
















Lipoprotein(a) and cardiovascular disease: prediction, attributable risk fraction, and estimating benefits from novel interventions

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Received 7 August 2020; revised 13 August 2020; editorial decision 25 August 2020; accepted 26 August 2020; online publish-ahead-of-print 7 October 2020

Aims

To investigate the population attributable fraction due to elevated lipoprotein (a) (Lp(a)) and the utility of measuring Lp(a) in cardiovascular disease (CVD) risk prediction.

Methods and results

In 413 734 participants from UK Biobank, associations of serum Lp(a) with composite fatal/non-fatal CVD ($n = 10\,066$ events), fatal CVD ($n = 3247$), coronary heart disease (CHD; $n = 18\,292$), peripheral vascular disease (PVD; $n = 2716$), and aortic stenosis ($n = 901$) were compared using Cox models. Median Lp(a) was 19.7 nmol/L (interquartile interval 7.6–75.3 nmol/L). About 20.8% had Lp(a) values >100 nmol/L; 9.2% had values >175 nmol/L. After adjustment for classical risk factors, 1 SD increment in log Lp(a) was associated with a hazard ratio for fatal/non-fatal CVD of 1.12 [95% confidence interval (CI) 1.10–1.15]. Similar associations were observed with fatal CVD, CHD, PVD, and aortic stenosis. Adding Lp(a) to a prediction model containing traditional CVD risk factors in a primary prevention group improved the C-index by +0.0017 (95% CI 0.0008–0.0026). In the whole cohort, Lp(a) above 100 nmol/L was associated with a population attributable fraction (PAF) of 5.8% (95% CI 4.9–6.7%), and for Lp(a) above 175 nmol/L the PAF was 3.0% (2.4–3.6%). Assuming causality and an achieved Lp(a) reduction of 80%, an ongoing trial to lower Lp(a) in patients with CVD and Lp(a) above 175 nmol/L may reduce CVD risk by 20.0% and CHD by 24.4%. Similar benefits were also modelled in the whole cohort, regardless of baseline CVD.

Conclusion

Population screening for elevated Lp(a) may help to predict CVD and target Lp(a) lowering drugs, if such drugs prove efficacious, to those with markedly elevated levels.

Keywords

Lipoprotein(a) • Cardiovascular disease • Epidemiology • Risk prediction

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Introduction

Lipoprotein (a) (Lp(a)) is a low-density lipoprotein (LDL) particle made by the liver, comprised of both an apolipoprotein(a) and an apolipoprotein B protein. Its structure is highly heterogeneous, but levels of Lp(a) are 80–90% genetically determined and relatively stable across the life course.

Epidemiological evidence shows strong associations of circulating Lp(a) with atherogenesis and consequent risk of cardiovascular disease (CVD). For instance, in a recent meta-analysis of statin trial data, those with Lp(a) concentrations above 50 mg/dL were at 35% higher risk of incident CVD events [95% confidence interval (CI) 11–66%] compared to those with Lp(a) <15 mg/dL (~30 nmol/L) after adjusting for confounders.¹ Similar data have been reported in population studies.^{2,3} Furthermore, genetic data and basic science support the notion that the association is causal.^{4,5} This has led to interest both in the potential for Lp(a) to serve as a biomarker to enhance CVD risk prediction,⁶ and as a therapeutic target. Indeed, Lp(a) lowering drugs may be a viable therapeutic option, with at least one drug moving to Phase 3 in the Lp(a)HORIZON trial.⁷ Further, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which lower Lp(a) concentrations by around 27%, may be particularly beneficial in reducing risk in patients with previous CVD and substantially raised Lp(a).^{8,9}

Currently, most guidelines and consensus statements do not advocate widespread screening for elevated Lp(a) and suggest focused measurement considering high Lp(a) as a risk enhancer.^{10–12} However, the recently released ESC/EAS guidelines suggested a 'one-off measurement of Lp(a) may help to identify people with very high inherited Lp(a) levels who may have a substantial lifetime risk of atherosclerotic cardiovascular disease (ASCVD).¹³ Although Lp(a) is sometimes measured in patients with suspected familial hypercholesterolaemia,¹⁴ it is currently not routinely measured in general practice.¹¹ In addition, there is conflicting advice on what constitutes a 'high' Lp(a) level. Several guidelines and consensus statements advocate the 50 mg/dL (~125 nmol/L) cut-off^{10,11,15} as this corresponds to the 80th percentile in one cohort study,¹⁶ but the 2016 Canadian Cardiovascular Society Guidelines use 30 mg/dL on the basis of elevated CVD risk (~75 nmol/L).¹⁷ The Lp(a)HORIZON trial uses 70 mg/dL (~175 nmol/L) as an inclusion criterion.⁷ The lack of data from a single large cohort with consistent phenotyping is a significant limitation in interpreting the existing literature, impacting our understanding of the prevalence of high Lp(a), and its consequences for CVD risk.

UK Biobank is a large prospective population-based cohort study carried out in the UK, with information on baseline biochemistry measurements including routine lipids and Lp(a) measured in a central laboratory. We aimed to use this resource to explore the shape of the association of Lp(a) with a range of distinct CVD outcomes to investigate the population attributable risk fraction for CVD that might be explained by elevated Lp(a), and to predict what might be the effect of novel Lp(a)-lowering therapies based on these data and recent relevant trials.

Methods

UK Biobank was conducted across 22 assessment centres across the UK between March 2006 and December 2010 and recruited 502 624

participants aged 37–73. A repeat visit was conducted between 2009 and 2013 for 20 345 individuals. Baseline biological measurements were recorded and touch-screen questionnaires were administered according to a standardized protocol.^{18,19} UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

For the present analysis, ethnicity was coded as White, South Asian, Black, or mixed/other. Smoking status was categorized into never or former/current smoking. Systolic and diastolic blood pressure were measured at the baseline visit, preferentially using an automated measurement, but using manual measurement where this was not available. Blood collection sampling procedures for the study have been previously described and validated.²⁰ The definition of baseline diabetes included self-reported type 1 or type 2 diabetes, those with a primary or secondary hospital diagnoses relating to diabetes at baseline (ICD-10 codes E10–E14.9), and those who reported using diabetes medications. Statin (categorized to include other cholesterol lowering medications) and blood pressure medication use were also recorded from self-report. Baseline CVD was defined as self-reported myocardial infarction, stroke, or transient ischaemic attack.

Biochemistry measures were performed at a dedicated central laboratory on around 480 000 baseline samples between 2014 and 2017. During the project, the UK Biobank laboratories were successfully externally audited against the ISO 17025:2005 standard. Assays included serum total cholesterol and high-density lipoprotein (HDL) cholesterol (Beckman Coulter, UK on an AU5800 platform) and Lp(a) (Randox Bioscience, UK on an AU5800 platform) and all were run using internal controls and an external quality assurance scheme. Data were adjusted by UK Biobank centrally before release to adjust for pre-analytical variables. For Lp(a), low-, medium-, and high-quality control materials ran with coefficients of variation of ≤6.1%. Further details of these measurements can be found in the UK Biobank online showcase and protocol (<http://www.ukbiobank.ac.uk>, accessed 9 September 2020). The Randox Lp(a) assay is calibrated in nmol/L, reflecting the concentration of particles rather than the mass of particles and is traceable to the WHO/IFCC reference material. The minimum reported concentration of Lp(a) was 3.8 nmol/L and the maximum was 189 nmol/L; participants who had levels below the lower level ($n = 48\ 360$) were coded as having an Lp(a) concentration of 2.88 nmol/L, and above the upper level ($n = 34\ 195$) coded as 250 nmol/L for continuous analyses.

Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. Only primary causes of death listed on the death certificate were included in this analysis. Non-fatal outcomes were ascertained by linkage of participant study data to Hospital Episode Statistics from the National Health Service. The primary outcome of interest was ASCVD; this and secondary outcomes are defined in [Supplementary material online](#).

End of follow-up for each participant was recorded as the date of death or the date of end of follow-up for the assessment centre attended, whichever came first. The period at risk of each participant began on the date of their assessment.

Statistical analyses

The association of continuous log-transformed Lp(a) with other lipid variables was tested using Pearson correlation coefficients. Lp(a) was analysed using a number of different models, reflecting existing uncertainty regarding cut-offs for 'abnormal' levels. Lp(a) was categorized into

multiple distinct categorical variables, with upper cut-offs at 20 nmol/L and 100 nmol/L or 125 nmol/L or 150 nmol/L or 175 nmol/L. Sex and ethnicity-specific centiles (50th, 75th, 80th, 90th, and 95th centiles) for Lp(a) were also developed, using binomial exact CIs to yield 95% CIs for the centiles. The sex and ethnicity-specific 80th centile were chosen to create a binary 'high' category for Lp(a). Log-transformed Lp(a) was also analysed as a continuous variable. Classical risk factors were expressed as mean (standard deviation) if symmetrically distributed, median (interquartile range) if skewed, and number (%) if categorical. The distribution of classical risk factors by categories of outcome or exposure of interest was assessed using unpaired two-tail *t*-tests, a Wilcoxon rank-sum, or a χ^2 test, respectively.

Prospectively, the cohort was analysed as a whole cohort and was also stratified as a primary prevention cohort (participants without baseline CVD and not taking a statin) and as a high-risk cohort (participants with baseline CVD and/or taking a statin). We assessed agreement between baseline and repeated Lp(a) measurements in those with available data using Lin's Correlation coefficient and the mean difference in measurement, along with 95% limits of agreement, and using the coefficient of variation across the two visits.

Rates of the primary composite CVD outcome were investigated in unadjusted models, splitting the cohort by the specified Lp(a) categories. Associations of continuous and categorical Lp(a) with outcomes of interest were investigated using Cox-proportional hazard models in the whole cohort adjusting for classical risk factors. The ability of Lp(a) to improve prediction of CVD was tested by assessing improvement over a base model containing all elements from the Pooled Cohort Equation (Supplementary material online).

Population attributable fractions in the exposed, with 95% CIs, were estimated using two adjusted Cox models and the `punafcc` post-estimate command in STATA. The model added Lp(a) at a number of binary cut-offs and was designed to estimate the causal effect of 'elevated' Lp(a) in the whole cohort for each outcome. The second model, intended to represent anticipated benefit of therapeutic intervention in those with elevated Lp(a), added Lp(a) as a four-category variable with concentration >175 nmol/L (representing the Lp(a) HORIZON trial recruitment criterion⁷), 40–175 nmol/L, 30–40 nmol/L (the estimated attained Lp(a) assuming an 80% reduction on-treatment²¹), and <30 nmol/L. This model was then used to test the estimated proportional reduction in CVD events among those with Lp(a) >175 nmol/L when concentration was lowered to the 30–40 nmol/L range. The model was run specifically in those with baseline CVD and in the whole cohort.

All analyses were performed using STATA 15.1 (StataCorp LP) and R (version 3.5.1).

Results

Cross-sectional associations

Of 502 624 people included in the study, complete data on covariates, including Lp(a) were available in 413 734 participants. Median Lp(a) in the cohort was 19.7 nmol/L (interquartile interval 7.6–75.3 nmol/L). In participants without baseline CVD and not taking a statin ($n = 340\,339$) median Lp(a) was 19.1 nmol/L (interquartile interval 7.6–70.5 nmol/L). The 80th centile in the whole cohort was 104.5 nmol/L (95% CI 103.8–105.3). In the whole cohort, 85 932 (20.8%) had Lp(a) above 100 nmol/L, 68 603 (16.6%) above 125 nmol/L, 52 159 (12.6%) above 150 nmol/L, and 38 111 (9.2%) above 175 nmol/L. Sex and ethnicity-specific cut-offs show that

women and participants with black ethnicity had higher Lp(a) concentrations (Figure 1).

Lipoprotein (a) had weak positive associations with total cholesterol ($r = 0.11$), HDL cholesterol ($r = 0.04$), and LDL cholesterol ($r = 0.12$) (P for all < 0.0001). These associations were only nominally stronger in the population who did not report taking statins ($r = 0.14$, 0.05, 0.16, respectively). Participants with elevated Lp(a) were generally slightly older, had slightly higher systolic blood pressure and total cholesterol and were more likely to have baseline CVD (Table 1).

Repeated measures of lipoprotein (a)

Fourteen thousand, two hundred, and forty-eight participants from the baseline cohort had repeated measures of Lp(a) available. At the follow-up visit, Lp(a) was 2.9 nmol/L higher, the 95% limits of agreement for Lp(a) between the two visits were -37.5, 43.3 nmol/L, and the median coefficient of variation was 12.6% (interquartile range 3.8–24.7%). The concordance coefficient was 0.958 (95% CI 0.957–0.959) (Supplementary material online, Figure S1).

Univariable association of lipoprotein (a) with outcomes

Median follow-up time for the composite CVD outcome was 8.9 years (interquartile range 8.2–9.5) in the whole cohort. The composite CVD outcome occurred in 10 066 participants (2.4%), and fatal CVD occurred in 3247 participants (0.8%) in the whole cohort. The composite CVD outcome occurred in 6125 participants (1.8%), and fatal CVD occurred in 1627 participants (0.5%) in the subgroup without baseline CVD and not taking a statin.

Baseline Lp(a) was higher among the participants who went on to experience the composite CVD outcome and the fatal CVD outcome (Supplementary material online, Table S1). Lp(a) was also higher among those who went on to experience coronary heart disease (CHD), peripheral vascular disease (PVD), or aortic valve stenosis but was not higher among those who went on to experience ischaemic stroke, heart failure (Supplementary material online, Table S1).

Multivariable association of lipoprotein (a) with outcomes

In the whole cohort, there was an independent association of 1 SD increase in log Lp(a) with the primary composite CVD outcome [hazard ratio (HR) 1.12 (95% CI 1.10–1.15)] after adjusting for classical risk factors statin use and baseline CVD. In the whole cohort, an 18 nmol/L (~10 mg/dL) increase in Lp(a) was associated with an increased risk of CVD and CHD: HR 1.029 (95% CI 1.024–1.033) and HR 1.035 (95% CI 1.031–1.038), respectively.

For the primary outcome of CVD there was no interaction of Lp(a) with age (above or below the median of 57 years) ($P = 0.16$), sex ($P = 0.27$), ethnicity ($P > 0.23$ for each ethnic group compared to white), baseline CVD ($P = 0.24$), baseline diabetes ($P = 0.17$), statin use ($P = 0.61$), total cholesterol (above or below 8.0 mmol/L cut-off) ($P = 0.38$), or LDL cholesterol (above or below 2.5 mmol/L cut-off) ($P = 0.72$). However, there was a borderline interaction of log Lp(a) with LDL cholesterol using a cut-off of 3.5 mmol/L (P for interaction 0.055). In this model each standard deviation increase in log Lp(a) had an HR of 1.11 (95% CI 1.08–1.13) in the group with LDL cholesterol

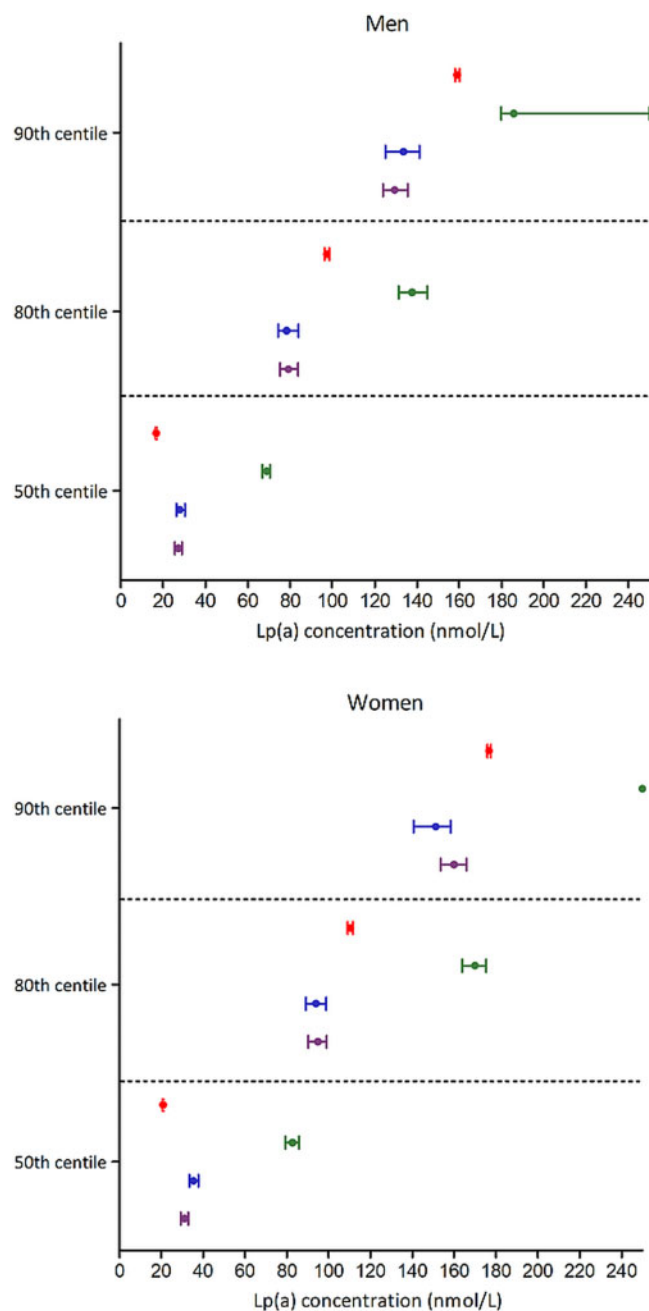


Figure 1 Centiles of lipoprotein (a), along with 95% confidence intervals, by sex and ethnicity in the whole cohort. Red denotes white ethnicity, green denotes black ethnicity, blue denotes South Asian, and purple denotes other or mixed ethnicity. Lp(a), lipoprotein (a); nmol/L, nanomoles per litre.

<3.5 mmol/L and an HR of 1.15 (95% CI 1.12–1.18) in the group with LDL cholesterol \geq 3.5 mmol/L.

Data were split into the primary prevention cohort and the high-risk cohort to further explore associations with outcomes. Among the primary prevention group not taking a statin, after adjusting for classical risk factors, the shape of the association of Lp(a) with composite CVD, fatal CVD, CHD, and aortic valve stenosis was positive and broadly linear (Figure 2). There was also a positive association

with PVD, but no evidence of an association with stroke, or heart failure (Figure 2).

Using continuous and multiple different categorical models of Lp(a) there was a positive association with composite primary CVD outcome (Table 2). Lp(a) as a continuous and categorical variable was also associated with fatal CVD, CHD, PVD, and aortic valve stenosis as well as demonstrating a borderline association with ischaemic stroke after adjusting for classical risk factors, in both the

Table 1 Association of categories of lipoprotein (a) with classical risk factors for cardiovascular disease at baseline (*n* = 413 724)

	Lp(a) <20 nmol/L <i>n</i> = 207 908	Lp(a) 20–99.9 nmol/L <i>n</i> = 119 894	Lp(a) ≥100 nmol/L <i>n</i> = 85 932	P-value for trend
Age (years)	56.3 ± 8.2	56.7 ± 8.1	56.9 ± 8.0	<0.001
Male sex (%)	101 214 (48.7%)	52 542 (43.8%)	37 403 (43.5%)	<0.001
Ethnicity (%)				
White	201 070 (96.7%)	109 952 (91.7%)	80 955 (94.2%)	<0.001
Black	717 (0.3%)	3327 (2.8%)	2404 (2.8%)	
South Asian	2427 (1.2%)	2931 (2.4%)	1064 (1.2%)	
Other	3694 (1.8%)	3684 (3.1%)	1509 (1.8%)	
Systolic blood pressure (mmHg)	137.9 ± 18.6	137.7 ± 18.7	138.4 ± 18.7	<0.001
Diastolic blood pressure (mmHg)	82.3 ± 10.2	82.2 ± 10.1	82.4 ± 10.1	0.008
Ever smoker (%)	22 089 (10.6%)	12 761 (10.6%)	8995 (10.5%)	0.38
Total cholesterol (mmol/L)	5.59 (1.12)	5.75 (1.15)	5.86 (1.18)	<0.001
HDL cholesterol (mmol/L)	1.44 (0.39)	1.45 (0.38)	1.48 (0.38)	<0.001
Baseline diabetes (%)	11 463 (5.5%)	5764 (4.8%)	4453 (5.2%)	<0.001
Baseline CVD (%)	11 133 (5.4%)	6900 (5.8%)	6614 (7.7%)	<0.001
Statin use (%)	31 230 (15.0%)	18 620 (15.5%)	17 376 (20.2%)	<0.001
BP medication (%)	42 159 (20.3%)	24 578 (20.5%)	19 571 (22.8%)	<0.001

BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoproteins; mmHg, millimetres of mercury; mmol/L, millimoles per litre; nmol/L, nanomoles per litre.

primary prevention cohort and the high-risk cohort (Supplementary material online, Table S2). The association with heart failure was weak. In terms of strength of the point estimates, the association of Lp(a) with aortic valve stenosis was strong and consistent; those with Lp(a) ≥175 nmol/L were at ~85% increased risk of both outcomes in both the primary prevention cohort and the high-risk cohort (Supplementary material online, Table S2).

Lipoprotein (a) and prediction of cardiovascular disease

Prediction of incident CVD was specifically explored in the primary prevention cohort. In a model of CVD prediction based on pooled cohort equation risk factors, classical risk factors yielded a C-index of 0.7459 (95% CI 0.7402–0.7517). Addition of Lp(a) as a continuous variable to these risk factors increased the C-index by +0.0017 (95% CI 0.0008–0.0026) (Table 3). On addition of Lp(a) to the model, the improvement in the categorical net reclassification index was +0.0112% (95% CI +0.0039 to +0.0184) and most of the improvement was due to upward classification of risk among cases (Table 3). Similar improvements in prediction were obtained when Lp(a) was added as a categorical variable, with no clear advantage of one model over another (Table 3). There was a more sizeable improvement in reclassification among the intermediate-risk group at 5–7.49% 10-year risk (*n* = 16 292); on addition of continuous Lp(a), the overall net reclassification index in this intermediate-risk group was +0.0721 (95% CI +0.0323, +0.1107).

Population attributable fraction of lipoprotein (a)

In the whole cohort, an Lp(a) above 100 nmol/L accounted for 5.8% (95% CI 4.9–6.7%) of the composite CVD outcome (Figure 3). Moving the threshold for 'high' Lp(a) to higher cut-offs resulted in somewhat lower, but still substantial, attributable fractions due to reduced prevalence of the higher cut-offs (Figure 3). The overall PAF lowered to 3.0% (95% CI 2.4–3.6%) for a cut-off of Lp(a) above 175 nmol/L. The proportion of CVD attributable due to any Lp(a) >3.8 nmol/L in the whole cohort was 8.8% (95% CI 7.6–10.0%); this is the reduction in risk expected if the whole cohort had Lp(a) of 3.8 nmol/L (Supplementary material online, Figure S2).

Expected benefit of lipoprotein (a) reduction

We then specifically modelled the scenario in the ongoing Phase 3 trial of an Lp(a) lowering agent. First, among all participants regardless of baseline CVD status (*n* = 413 734), the CVD event rate was 2.80 (95% CI 2.74–2.85) per 1000 person-years. Among those with an Lp(a) above 175 nmol/L (*n* = 38 111), reducing Lp(a) by ~80% so that participants have Lp(a) 30–40 nmol/L range, results in an estimated risk reduction of 23.1% (95% CI 14.9–30.5%). For prevention of CHD, the same Lp(a) reduction was estimated to result in a 28.3% decrease in risk (95% CI 22.8–33.4%). In a sensitivity analysis removing individuals with Lp(a) above the reported measurable range

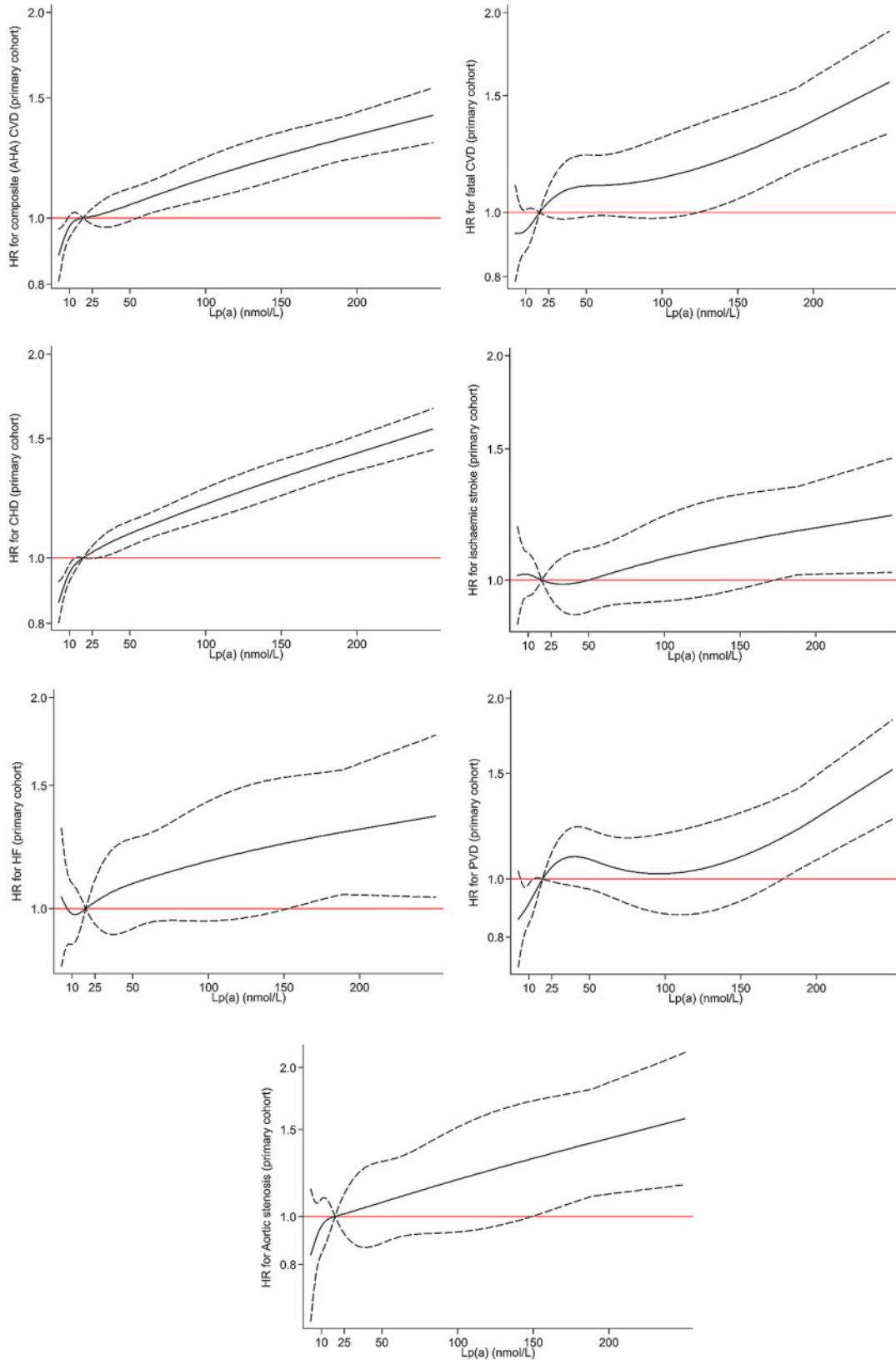


Figure 2 Association of Lp(a) with outcomes after adjusting for classical risk factors among participants without baseline cardiovascular disease and not taking a statin. Referent (hazard ratio = 1.0) at 19 nmol/L. AHA, American Heart Association; HF, heart failure; HR, hazard ratio; Lp(a), lipoprotein (a); nmol/L: nanomoles per litre; PVD, peripheral vascular disease.

Table 2 Association of Lp(a) (hazard ratio and 95% CI) as a continuous variable (per 1 SD increase in log Lp(a)) and as a categorical variable with the primary composite CVD outcome after adjusting for classical risk factors^a

Lp(a) conc.	Primary prevention cohort		High-risk cohort ^b	
	N (n events)	HR (95% CI)	N (n events)	HR (95% CI)
Per 1 SD	340 339 (6125)	1.13 (1.10–1.16)	73 395 (3941)	1.11 (1.08–1.14)
<20 nmol/L	173 639 (2857)	Ref	34 269 (1689)	Ref
20–99.9 nmol/L	99 499 (1802)	1.11 (1.05–1.18)	20 395 (1086)	1.11 (1.03–1.20)
≥100 nmol/L	67 201 (1466)	1.37 (1.28–1.46)	18 731 (1166)	1.30 (1.21–1.41)
<20 nmol/L	173 639 (2857)	Ref	34 269 (1689)	Ref
20–124.9 nmol/L	114 093 (2086)	1.13 (1.06–1.19)	23 130 (1241)	1.11 (1.03–1.20)
≥125 nmol/L	52 607 (1182)	1.40 (1.31–1.50)	15 996 (1011)	1.34 (1.24–1.45)
<20 nmol/L	173 639 (2857)	Ref	34 269 (1689)	Ref
20–149.9 nmol/L	127 636 (2371)	1.15 (1.09–1.21)	26 031 (1428)	1.13 (1.06–1.22)
≥150 nmol/L	39 064 (897)	1.43 (1.33–1.55)	13 095 (824)	1.35 (1.24–1.47)
<20 nmol/L	173 639 (2857)	Ref	34 269 (1689)	Ref
20–174.9 nmol/L	138 836 (2626)	1.17 (1.11–1.23)	28 879 (1608)	1.15 (1.08–1.23)
≥175 nmol/L	27 864 (642)	1.44 (1.32–1.58)	10 247 (644)	1.36 (1.24–1.49)
Below the sex and ethnicity-specific 80th centile	275 892 (4672)	Ref	54 886 (2768)	Ref
Above the sex and ethnicity-specific 80th centile	64 447 (1453)	1.31 (1.24–1.39)	18 509 (1173)	1.26 (1.18–1.35)

CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; Lp(a), lipoprotein (a); nmol/L, nanomoles per litre; SD, standard deviation.

^aAge, sex, total cholesterol, HDL cholesterol, ethnicity, smoking, systolic blood pressure, blood pressure medications, and baseline diabetes.

^bParticipants with baseline CVD or taking a statin; additionally, adjusted for baseline CVD and statin use.

(>189 nmol/L), reduction of Lp(a) in the range of 175–189 nmol/L to 30–40 nmol/L results in an estimated CVD risk reduction of 16.3% (95% CI 2.5–28.2%).

Specifically investigating participants with baseline CVD ($n = 24\,647$) the CVD event rate was 11.7 (95% CI 11.3–12.2) per 1000 person years. Among those with an Lp(a) above 175 nmol/L ($n = 3568$), similar Lp(a) reductions are estimated to reduce CVD risk by 20.0% (95% CI 2.1–34.6%) and CHD risk by 24.4% (95% CI 13.5–33.9%).

Discussion

In this large cohort of over 400 000 individuals, a high proportion of the UK Biobank cohort had what might conventionally be called high Lp(a) levels; 20.8% above 100 nmol/L and 9.2% above 175 nmol/L. Intra-individual concordance in Lp(a) levels across visits years apart was high. We noted a broadly linear relationship of Lp(a) with composite fatal or nonfatal CVD, fatal CVD, and fatal or non-fatal CHD, PVD, and aortic stenosis with associations largely unaffected by other risk factors. Therefore, population attributable fractions for Lp(a) were sizable. Further, we estimate that targeting Lp(a) lowering therapy in ongoing trials to those with Lp(a) concentrations above 175 nmol/L would reduce CVD incidence by around 20% (regardless of baseline CVD status). This extends estimates²² from smaller studies to a current ongoing trial. Collectively, our results seem to justify the recent ESC/EAS guidelines¹³ suggesting consideration for at least a one-time Lp(a) measurement in all people being screened for CVD risk.

Genetic data suggest large reductions in Lp(a) are required to show clinical benefit, although there is some disagreement as to the extent of the reduction required.^{4,5} The study of Burgess *et al.*⁴ estimated that a 10 mg/dL decrease in Lp(a) (~18 nmol/L) would cause a 5.8% decrease in odds of CHD, whereas Lamina and Kronenberg⁵ estimated it would be an 8.8% reduction in odds. Our estimate that an 18 nmol/L increase in Lp(a) would be associated with a 3.5% increased CHD risk is therefore somewhat more conservative than the genetic data. Mendelian randomization studies may offer better causal insights than observational studies for many traits, although pleiotropy and lifelong exposure to elevated levels of Lp(a) may also have an impact on estimates.²³ Our more conservative estimate, if correct, would imply a requirement for greater Lp(a) reduction to achieve reduced CVD risk. Despite this, recent Phase 2 trial data show that the drug AKCEA-APO(a)-LRx (also called TQJ230) reduces Lp(a) substantially, with 80–90% reductions in patients with established CVD and high Lp(a) levels, depending on dosing.^{21,24} This antisense oligonucleotide inhibits the production of apolipoprotein(a), thereby reducing Lp(a). Phase 3 outcome trials are underway⁷ and specifically target those with elevated Lp(a). Furthermore, there is also emerging evidence that proprotein convertase subtilisin/kexin type 9 inhibitors lower Lp(a) independent of LDL cholesterol reduction, and this reduction contributes to CVD event reduction⁹ and lowering of PVD risk.^{25,26} These findings provide a currently licensed drug to help lower Lp(a) by a modest amount.

Our data suggest that a drug that prevents CVD through Lp(a) lowering may also have benefits for individual components of the CVD composite, and for PVD outcomes, as well as aortic stenosis.

Table 3 Improvement in prediction of cardiovascular disease among participants in the primary prevention cohort measured by the C-statistic and categorical net reclassification index (across 10-year risk boundaries of <5%, 5–7.49%, ≥7.5%)

Model	C-index (95% CI)	Change in C-index (95% CI)	Overall NRI (95% CI)	Case NRI (95% CI)	Control NRI (95% CI)
Classical risk factors ^a	0.7459 (0.7402–0.7517)				
Classical risk factors + continuous log Lp(a)		+0.0017 (0.0008–0.0026)	+0.0112 (+0.0039, +0.0184)	0.0118 (+0.0046, +0.0190)	-0.0007 (-0.0012, -0.0002)
Classical risk factors + categorical Lp(a) at <20, 20–99.9, and >100 nmol/L		+0.0018 (0.0009–0.0026)	+0.0108 (+0.0040, +0.0175)	0.0118 (+0.0050, +0.0184)	-0.0009 (-0.0014, -0.0004)
Classical risk factors + categorical Lp(a) at <20, 20–149.9, and >150 nmol/L		+0.0016 (0.0007–0.0024)	+0.0135 (+0.0063, +0.0203)	0.0144 (+0.0063, +0.0203)	-0.0009 (-0.0014, -0.0004)
Classical risk factors + binary Lp(a) at sex and ethnicity-specific 80th percentile		+0.0015 (0.0007–0.0023)	+0.0111 (+0.0045, +0.0180)	0.0115 (+0.0050, +0.0184)	-0.0004 (-0.0009, -0.0001)

CVD, cardiovascular disease; HDL, high-density lipoprotein; Lp(a), lipoprotein (a); nmol/L, nanomoles per litre; NRI, net reclassification index.

^aAge, sex, total cholesterol, HDL cholesterol, ethnicity, smoking, systolic blood pressure, blood pressure medications, and baseline diabetes.

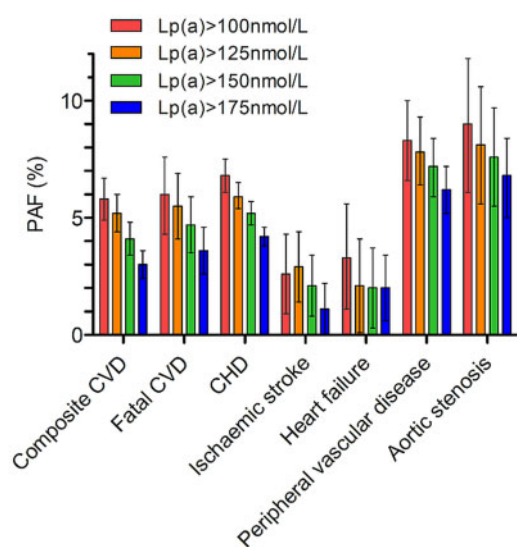


Figure 3 Population attributable fractions (with 95% confidence intervals) of lipoprotein (a) in the whole cohort, at a range of cut-offs, for each outcome of interest. ACC, American College of Cardiology; AHA, American Heart Association; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; Lp(a), lipoprotein (a); nmol/L: nanomoles per litre; PVD, peripheral vascular disease; SCORE, Systematic Coronary Risk Estimation.

Our models suggest potential benefit in both primary and secondary prevention. Although Lp(a) only adds moderate information to risk discrimination metrics and is more expensive than traditional lipid measurements,²⁷ the fact that the marker is (i) causal, (ii) largely orthogonal to other risk factors, (iii) stable across life course, (iv) has a

substantial population attributable fraction, and (v) may help guide therapy allocation, enhances arguments that measurement of Lp(a) should become more common in the evaluation of CVD risk. Notably, the reported improvement in C-statistics with Lp(a) was around four times higher than previously reported for C-reactive protein.²⁸ In particular, we show that incorporation of Lp(a) into risk scores targeted at intermediate-risk groups would lead to changes in a greater proportion of treatment decisions than measurement in the whole general population. This may be a method to tie-break treatment decisions in a targeted manner, in line with current US guidelines. There are a range of suggested cut-offs for Lp(a) in clinical practice.^{10,15,29} The data reported here are consistent with the approach of the Lp(a)HORIZON trial in identifying >175 nmol/L as a risk marker. The results of this and other trials should help inform on the most cost-effective cut-offs used in future for clinical care.

The ethnicity-specific centiles we report confirm and extend observations in other cohorts, most noticeably higher Lp(a) in black people.³⁰ We would expect a higher PAF for CVD outcomes in black ethnicities due to higher prevalence of the exposure, but low numbers of black participants restrict our ability to formally test this hypothesis in this cohort. Overall, we note no strong interaction of Lp(a) with demographics or other risk factors suggesting that Lp(a) is similarly associated with risk in different subgroups. Previous work in primary prevention cohorts from EPIC-Norfolk and the Copenhagen City Heart Study ($n = 16\,654$) has suggested that the association between elevated Lp(a) (>80th percentile) and CVD events is attenuated at LDL cholesterol levels below 2.5 mmol/L.³¹ Likewise, data from the Women's Health Study and JUPITER trials reported stronger associations of Lp(a) above 50 mg/dL with CVD risk at total cholesterol levels above 5.7 mmol/L.³ We report borderline evidence that continuous Lp(a) may have a slightly weaker risk association in people with directly measured LDL cholesterol <3.5 mmol/L, but this is not evident at a cut-off of 2.5 mmol/L, and the association with

CVD remains clinically relevant and statistically significant in both LDL cholesterol groups.

The PAFs we report for Lp(a) may usefully be put in context of estimates of PAFs for other risk factors. The ARIC study reported PAFs at examination four (among white participants) of 21% for hypertension, 13% for diabetes, 10% for hypercholesterolaemia, and 12% for smoking.³² Similarly, in the Emerging Risk Factors Collaboration, the PAF for diabetes in vascular death has been estimated at 11% (assuming a 10% diabetes prevalence).³³ In terms of CVD risk prediction, our data are also broadly in line with the Emerging Risk Factors Collaboration (ERFC), where data from 165 544 participants in 37 prospective studies showed Lp(a) improved the C-index by +0.0016 (95% CI 0.0009–0.0023),³⁴ lending strong external validity to these new reported findings. It is also in agreement with data from other large cohort studies.^{35–38} Our data extend these findings in a large cohort with substantial power, using a single methodologically strong Lp(a) measurement, where we also estimated the PAF for a range of CVD outcomes independently due to Lp(a) elevation.

The strengths of our study include the large cohort size at an age-relevant to CVD risk scoring and biochemistry assays performed in a single dedicated central laboratory. We were also able to extensively adjust our models for classical risk factors and separately analysed participants already on statins as well as those with previous CVD. We were also able to investigate at other cardiovascular outcomes. Potential limitations include the relatively low average CVD risk of participants, although risk prediction models performed broadly in line with expectations. UK Biobank is not representative of the whole UK population,³⁵ and while this is generally not a concern in investigating risk associations³⁹ it will have an impact on calculated population attributable fractions. The population attributable fractions we observe here cannot be taken as representative of the UK population as a whole. However, due to the under-representation of black people in UK Biobank, it may be that our estimates are conservative. In addition, the 80th centile we report here of 105 nmol/L corresponds broadly to previously reported 80th centiles in 3000 men and 3000 women from the Copenhagen General Population Study (50 mg/dL).¹¹ The upper reported Lp(a) concentration in UK Biobank is 189 nmol/L, limiting our ability to investigate associations higher than this concentration. Finally, UK biobank is a primarily primary prevention low-risk population, and extrapolation to secondary prevention settings and modelled therapeutic benefits (such as the Lp(a)HORIZON trial) must be interpreted with caution. However, the secondary prevention group is still sizeable and has appreciably higher CVD events rates than the cohort as a whole, and we observe no evidence of interaction of the PAF for Lp(a) lowering by baseline CVD status. Our estimates of expected therapy effects among the exposed (Lp(a) above 175 nmol/L) should be robust to differences in representativeness, since we only consider those with high Lp(a) as exposed.

In conclusion, in this, the largest single prospective study of Lp(a) levels, our findings add strong support for recent guideline recommended one-time measurement of Lp(a) in cardiovascular risk assessment to identify a large proportion with markedly elevated levels sufficient to contribute to atherothrombotic risk. Our work also

provides support to the ongoing programmes to develop efficacious Lp(a) lowering drugs.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Acknowledgements

This research was conducted using the UK Biobank resource. We thank the participants of the UK Biobank. The work was performed under UK biobank project number 9310. We thank Liz Coyle (University of Glasgow) for assistance with manuscript preparation.

Funding

This work was supported by a grant from Chest, Heart & Stroke Scotland [Res16/A165], and by the British Heart Foundation Research Excellence Award [RE/18/6/34217].

Conflict of interest: P.Welsh. reports grant income from Roche Diagnostics. P.B.M. reports speaker honoraria from AstraZeneca and Novartis. J.A.d.L. reports consulting income from Amgen for participation in steering committee, Regneron for participation on Data Safety Monitoring Board, and grant support from Roche Diagnostics, and Abbott Diagnostics. P.Willeit. reports personal fees from Novartis Pharmaceuticals. N.S. has consulted for Amgen and Sanofi. All conflicts are outside the submitted work. All other authors have no conflict of interest to declare.

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