic vascular disease as well as its usefulness in identifying participants at higher risk for major atherosclerotic complications. We show that higher concentrations of Lp(a) are associated with both incident PAD and carotid stenosis after adjusting for common atherosclerotic risk factors. Among participants with PAD, high Lp(a) concentrations are also associated with progression to MALEs. These findings make a strong case to explore the effect of therapies to lower Lp(a) in participants with PAD and carotid stenosis towards the goal of slowing disease progression and reducing major complications of amputation and stroke.

ARTICLE INFORMATION

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Affiliations

Program in Medical and Population Genetics and the Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Cambridge, MA (T.R.B., E.E.B., J.L., S.U., A.F., Z.Y., S.K., B.T., S.H., P.N., A.P.P.). Division of Vascular and Endovascular Surgery (T.R.B., A.F., M.J.E.), Division of Cardiology, Noninvasive Cardiac Laboratory (S.U., S.K., P.N., A.P.P.), and Center for Genomic Medicine, Department of Medicine (S.K., P.N., A.P.P.), Massachusetts General Hospital, Boston, MA.

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Disclosures

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Supplemental Material

Supplemental Tables 1–7
Supplemental Figures 1–11
Supplemental Results

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