

Elevated lipoprotein(a) increases risk of subsequent major adverse cardiovascular events (MACE) and coronary revascularisation in incident ASCVD patients: A cohort study from the UK Biobank

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ABSTRACT

Background and aims: Elevated lipoprotein(a) [Lp(a)] is a genetic driver for atherosclerotic cardiovascular disease (ASCVD). We aimed to provide novel insights into the associated risk of elevated *versus* normal Lp(a) levels on major adverse cardiovascular events (MACE) in an incident ASCVD cohort.

Methods: This was an observational cohort study of incident ASCVD patients. MACE counts and incidence rates (IRs) per 100-person-years were reported for patients with normal (<65 nmol/L) and elevated (>150 nmol/L) Lp(a) within the first year after incident ASCVD diagnosis and overall follow-up. Cox proportional hazard models quantified the risk of MACE associated with a 100 nmol/L increase in Lp(a).

Results: The study cohort included 32,537 incident ASCVD patients; 5204 with elevated and 22,257 with normal Lp(a). Of those with elevated Lp(a), 41.2% had a subsequent MACE, *versus* 35.61% with normal Lp(a). Within the first year of follow-up, the IRs of composite MACE and coronary revascularisation were significantly higher ($p < 0.001$) in patients with elevated *versus* normal Lp(a) (IR difference 6.79 and 4.66). This trend was also observed in the overall follow-up (median 4.7 years). Using time to first subsequent MACE, a 100 nmol/L increase in Lp(a) was associated with an 8.0% increased risk of composite MACE, and 18.6% increased risk of coronary revascularisation during the overall follow-up period.

Conclusions: The association of elevated Lp(a) with increased risk of subsequent MACE and coronary revascularisation highlights a population who may benefit from earlier and more targeted intervention for cardiovascular risk including Lp(a), particularly within the first year after ASCVD diagnosis. Proactive Lp(a) testing as part of routine clinical practice can help identify and better manage these higher-risk individuals.

1. Introduction

Epidemiological and genetic studies have shown that elevated levels of lipoprotein(a) [Lp(a)] are independently and causally associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) [1–6]. Guidelines and consensus statements from several international medical societies recognize elevated Lp(a) as an independent genetic

driver for cardiovascular (CV) disease [7–22].

Circulating concentrations of Lp(a) are largely genetically determined, with heritability estimated at over 90%, and remain relatively stable throughout one's lifespan with little impact from lifestyle interventions [23]. Currently, there are no approved Lp(a) lowering drug therapies nor available lipid-lowering therapies, e.g., statins or PCSK9 inhibitor therapies [2,6], that can effectively reduce Lp(a) levels. Lp(a)

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is not routinely measured in clinical practice, with only ~1% of the global ASCVD population being tested for Lp(a) [24,25], and the majority of healthcare practitioners in primary and secondary care remain unaware of the Lp(a) status of their patients [26]. However, an estimated 20% of the global population are potentially at high risk of ASCVD due to Lp(a) > 125 nmol/L [5,6,12,27–30]. Therefore, the European Atherosclerosis Society and the European Society of Cardiology now recommend Lp(a) measurement at least once in each adult's lifetime, to identify individuals with elevated Lp(a), and associated high lifetime risk of ASCVD [11].

Research around Lp(a) mediated risk and management has increased with the development of novel Lp(a) targeted RNA therapies including antisense oligonucleotides (ASOs) and small interfering RNA (siRNAs), which are expected to reduce circulating Lp(a) by 80% to over 90% [31, 32]. Currently, two phase 3 (Lp(a)HORIZON [NCT04023552]; OCEAN (a) [NCT05581303]) [33] trials are underway to assess safety and efficacy of Lp(a) lowering interventions to reduce recurrent cardiovascular (CV) events in patients with elevated Lp(a) [31,32,34,35], as well as several phase 2 trials (NCT05563246, NCT02160899, NCT03070782, and NCT04270760). However, the association of elevated Lp(a) and risk of subsequent CV events in a secondary prevention population is still not well understood. There is a particular lack of evidence on the risk of elevated Lp(a) in newly diagnosed, i.e., incident, ASCVD patients, making it difficult to provide risk assessment and secondary prevention plans for these patients. Therefore, this study aimed to compare and highlight the additional risk of major adverse cardiovascular event (MACE) in those with elevated vs normal Lp(a) levels, in a newly diagnosed ASCVD cohort, representative of an acute setting. Highlighting such an association may increase uptake of routine Lp(a) testing and enhance management in these higher risk patients.

2. Patients and methods

2.1. Study design

The UK Biobank is a large-scale prospective cohort study and research resource, containing in-depth genetic and health information. Participants were enrolled from 22 assessment centres across the UK between March 2006 and December 2010. In total, more than 502,000 participants aged between a target range of 40–69 years were recruited, for which baseline biological measurements were recorded, and touch-screen questionnaires were administered according to a standard protocol. The UK Biobank has linked Hospital Episode Statistics (HES) data, spanning from 1997 until September 2020 for English and Scottish residents, and February 2018 for Welsh residents. Lp(a) was measured on blood samples taken at UK Biobank enrolment date, pre-incident ASCVD diagnosis, in a single accredited biochemistry centre using a Randox assay traceable to the WHO/IFCC reference material (IFCC SRM 2B). Further details on key variables are provided in the [Supplementary materials](#).

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.

The current investigation is a retrospective cohort study of incident ASCVD patients recruited to the UK Biobank and was conducted under approved project number 59456.

2.2. Incident ASCVD cohort

The incident ASCVD cohort for this study included adult patients with a valid Lp(a) measurement whose first ASCVD diagnosis (index date) occurred after their UK Biobank enrolment date (Fig. 1). Patients with a first ASCVD diagnosis prior to enrolment were excluded to avoid introducing immortal time bias. ASCVD diagnosis was captured from linked HES data via International Classification of Disease version 10 (ICD 10) and Classification of Interventions and Procedures version 4 (OPCS4) procedure codes and defined as any of myocardial infarction (MI), ischaemic stroke (IS), transient ischaemic attack (TIA), coronary artery disease, cerebrovascular disease, stent placement and/or revascularisation (including coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), peripheral artery disease (PAD), unstable angina, or stable angina. End of patient follow-up was the last date of available regional HES data of the participant or death, whichever was earliest. This gave a maximum available follow-up of 13 years for our incident ASCVD cohort, which had a median follow-up of 4.7 years.

The incident ASCVD cohort was stratified into those with 'normal' (<65 nmol/L) and 'elevated' (>150 nmol/L) Lp(a) concentrations to understand and contrast the additional risk associated with elevated versus normal Lp(a) levels in an already high-risk acute patient population. The elevated threshold of 150 nmol/L aligns with the inclusion criteria of the Lp(a)HORIZON phase 3 trial of 70 mg/dL, using a unit conversion factor of 2.15 [30,33,36–39].

2.3. MACE outcome

The primary outcome of this study was occurrence of MACE. Both time to first MACE and rates of all MACE after incident ASCVD diagnosis were investigated. MACE was defined as a composite outcome including any of CV death, non-fatal MI, non-fatal IS, or coronary revascularisation. CV death was captured in the linked Death Register data, where primary cause of death corresponded to ICD-10 codes I20–I79. Non-fatal MI and non-fatal IS were identified in the linked HES data via ICD-10 code and coronary revascularisation using OPCS-4. All ICD-10 and OPCS-4 codes used are included in the [Supplementary materials](#). MACE were captured using episode start date in the linked HES data, and were conditional on having a unique spell index to ensure MACE was a separate event to the incident ASCVD diagnosis.

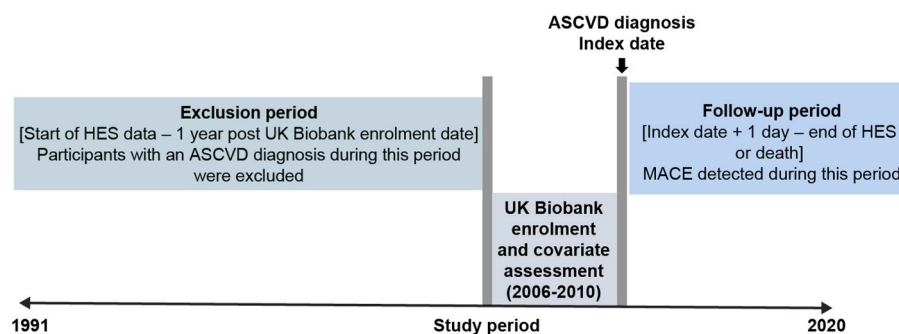


Fig. 1. Visualization of study periods. ASCVD, atherosclerotic cardiovascular disease.

2.4. Statistical analysis

With the sample size of 32,537, and approximate event rate of 0.4, a Cox regression model of Lp(a) (nmol/L; standard deviation = 0.85) can detect a minimum hazard ratio of 1.038 with a power of 95% ($\beta = \leq 0.05$) at $\alpha = 0.05$.

Baseline demographics and clinical characteristics were summarized using descriptive statistics. Continuous variables were summarized as either mean \pm standard deviation (SD) or median (IQR), while all categorical variables were summarized as frequencies and percentages.

Incidence rate (IR) of composite and disaggregated MACE components were calculated as the total number of MACE recorded over the follow-up period, divided by 100 person-years of follow-up. Rates were calculated for both the overall follow-up and the first-year post-index. The incidence rate difference (IRD) was calculated as the absolute difference between Lp(a) stratified IRs. Age, sex, and low-density lipoprotein cholesterol (LDL-C) adjusted incidence rate ratios (IRR) were calculated using a multivariate Poisson model. IRs of MACE were calculated for the total incident ASCVD cohort as well as sub-groups of the cohort stratified by incident ASCVD diagnosis type and baseline LDL-C level above or below the cohort median value.

Time to first MACE was analysed using Cox proportional hazard models. Time to first MACE was taken as the elapsed time in days between the index date and the first record of MACE after index diagnosis. Cox proportional hazard models were used to estimate hazard ratios for a 100 nmol/L continuous increase in Lp(a) adjusted for age, sex, incident ASCVD diagnosis type, ethnicity, smoking status, diabetes, chronic kidney disease, systolic blood pressure, pulse pressure, body mass index (BMI), use of cholesterol lowering medications, LDL-C, and high sensitivity C-reactive protein (hsCRP).

All analyses were performed using the programming language Python 3, querying UK Biobank dataset and cohort extraction using PySpark and packages pandas, numpy, and lifelines.

3. Results

3.1. Study population baseline demographics and characteristics

Among 32,537 patients with incident ASCVD, 22,257 (68.4%) had normal and 5204 (16.0%) had elevated Lp(a). The mean (SD) age of the total cohort was 66.1 years (7.5) and was consistent across normal and elevated Lp(a) levels. The majority of the cohort were male (37.7% female), although the proportion of females was higher (43.5%) in those with elevated Lp(a) (Table 1). While the cohort was predominantly of White ethnicity (94.4%), there was a higher proportion of Black or Black British participants among those with elevated Lp(a) compared to those with normal Lp(a) and the total cohort (1.7% versus 0.7% and 1.2%, respectively). The median Lp(a) (IQR) and mean (SD) LDL-C values were 23.8 (8.3–98.9) nmol/L and 137.2 (36.8) mg/dL in the total cohort, with mean LDL-C increased to 144.4 (38.9) mg/dL in those with elevated Lp(a). At baseline, frequency of hypertension and self-reported cholesterol lowering medications use in the total cohort was 56.5% and 32.1%, respectively (Table 1). Among those with elevated Lp(a), frequencies were 57.9% and 39.9%, respectively (Table 1).

3.2. Counts and proportions of incident ASCVD patients with subsequent MACE, stratified by Lp(a) status

Of the 22,257 patients with normal Lp(a), 35.6% had at least one subsequent MACE with an average of 2.75 MACE per person during the available follow-up (Figs. 2 and 5). In contrast, of the 5204 patients with elevated Lp(a), 41.2% had at least one subsequent MACE and an average of 2.88 MACE. In particular, 25.9% and 22.6% of those with elevated and normal Lp(a), respectively had a subsequent MI, and 16.4% and 10.9% had a subsequent coronary revascularisation. Thus, the proportion of incident ASCVD patients with a subsequent MACE increased with elevated Lp(a). Most of these MACE occurred within the first year of ASCVD diagnosis (Supplementary Table S1).

Table 1
Baseline patient demographics and characteristics.

Baseline characteristics	Incident ASCVD cohort N = 32,537	Lp(a) < 65 nmol/L N = 22,257	Lp(a) > 150 nmol/L N = 5204
Age, Mean (SD)	66.1 (7.5)	66.2 (7.5)	66.1 (7.2)
Sex, N (%)			
Male	20,286 (62.3)	14,049 (63.1)	2941 (56.5)
Female	12,251 (37.7)	8208 (36.9)	2263 (43.5)
Ethnicity, N (%)			
Asian or Asian British	896 (2.8)	629 (2.8)	93 (1.8)
Black or Black British	395 (1.2)	160 (0.7)	91 (1.7)
Mixed	361 (1.1)	242 (1.1)	41 (0.8)
Unknown	136 (0.4)	93 (0.4)	20 (0.4)
White	30,711 (94.4)	21,105 (94.8)	4956 (95.2)
BMI (Kg/m²), Mean (SD)	28.6 (4.9)	28.6 (4.9)	28.4 (4.9)
Smoking status, N (%)			
Current	4933 (15.2)	3383 (15.2)	782 (15.0)
Previous	13,066 (40.2)	8992 (40.4)	2115 (40.6)
Never	14,369 (44.2)	97,69 (43.9)	2272 (43.7)
Prefer not to answer	169 (0.5)	113 (0.5)	35 (0.7)
Time (days) from UK Biobank enrolment date* to incident ASCVD diagnosis, Median (IQR)	2298 (1242–3288)	2319 (1269–3296)	2198 (1126–3235)
Lp(a) (nmol/L), Median (IQR)	23.8 (8.3–98.9)	12 (5.7–25.43)	209.9 (174.6–258.6)
LDL-C (mg/dL), Mean (SD)	137.2 (36.8)	134.9 (36.2)	144.4 (38.9)
hsCRP (mg), Mean (SD)	3.29 (5.14)	3.26 (5.08)	3.44 (5.2)
Systolic blood pressure (mmHg), Mean (SD)	146.1 (20.1)	146.1 (20.1)	146.6 (20.2)
Comorbidities, N (%)			
Hypertension	18,375 (56.5)	12,600 (56.6)	3014 (57.9)
CKD	2441 (7.5)	1705 (7.7)	399 (7.7)
Diabetes	5272 (16.2)	3788 (17.0)	710 (13.6)
Cholesterol lowering medications, N (%)	10,432 (32.1)	6890 (31.0)	2078 (39.9)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; SD, standard deviation; IQR, interquartile range; hsCRP, high-sensitivity C-reactive protein; CKD, chronic kidney disease; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); N = number of patients; *UK Biobank enrolment date represents the date of baseline blood sample draw for UK Biobank participants.

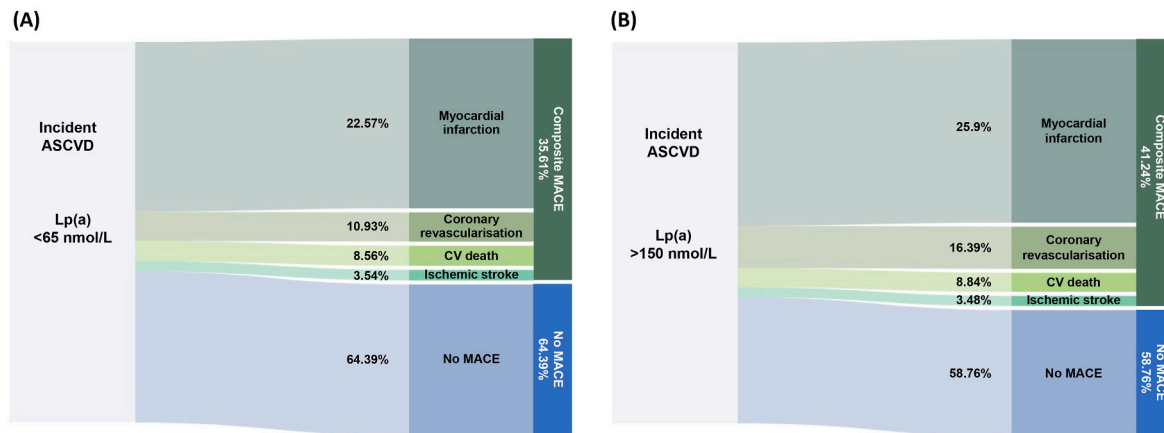


Fig. 2. Proportion of incident ASCVD patients with subsequent MACE stratified by (a) normal and (b) elevated Lp(a).

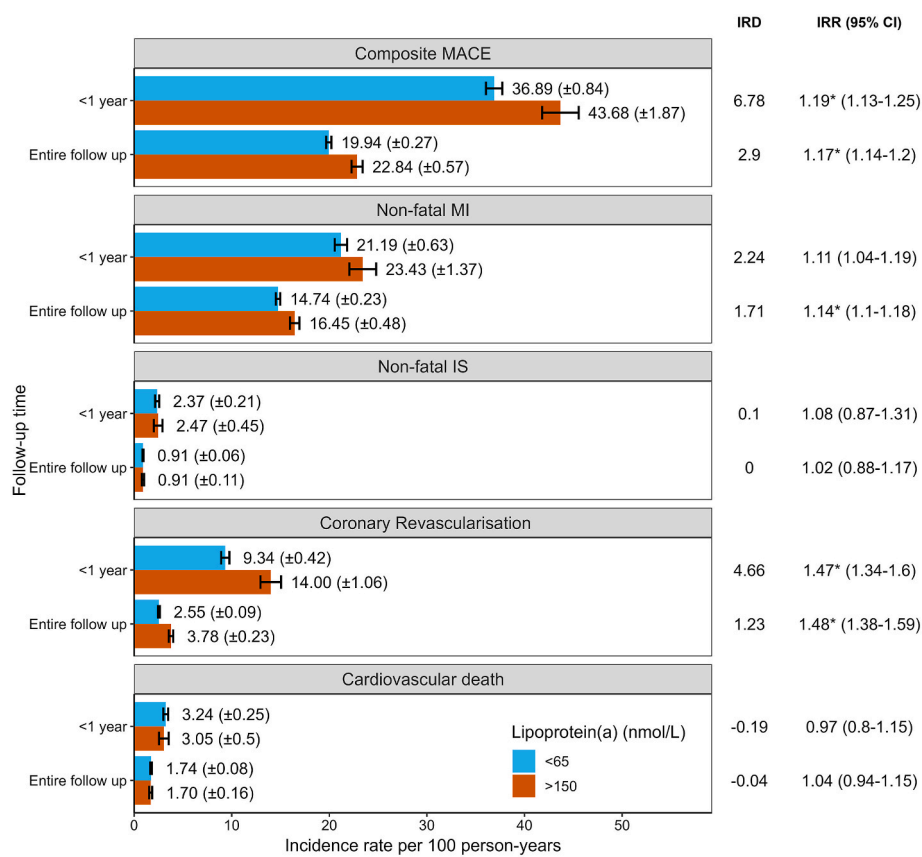


Fig. 3. Incidence rate (IR), incidence rate difference (IRD), and incidence rate ratio (IRR) of all composite and disaggregated MACE, stratified by Lp(a) status and follow-up period.

IS, ischaemic stroke; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular event; MI, myocardial infarction.

3.3. Incidence rate (IR) of MACE by Lp(a) status

Over the entire follow-up period, IRs of composite MACE of 22.85 (95% CI: 22.28–23.42) and 19.94 (95% CI: 19.68–20.21) per 100 person-years were observed in elevated and normal Lp(a) levels, respectively (Figs. 3 and 5). Hence, among incident ASCVD patients, there were 2.90 (IRD; IRR = 1.17, $p < 0.001$) excess cases of MACE per 100 person-years of follow-up potentially attributed to elevated Lp(a). Within the first year of follow-up, the IR of MACE was higher than the overall follow-up, and again was significantly higher in patients with elevated (43.68; 95% CI: 41.81–45.55) vs normal Lp(a) (36.89; 95% CI:

36.06–37.73), giving an excess of 6.79 MACE per 100 person-years (IRD; IRR = 1.17, $p < 0.001$) in the first year of index diagnosis (Fig. 3).

The IR of MACE in both Lp(a) strata were driven largely by non-fatal MI and coronary revascularisation. During the overall follow-up period, the IR of non-fatal MI was significantly higher in patients with elevated Lp(a) (16.45; 95% CI: 15.97–16.94; IRD = 1.71; IRR = 1.12, $p < 0.001$) compared to normal Lp(a) (14.74; 95% CI: 14.51–14.97). Similarly, the IR of coronary revascularisation increased in patients with elevated Lp(a) (3.78; 95% CI: 3.55–4.02; IRD = 1.23; IRR = 1.48, $p < 0.001$) compared to normal Lp(a) (2.55; 95% CI: 2.45–2.64). This trend was also seen within the first year of follow-up, with IRD = 2.24; IRR = 1.11,

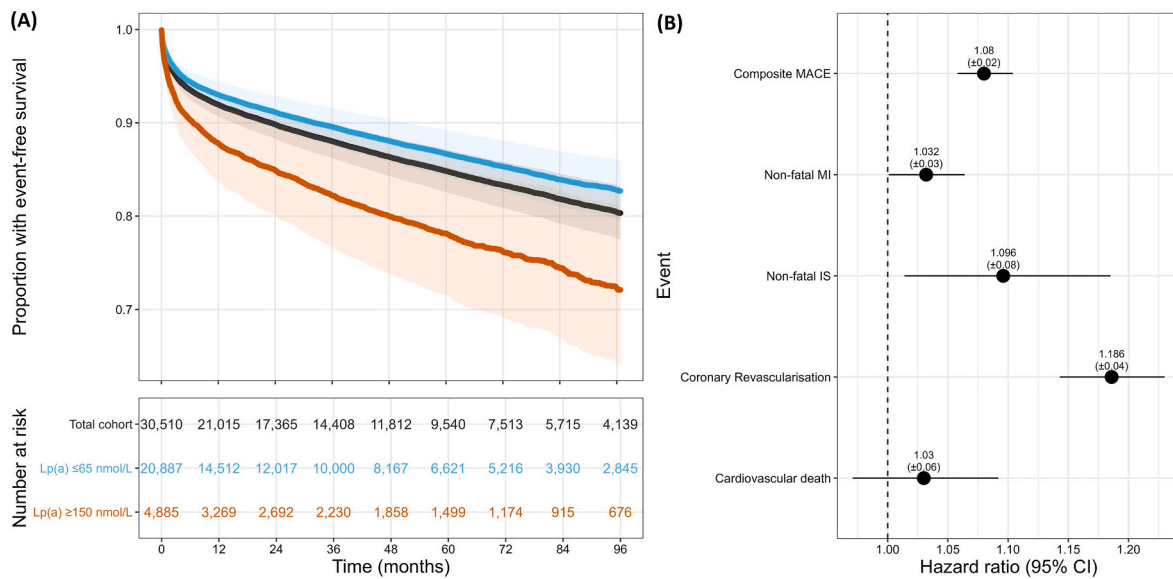


Fig. 4. (A) Association of normal and elevated Lp(a) with first composite MACE over the full available follow-up time. (B) Adjusted association (hazard ratio) of 100 nmol/L Lp(a) with first composite and disaggregated MACE over the full available follow-up period. Lp(a), lipoprotein(a); MACE, major adverse cardiovascular event; MI, myocardial infarction; IS, ischaemic stroke. Notes: Cox proportional hazard model adjusting for age, sex, index event type, ethnicity, smoking, diabetes, chronic kidney disease, systolic blood pressure, pulse pressure, BMI, cholesterol lowering medications, LDL-cholesterol, and C-reactive protein.

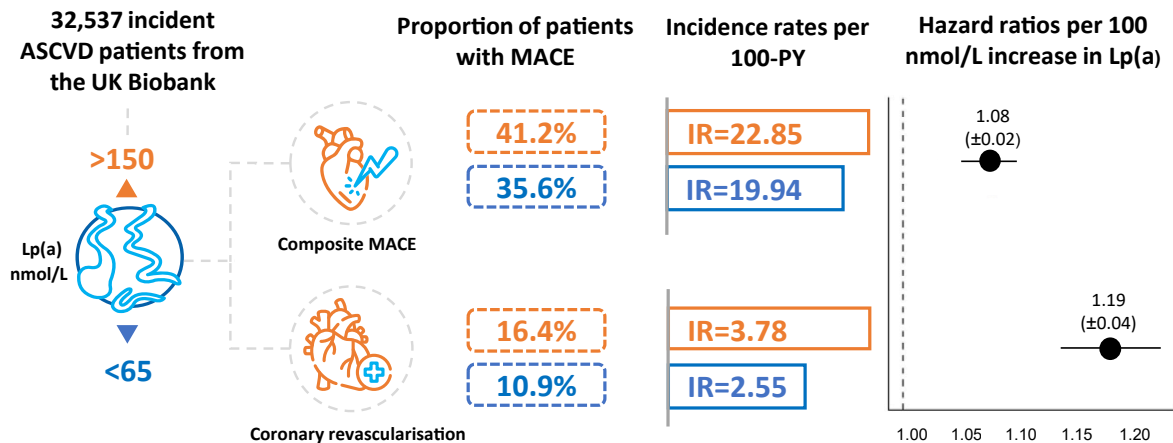


Fig. 5. Graphical representation of the key findings from this study and visualization of the study narrative. Among incident ASCVD patients, elevated Lp(a) > 150 nmol/L was associated with significantly higher incidence of MACE, particularly coronary revascularisation, compared to normal Lp(a) < 65 nmol/L.

$p = 0.002$ and $IRD = 4.66$; $IRR = 1.47$, $p < 0.001$ for non-fatal MI and coronary revascularisation, respectively. No significant increase in IR of CV death nor non-fatal IS was observed in patients with elevated Lp(a) in either follow-up period.

We also considered IR of MACE according to incident ASCVD diagnosis, focusing on incident MI, IS, and coronary revascularisation. The IR of MACE was significantly higher among incident MI and IS patients with elevated Lp(a), over the entire (Supplementary Table S2) and 1-year follow-up period (Supplementary Table S3), but not among incident coronary revascularisation patients. IRs of coronary revascularisation were significantly ($p < 0.005$) higher among patients with elevated Lp(a) and MI ($IRD = 5.96$ and 1.73) and coronary revascularisation ($IRD = 3.72$ and 1.01) as their incident ASCVD diagnosis, in the one year and overall follow-up respectively, and among incident IS ($IRD = 0.39$; $IRR = 2.27$, $p = 0.007$) patients in the overall follow-up.

3.4. Lp(a) and adjusted risk of first MACE

We conducted a complete case analysis to investigate the association of Lp(a) and post-index MACE in 30,510 incident ASCVD patients with covariates of age, sex, incident ASCVD diagnosis type, ethnicity, smoking status, diabetes, chronic kidney disease, systolic blood pressure, pulse pressure, BMI, cholesterol lowering medications, LDL-C, and hsCRP. Of the 30,510 patients, 20,887 had normal Lp(a) and 4885 had elevated Lp(a). Over the entire follow-up period, a 100 nmol/L continuous increase in Lp(a) was associated with an 8% ($HR = 1.08$; 95% CI: 1.06–1.10; $p < 0.001$) increased risk of composite MACE, a 3.2% increased risk of non-fatal MI, a 9.6% increased risk of non-fatal IS, and a 19% increased risk of coronary revascularisation (Figs. 4 and 5). There was no association with elevated Lp(a) and CV death. In those whose incident ASCVD diagnosis was a non-fatal MI or coronary revascularisation, a 100 nmol/L continuous increase in Lp(a) was associated with a 18% ($HR = 1.18$, $p < 0.001$) and 12% ($HR = 1.12$, $p = 0.003$) increased

risk of a subsequent coronary revascularisation (Supplementary Table S4). Among those with an incident IS diagnosis, a 100 nmol/L increase in Lp(a) was associated with an 18% increase in risk of recurrent non-fatal IS (HR = 1.18, $p = 0.001$).

When stratifying the participants by LDL-C levels below or above cohort median, the HR for composite MACE remained unchanged, at 1.08 (95% CI, 1.05–1.12) and 1.08 (95% CI, 1.05–1.11), respectively (Supplementary Table S4). There was also little difference in HR when stratifying by age or sex (Supplementary Table S4). For disaggregated MACE, the HR for non-fatal MI was slightly higher in those with LDL-C below [1.05 (95% CI, 1.01–1.10)] versus above median [1.01 (95% CI, 0.97–1.06)], while HR for non-fatal IS and CV death was higher in those with LDL-C above median (Supplementary Table S4). The association between increasing Lp(a) and coronary revascularisation was generally strong regardless of baseline LDL-C or incident ASCVD diagnosis (Supplementary Table S4).

4. Discussion

This analysis of a large observational dataset expands our understanding of the risk of MACE associated with elevated Lp(a), with novel evidence from an incident ASCVD cohort. This study models the anticipated consequences of Lp(a) mediated risk of MACE in a clinically relevant acute, secondary prevention setting when patients may be most amenable to lifestyle and pharmacological interventions.

Our analysis differentiates the risk profile associated with elevated Lp(a) from what we defined as normal Lp(a) levels to reflect decision making in routine care. Among this incident ASCVD cohort, 35.6% with normal and 41.2% with elevated Lp(a) had a subsequent MACE. We observed that incident ASCVD patients with elevated Lp(a) (>150 nmol/L) had significantly higher adjusted IRs of subsequent MACE compared to patients with normal Lp(a) (<65 nmol/L). Per 100 person-years of follow-up, we observed an excess of 2.90 MACE attributable to elevated Lp(a), with an excess of 6.79 MACE in the first year of follow-up. This suggests that incident ASCVD patients with elevated Lp(a) experience more MACE, particularly within the first year of their ASCVD diagnosis. The observed rates of MACE were driven largely by MI and coronary revascularisation, with 22.6% of patients with normal Lp(a) and 25.9% of patients with elevated Lp(a) experiencing an MI and 10.9% and 16.4%, respectively, experiencing coronary revascularisation after incident ASCVD diagnosis.

Considering coronary revascularisation as an outcome, rates were significantly higher among patients with elevated Lp(a), reporting an excess of 4.66 procedures per 100 person-years in the first year of ASCVD diagnosis. This suggests that patients with elevated Lp(a) who have recently experienced their first ASCVD event, particularly MI or IS, or undergone a coronary revascularisation, are likely to require repeat procedures, burdensome for both the individual and the healthcare system. In Cox models of time to coronary revascularisation, a 100 nmol/L continuous increase in Lp(a) was associated with a 18.6% increased hazard. These findings are in line with a causal role of Lp(a) in atherosclerosis [40]. National Institute for Health and Care Excellence (NICE) guidelines recommend early invasive treatment (coronary angiography with PCI if needed) for patients with acute ST-elevation myocardial infarction (STEMI), non-STEMI, or unstable angina [41]. Thus, the high rates of MI and coronary revascularisation observed within one year of diagnosis in this study may reflect the implementation of these guidelines in UK clinical practice. Furthermore, the high rate of coronary revascularisations may explain our observed lower rates of other MACE in the years beyond the first year of follow-up, particularly after incident coronary revascularisation.

The high rate of coronary revascularisations within our elevated Lp(a) cohort after ASCVD diagnosis present a patient population with large potential economic burden, who may benefit from additional risk factor management. While pharmacological or surgical interventions such as coronary revascularisation have shown to increase overall survival [42],

repeated surgical interventions, like those observed in our study, are associated with worsening prognosis and related economic health care implications. Elevated Lp(a) in incident ASCVD patients, even if not an MI, may indicate a clinical need for further investigations to identify and treat atherosclerotic lesions. Early Lp(a) testing as part of routine clinical practice to identify those with elevated Lp(a) has potential to improve early management of CV risk factors, thus mitigating risk of multiple subsequent events and the need for more burdensome interventions.

Our observations support the association of elevated Lp(a) with high risk of subsequent MACE in a secondary prevention setting [37], with insights from the acute ASCVD setting. Additionally, we show a clear relationship between increasing Lp(a) and risk of MACE. We report an 8% increase in the risk of MACE per 100 nmol/L increase in Lp(a), which remained stable regardless of stratification by age, sex or LDL-C. A previous study from the UK Biobank conducted by Patel et al. reported a similar HR of 1.04 per 50 nmol/L continuous increase in Lp(a) for recurrent ASCVD [39]. However, results must be interpreted and compared considering important differences in methodology including their defined ASCVD outcome vs. our MACE, their selected prevalent ASCVD cohort (first ASCVD diagnosis captured prior to UK Biobank enrolment), and consequently, their longer follow-up period (median 12.2 vs 4.7 years). Despite such methodological differences in existing Lp(a) research, the linear relationship of increasing Lp(a) levels with CV risk has been well established [1,3,5,12,39].

The results from this study should be interpreted within the context of potential limitations of an observational study. Our study showed no significant association of elevated Lp(a) with CV death [43–45] and only weak associations with non-fatal MI and non-fatal IS using Cox models [44]. These findings might be attributed to the high rates of revascularisation procedures observed among patients with elevated Lp(a), reducing the risk of subsequent MI, IS, or CV death. Alternatively, the lack of significant association may be attributed to relatively younger age of the cohort (48–62 years) as recurrent IS and CV death are more commonly observed in older patients (70–85 years of age) [46,47]. In the small subgroup with incident PAD, we report a borderline inverse association of elevated Lp(a) with MACE (Supplementary Tables S2 and S3). This observation requires further investigation, but it may be a spurious association or inconclusive due to low sample size for this subgroup. In terms of representativeness, firstly, UK Biobank includes healthy volunteers, with less participants overweight or obese than the general UK population, as well as fewer smokers and daily alcohol consumption as compared to the general UK population [48]. There is also a lower prevalence of self-reported diseases, including CV disease as compared to the general population in the UK [48]. However, these do not necessarily impact the strength of associations in exposure-outcome models. Secondly, in terms of ethnicity, the UK Biobank comprises of primarily White participants (94.6%), which limits the generalizability of the analysis in different ethnic groups [48].

4.1. Conclusions

To conclude, our observations demonstrate the impact of elevated Lp(a) as a driver for CV risk, in a clinically relevant incident ASCVD cohort. The association of elevated Lp(a) with increased rate of subsequent MACE and coronary revascularisation highlights an acute population who may benefit from earlier and more targeted intervention for Lp(a) and other CV risk factors, particularly within the first year after ASCVD diagnosis. Proactive Lp(a) testing as part of routine clinical practice can help to identify and better manage these high-risk individuals.

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CRedit author contribution statement

Paul Welsh: Conceptualization; Methodology; Investigation; Writing – review & editing. **Anas Al Zabiby:** Methodology; Investigation; Writing – review & editing. **Hannah Byrne:** Methodology; Investigation; Writing – review & editing. **Harriet R. Benbow:** Methodology; Investigation; Writing – review & editing. **Taha Itani:** Conceptualization; Investigation; Writing – review & editing. **Gabriella Farries:** Methodology; Investigation; Writing – review & editing. **Madlaina Costa-Scharplatz:** Investigation; Writing – review & editing. **Philippe Ferber:** Conceptualization; Investigation; Writing – review & editing. **Lorraine Martin:** Investigation; Writing – review & editing. **Rosemary Brown:** Investigation; Writing – review & editing. **Ana Filipa Fonseca:** Conceptualization; Investigation; Writing – review & editing. **Naveed Sattar:** Conceptualization; Investigation; Writing – review & editing.

Data availability

The data underlying this article are available in the article and in its online [Supplementary materials](#).

Declaration of competing interest

Paul Welsh reports grants from Novartis Pharma AG, Basel, Switzerland during the conduct of the study, grants from Boehringer Ingelheim, Roche Diagnostics, Astrazeneca, and personal fees from Novo Nordisk, and Raisio, outside the submitted work. Naveed Sattar reports grants and personal fees from Novartis Pharma AG, Basel, Switzerland, consulted for and/or received speaker honoraria from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and received grant support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work. Rosemary Brown reports grant from Novartis Pharma AG, Basel, Switzerland during the conduct of the study. Anas Al Zabiby was an employee of Novartis, Kuala Lumpur, Malaysia at time of study. Hannah Byrne, Harriet R. Benbow and Gabriella Farries are employees of Novartis Pharma AG, Dublin, Ireland. Ana Filipa Fonseca and Philippe Ferber are employees of Novartis Pharma AG, Basel, Switzerland. Madlaina Costa-Scharplatz is an employee of Novartis Sweden AB, Stockholm, Sweden. Lorraine Martin is an employee of Novartis Pharmaceuticals UK Limited, United Kingdom. Taha Itani was an employee of Novartis Pharma AG, Basel, Switzerland at the time of conduct of this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2023.117437>.

References

- [1] J.J. Albers, et al., Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (atherothrombosis intervention in metabolic syndrome with low HDL/high triglyceride and impact on global health outcomes), *J. Am. Coll. Cardiol.* 62 (17) (2013) 1575–1579.

- [2] E.A. Enas, et al., Lipoprotein(a): an underrecognized genetic risk factor for malignant coronary artery disease in young Indians, *Indian Heart J.* 71 (3) (2019) 184–198.
- [3] A.V. Khera, et al., Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER trial (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin), *Circulation* 129 (6) (2014) 635–642.
- [4] P.J. Nestel, et al., Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease, *Arterioscler. Thromb. Vasc. Biol.* 33 (12) (2013) 2902–2908.
- [5] S. Tsimikas, A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies, *J. Am. Coll. Cardiol.* 69 (6) (2017) 692–711.
- [6] S. Tsimikas, et al., NHLBI working group recommendations to reduce lipoprotein (a)-mediated risk of cardiovascular disease and aortic stenosis, *J. Am. Coll. Cardiol.* 71 (2) (2018) 177–192.
- [7] S.M. Grundy, et al., 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines, *Circulation* 139 (25) (2019) e1082–e1143.
- [8] D.K. Arnett, et al., ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines, *Circulation* 140 (11) (2019) e596–e646.
- [9] G. Reyes-Soffer, et al., Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American heart association, *Arterioscler. Thromb. Vasc. Biol.* 42 (1) (2022) e48–e60.
- [10] Y. Handelsman, et al., Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm - 2020 executive summary, *Endocr. Pract.* 26 (10) (2020) 1196–1224.
- [11] F. Mach, et al., ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, *Atherosclerosis* 290 (2019) 140–205.
- [12] B.G. Nordestgaard, et al., Lipoprotein(a) as a cardiovascular risk factor: current status, *Eur. Heart J.* 31 (23) (2010) 2844–2853.
- [13] M.R. Langlois, et al., Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM, *Clin. Chem.* 64 (7) (2018) 1006–1033.
- [14] B.G. Nordestgaard, et al., Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM, *Atherosclerosis* 294 (2020) 46–61.
- [15] D.P. Wilson, et al., Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association, *J Clin Lipidol* 13 (3) (2019) 374–392.
- [16] J. Cegla, et al., HEART UK consensus statement on Lipoprotein(a): a call to action, *Atherosclerosis* 291 (2019) 62–70.
- [17] V. Durlach, et al., Lipoprotein(a): pathophysiology, measurement, indication and treatment in cardiovascular disease. A consensus statement from the Nouvelle Société Française d'Athérosclérose (NSFA), *Arch Cardiovasc Dis* 114 (12) (2021) 828–847.
- [18] G.J. Pearson, et al., Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults, *Can. J. Cardiol.* 37 (8) (2021) 1129–1150.
- [19] R. Puri, et al., Lipoprotein(a) and ASCVD risk, *J. Assoc. Phys. India* 68 (11) (2020) 42–46 [Special].
- [20] M. Banach, et al., PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021, *Arch. Med. Sci.* 17 (6) (2021) 1447–1547.
- [21] D.B. Prêcoma, et al., Updated cardiovascular prevention guideline of the Brazilian society of Cardiology - 2019, *Arq. Bras. Cardiol.* 113 (4) (2019) 787–891.
- [22] Expert statement on the relationship between lipoprotein (a) and cardiovascular disease risk and clinical management [in Chinese], *Chinese Circulation Journal* 12 (2021) 1158–1167.
- [23] F. Kronenberg, Human genetics and the causal role of lipoprotein(a) for various diseases, *Cardiovasc. Drugs Ther.* 30 (1) (2016) 87–100.
- [24] D.E. MacDougall, M.P. M, K.A. Wilemon, C.D. Ahmed, K.D. Myers, Characterization of Lp(a) Measurement in a Large U.S. Health Care Dataset, *National Lipid Association*, 2022.
- [25] A.F. Fonseca, B. H, A. Laguna, T. Itani, R. Studer, J. Heo, A. Dillon, F. Ferber, M. Costa-Scharplatz, Burden of lipoprotein(a) for patients with atherosclerotic cardiovascular disease: a retrospective analysis from the United States, *J Manag Care Spec Pharm* 29 (5) (2023) 519–529.
- [26] R. Lahoz, et al., LP(A) distribution and correlation with LDL-C in patients with atherosclerotic cardiovascular disease (ASCVD) in the US, *J. Am. Coll. Cardiol.* 77 (18_Supplement_1) (2021), 1564–1564.
- [27] S.E. Nissen, et al., Lipoprotein(a) levels in a global population with established atherosclerotic cardiovascular disease, *Open Heart* 9 (2) (2022).
- [28] A.L. Catapano, et al., 2016 ESC/EAS guidelines for the management of dyslipidaemias, *Eur. Heart J.* 37 (39) (2016) 2999–3058.
- [29] S. Varvel, J.P. McConnell, S. Tsimikas, Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States, *Arterioscler. Thromb. Vasc. Biol.* 36 (11) (2016) 2239–2245.
- [30] F. Kronenberg, et al., Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, *Eur. Heart J.* 43 (39) (2022) 3925–3946.

- [31] S. Tsimikas, et al., Lipoprotein(a) reduction in persons with cardiovascular disease, *N. Engl. J. Med.* 382 (3) (2020) 244–255.
- [32] M.L. O'Donoghue, et al., Study design and rationale for the Olpasiran trials of Cardiovascular Events and lipoprotein(a) reduction-DOSE finding study (OCEAN (a)-DOSE), *Am. Heart J.* 251 (2022) 61–69.
- [33] Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp(a)HORIZON). [cited 2022 03-March-2022]; Available from: <https://clinicaltrials.gov/ct2/show/NCT04023552>.
- [34] M.L. O'Donoghue, et al., Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease, *N. Engl. J. Med.* 387 (20) (2022) 1855–1864.
- [35] N.J. Viney, et al., Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials, *Lancet* 388 (10057) (2016) 2239–2253.
- [36] Francisco, U.o.C.S. Lipoprotein-a. [cited 2022 02-March-2022]; Available from: <https://www.ucsfhealth.org/medical-tests/007262..>
- [37] C.M. Madsen, et al., Lipoprotein(a)-Lowering by 50 mg/dL (105 nmol/L) may Be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study, *Arterioscler. Thromb. Vasc. Biol.* 40 (1) (2020) 255–266.
- [38] S.J. Nicholls, et al., Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy, *Journal of lipid research* 51 (10) (2010) 3055–3061.
- [39] A.P. Patel, et al., Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national Biobank, *Arterioscler. Thromb. Vasc. Biol.* 41 (1) (2021) 465–474.
- [40] INVALID CITATION !!! [40].
- [41] (NICE), N.I.f.H.a.C.E, Acute Coronary Syndromes (NICE Guideline), 2020 [cited 2022 13-May-2022]; Available from: <https://www.nice.org.uk/guidance/ng185>.
- [42] B. Wein, et al., Systematic investment in the delivery of guideline-coherent therapy reduces mortality and overall costs in patients with ST-elevation myocardial infarction: results from the stent for life economic model for Romania, Portugal, Basque country and Kemerovo region, *Eur. Heart J.: Acute Cardiovascular Care* 9 (8) (2020) 902–910.
- [43] T. Sang, et al., Lipoprotein (a) is associated with poor long-term prognosis in patients aged 80 years and older with acute coronary syndrome, *J Clin Lipidol* 15 (3) (2021) 466–476.
- [44] H.H. Liu, et al., Predicting cardiovascular outcomes by baseline lipoprotein(a) concentrations: a large cohort and long-term follow-up study on real-world patients receiving percutaneous coronary intervention, *J. Am. Heart Assoc.* 9 (3) (2020) e014581.
- [45] M. Zhang, et al., Lipoprotein(a) and cardiovascular death in oldest-old (>=80 years) patients with acute myocardial infarction: a prospective cohort study, *Atherosclerosis* 312 (2020) 54–59.
- [46] R.-L. Chen, et al., Ischemic stroke in the elderly: an overview of evidence, *Nat. Rev. Neurol.* 6 (5) (2010) 256–265.
- [47] N.B. Allen, et al., Trends in one-year recurrent ischemic stroke among the elderly in the USA: 1994–2002, *Cerebrovasc. Dis.* 30 (5) (2010) 525–532.
- [48] A. Fry, et al., Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population, *Am. J. Epidemiol.* 186 (9) (2017) 1026–1034.