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FULL RESEARCH PAPER
Lipids & atherosclerosis

Lipoprotein (a) and incident coronary heart disease in the community: impact of traditional cardiovascular risk factors

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Aims Deleterious effects of Lipoprotein (a) (Lp(a)) might be mitigated by overall cardiovascular (CV) risk reduction. However, data on the relationship between increased Lp(a) and incident coronary heart disease (CHD) according to the distribution of modifiable CV risk factors (CVRF) at baseline are still scarce. We investigated the association between high Lp(a) and incident CHD in the general population, depending on the presence/absence of four major CVRFs (hypertension, diabetes, hypercholesterolemia, smoking) at baseline.

Methods and results Overall 66 495 CHD-free individuals from eight European prospective population-based cohorts were included. The cohort was stratified according to CVRF burden at baseline in '0/1 CVRF' (low risk; $n = 41\,770$) and '≥2 CVRFs' (increased risk;

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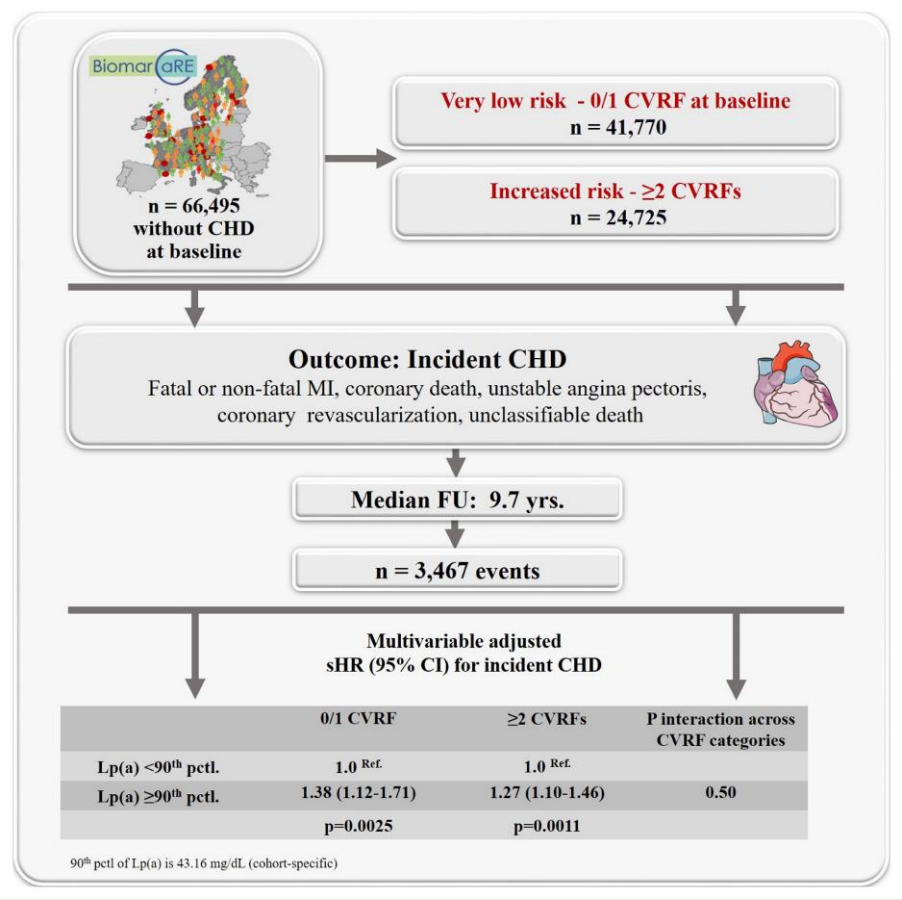
n = 24 725). Fine and Gray competing risk-adjusted models were calculated for the association between Lp(a) mass (<90th vs. ≥90th percentile (pctl.); cut-off 43.2 mg/dL) and future CHD events. During a median follow-up of 9.7 years, 3467 incident CHD events occurred. Despite being at very low absolute risk based on traditional CVRF, individuals with 0/1CVRF demonstrated a strong association between increased Lp(a) mass (≥90th pctl.) and future CHD events, which was comparable to the association observed among individuals with ≥2 CVRFs. The fully-adjusted sub-distribution Hazard Ratios [sHRs] for elevated Lp(a) were 1.38 (95% CI, 1.12–1.71) vs. 1.27 (95% CI, 1.10–1.46) in those having 0/1 vs. ≥2 CVRFs at baseline ($P_{interaction}$ 0.50).

Conclusion Among CHD-free subjects, high Lp(a) was related to adverse outcome even in individuals with no or only one CVRF at baseline, thereby generating substantial challenges in mitigating Lp(a)-associated CHD risk in very low risk populations.

Lay summary While therapeutic options for high Lipoprotein (a) (Lp(a)) are currently under investigation, the only possibility to mitigate the deleterious effects of a high Lp(a) level to date is through sufficient reduction of traditional cardiovascular risk factor (CVRF) burden. However, there are still uncertainties whether Lp(a)-related CV risk might differ between lower- and higher-risk individuals in the primary prevention setting. Therefore, the aim of the present analysis was to investigate whether the presence of classical CVRFs at baseline might affect the association between increased Lp(a) values and incident coronary heart disease (CHD) among subjects from the general population, who were free of CHD at time of enrollment.

- The study population, comprising 66 495 subjects from eight population-based cohorts, participating in the BiomarCaRE consortium was stratified for this analysis according to CVRF burden at baseline in '0/1 CVRF' (low risk; *n* = 41 770) and '≥2 CVRFs' (increased risk; *n* = 24 725).
- Increased Lp(a) concentrations (i.e. being ≥ 90th pctl. of Lp(a) distribution) were associated with incident CHD independently of absolute baseline risk. Similar risk estimates have been found in individuals at very low absolute risk, having no or only one CVRF at baseline and those at elevated absolute risk with two or more traditional modifiable CVRFs.
- Our findings not only highlight substantial challenges in mitigating Lp(a)-associated CHD risk in very low risk populations but also underscore the unmet need for upcoming Lp(a)-targeting compounds in the primary prevention setting.

Graphical Abstract



Keywords Lipoprotein (a) • Traditional modifiable risk factors • Incident coronary heart disease • Primary prevention • General population

Introduction

During the last decades, a large body of evidence has revealed an emerging role for elevated lipoprotein (a) (Lp(a)) in the development of atherosclerotic cardiovascular disease (ASCVD).[1–7] Being an LDL-like particle with potent pro-inflammatory properties, Lp(a) in contrast to other lipoproteins is mostly genetically determined. Although genetic data support Lp(a) as an independent and probably causal risk factor for ASCVD,[1] the final proof has yet to come from the currently ongoing phase III cardiovascular outcome trials (CVOT) (HORIZON (NCT04023552), OCEAN(a) (NCT05581303), and ACCLAIM-Lp(a) (NCT06292013)), which will tell us whether Lp(a) lowering may indeed provide additional cardiovascular benefit.

Until then, the only way to mitigate Lp(a)-mediated risk of ASCVD is a tighter control of traditional modifiable cardiovascular risk factors (CVRFs). Due to a strong genetic background, Lp(a) levels are hardly influenced by CVRFs.[8] Nonetheless, there is evidence that intensive CVRFs modification decreases the absolute CVD risk in subjects with high Lp(a) values.[9] Recent data from the UK Biobank showed a significant variation in estimated lifetime CVD risk in those with similarly high Lp(a) values but different baseline absolute risk.[1,10] Therefore, the latest European Atherosclerosis Society (EAS) Lp(a) consensus statement[1] recommends that Lp(a) elevation should be interpreted only in the context of a person's total absolute ASCVD risk, which is mostly derived from traditional risk factors such as age, sex, elevated blood cholesterol, high blood pressure, smoking, diabetes, a positive family history of ASCVD and BMI.

Although it is known that in Lp(a) hyperlipidemic individuals, improvement in the overall CVRF profile results in a significant CV risk reduction, there are still uncertainties regarding how to deal with subjects with high Lp(a) but very low absolute ASCVD risk, having e.g. no or only one major modifiable CVRF. The most important question that remains in this context is whether individuals at very low risk based on traditional CVRFs possess the same relative Lp(a)-related ASCVD risk as individuals with elevated Lp(a) concentrations and higher absolute risk.

Therefore, the aim of the present analysis was to investigate whether the presence of classical CVRFs at baseline might affect the association between increased Lp(a) values and incident CHD among subjects from the general population, who were CHD-free at time of enrollment.

Material and methods

Study overview

The present analysis was conducted within the collaborative BiomarCaRE project (Biomarker for Cardiovascular Risk assessment across Europe), which has the primary aim to determine the value of established and emerging biomarkers for improved CVD risk prediction. The design and rationale of the BiomarCaRE consortium have been published previously.[11] The study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki. All participating cohort studies had received approval by the responsible local ethical review boards. Written informed consent was obtained from each subject upon entry into the study.

Study population and outcome

Detailed cohort descriptions, including enrollment and follow-up procedures are provided elsewhere.[12] For the present analysis only subjects who were free of clinically diagnosed CHD at baseline were included. After exclusion of missing variables, the final study sample comprised 66 495 subjects, from eight population-based cohorts, enrolled between 1984 and 2010 (age-range 25–74 years; 48.9% males): Northern Sweden MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) ($n = 8726$), FINRISK ($n = 5836$), DAN-MONICA ($n = 7374$), SHHEC (Scottish Heart Health Extended Cohort) ($n = 12\,582$), MONICA/KORA Augsburg (Cooperative Health Research in the Region of Augsburg) ($n = 7158$), MATISS (Malattie ATerosclerotiche Istituto Superiore di Sanità) cohort ($n = 1548$), MONICA Brianza ($n = 4257$), Moli-Sani ($n = 21\,479$), and MONICA Catalonia ($n = 4909$). Due to significant variations in Lp(a) levels between DAN-MONICA surveys compared with the remaining BiomarCARE cohorts, this cohort was not included in this analysis.

All study participants were followed-up prospectively for 2.5–26 years for the occurrence of CHD events, defined as fatal or non-fatal (definite or possible) myocardial infarction (MI), coronary death, unstable angina pectoris or coronary revascularization (the last two were not available for MONICA/KORA Augsburg)), and unclassifiable death (i.e. death with insufficient evidence of coronary origin and no competing cause). Most centers clinically validated the events using MONICA diagnostic criteria. The description of MORGAM Cohorts provides further information on endpoint classifications.[13]

Data collection and risk factor definition

For detailed information on data collection and risk factor definition please see the online data supplement. The entire population was stratified in accordance with the CVRF burden at baseline into two groups: 'no CVRFs' (i.e. absence of all four major modifiable CVRF: arterial hypertension, diabetes mellitus, hypercholesterolemia and active smoking)[14] or 1 CVRFs at baseline and ≥2 CVRFs. Arterial hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥90 mmHg, documented history of hypertension or the use of antihypertensive medication. Hypercholesterolemia was defined as a medical history of hyperlipidemia, use of lipid-lowering medication, or laboratory values of total cholesterol (TC) ≥ 5.5 mmol/L (≥210 mg/dL) or low-density lipoprotein cholesterol (LDL-C) ≥ 3.5 mmol/L (≥135 mg/dL). Diabetes mellitus was defined as a clinically documented or self-reported history of diabetes or the use of glucose-lowering medications and smoking as 'daily smoking'.

Laboratory measurements

Baseline Lp(a) mass was determined in locally stored frozen blood samples and analyzed in the BiomarCaRE central laboratory in either Mainz (until 2011) or Hamburg (since 2011), Germany. Lp(a) measurement was performed by a fully automated, particle-enhanced turbidimetric immunoassay (Biokit Quantia Lp(a)-Test; Abbott Diagnostics, USA)

as reported previously.[12] The limit of detection was 0.38 mg/dL with a measurement range of 1.3–90 mg/dL. All Lp(a) values, exceeding 90 mg/dL were set at 90 mg/dL. The cohort-specific intra- and interassay coefficients of variation for Lp(a) are provided in Supplementary material online, *Table S1*.

Statistical analysis

Baseline characteristics of the study participants are reported in a descriptive way and shown as frequencies (percentage) for binary variables and as medians with their 25th and 75th percentiles for continuous variables.

The median follow-up times and event rates were estimated by the Kaplan-Meier potential follow-up estimator.[15] Event rates were calculated for the complete follow-up time. Due to competing risk, age-adjusted cumulative incidence curves for future CHD are shown for the entire population, as well as after stratification into low-to-moderate or high Lp(a) values using the cohort-specific 90th percentile as cut-offs (<90th pctl. ($n = 59\,830$) vs. ≥90th pctl. ($n = 6665$)). The mean 90th pctl. was found to be 43.2 mg/dL.

To assess a possible impact of CVRFs on Lp(a)-associated risk for CHD events, Fine and Gray models were calculated accounting for competing risk of death from a non-CHD cause, stratified by study cohort. An interaction term between Lp(a) and the CVRF groups was used in the regression models. For the present analysis, Lp(a) was first added in the regression analysis as a continuous variable per one standard deviation (SD) increase (cubic root transformed, SD = 0.84), as well as after stratification into low-to-moderate or high Lp(a) values using the cohort-specific 90th percentile as cut-offs. Several levels of adjustments were performed. Model 1 was adjusted for age, sex and fasting status. Model 2 was additionally adjusted for systolic blood pressure, diabetes mellitus, BMI, daily smoking and model 3 was additionally adjusted for family history of CHD. The results are presented as subdistribution Hazard Ratios (sHRs) with their 95% confidence interval (95% CI). Finally, events per 1000 person-years were calculated for all above mentioned models.

R version 4.2.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

Results

Overall, 66 495 individuals from 8 European prospective population-based cohorts (median age 49.5 years.; 51.1% females), who were free of clinically diagnosed CHD at the time of enrollment were included in the present analysis. At baseline, 41 770 study participants did not demonstrate any major modifiable CVRFs or had only one of them ($n = 15\,310$ participants without CVRFs and $n = 26\,460$ participants with one CVRF), whereas 24 725 individuals had two or more CVRFs at baseline. *Table 1* describes the baseline demographic, clinical and biochemical characteristics of the entire population, as well as stratified by CVRF burden (0–1 CVRF or ≥2 CVRFs). Individuals with no or one CVRF at baseline were younger than individuals with ≥2 CVRFs (median age 46.2 (0–1 CVRF) vs. 54.5 years. (≥2 CVRFs)), were predominantly female (54.3% and 45.7%) and reported higher levels of education (*Table 1*).

The concentrations of total cholesterol, non-HDL-C and LDL-C increased proportionally to the numbers of CVRFs (*Table 1*). A similar trend was observed for Lp(a) mass with a median Lp(a) of 8.5 (4.0–

Table 1 Baseline demographic, clinical and laboratory characteristics of the study participants

	All ($N = 66\,495$)	0–1 CVRF ($N = 41\,770$)	≥ 2 CVRFs ($N = 24\,725$)
Survey year	1984–2010	1984–2010	1984–2010
Examination age, years	49.5 (40.9–58.5)	46.2 (38.4–55.6)	54.5 (46.3–61.9)
Male %	48.9	45.7	54.3
Systolic blood pressure, mmHg	130.5 (118.5–145.0)	124.5 (115.0–135.0)	144.0 (130.0–157.0)
Body mass index, kg/m^2	26.2 (23.6–29.3)	25.6 (23.0–28.6)	27.2 (24.6–30.4)
Waist circumference, cm	91.0 (81.5–99.0)	88.0 (79.0–97.0)	95.0 (87.0–102.5)
Average daily alcohol consumption, g	5.0 (0–21.0)	5.0 (0–17.0)	6.0 (0–25.0)
Highest level of education: university, %	11.1	13.3	7.3
Highest level of education: intermediate, %	13.4	15.8	9.3
Highest level of education: secondary, %	36.2	35.0	38.3
Highest level of education: primary, %	39.3	35.8	45.1
Daily smoker, %	26.0	13.7	46.8
Arterial hypertension, %	39.9	19.3	74.7
Diabetes mellitus, %	3.8	0.7	9.00
Hypercholesterolemia, %	51.4	29.7	88.1
Family history of CHD, %	17.4	15.5	20.6
Use of lipid lowering medication, %	3.8	0.9	9.0
Use of antihypertensive drugs, %	13.8	6.9	25.4
Total cholesterol, mmol/L	5.6 (4.9–6.5)	5.2 (4.7–5.9)	6.3 (5.7–7.0)
Non-HDL cholesterol, mmol/L	4.2 (3.5–5.0)	3.8 (3.2–4.4)	4.9 (4.3–5.6)
LDL cholesterol, mmol/L	3.5 (2.9–4.2)	3.1 (2.6–3.6)	4.1 (3.6–4.7)
Lipoprotein(a), mg/dL	9.2 (4.2–20.5)	8.5 (4.0–18.7)	10.6 (4.7–23.5)

Data are presented as median with their interquartile range for continuous variables. Categorical variables are reported as percentages.
CVRFs, cardiovascular risk factors.

18.7) mg/dL in those with no or with only one of the four major CVRFs at baseline vs. 10.6 (4.7–23.5) mg/dL in subjects with at least two CVRFs. For the baseline characteristics of each individual cohort please see Supplementary material online (see Supplementary material online, *Table S2*).

During a median follow up of 9.7 years (95% CI 9.5–9.7), 3467 CHD events occurred (event rate 17.2%); 1191 events (event rate 9.7%) were recorded among those with no or one CVRF (177 events in individuals with no CVRFs at baseline (event rate 4.9%) and 1014 CHD events in individuals with one CVRF (event rate 12.3%) and 2276 events in those with two or more CVRFs at baseline (event rate 29.4%). *Figure 1* represents cumulative incidence curves for CHD, stratified by CVRF burden at baseline in the entire population (*Figure 1A*), as well as after stratification of participants according to their Lp(a) level (i.e. ≥ 90th pctl. vs. <90th pctl. of Lp(a) distribution) (*Figure 1B*).

Next we investigated the impact of absolute baseline risk, as reflected by the numbers of modifiable CVRFs, on the association between Lp(a) mass and incident CHD. Using regression analysis with different levels of adjustment, we found that in individuals who were at very low absolute risk due to the presence of no or only one of the four major modifiable CVRFs, the association between increased Lp(a) values (i.e. ≥ 90th pctl. vs. <90th pctl. of Lp(a) distribution) with outcome was similar to the association found among individuals with higher baseline risk (i.e. those having ≥2 CVRFs at baseline). The corresponding fully adjusted sHRs (95% CI) were 1.38 (1.12–1.71) ($P = 0.0025$) for those with no or only one CVRF at baseline and 1.27 (95% CI 1.10–1.46) ($P = 0.0011$) for those with two or more CVRFs (P for interaction between two CVRF categories = 0.50) (*Table 2*).

A similar pattern of association was found for Lp(a) as a continuous variable. For example, in the fully adjusted model, sHRs for Lp(a) per one SD increase of the cubic root transformed value were 1.16 (1.08–1.24) ($P < 0.001$) for no or one CVRF vs. 1.13 (1.08–1.18) ($P < 0.001$) for those with two or more CVRFs at baseline (P for interaction 0.51) (*Table 2*).

Incidence rates per 1000 person-years according to CVRF burden at baseline and after categorization for Lp(a) values are presentend in *Table 2*.

Discussion

Although the efficacy of specific Lp(a)-lowering therapies is currently under investigation in several CV outcome trials,[10,16] the only possibility to mitigate the deleterious effects of a high Lp(a) level to date is through sufficient reduction of traditional modifiable CVRF burden. Indeed, the latest EAS Lp(a) consensus statement recommended that in the presence of Lp(a) hyperlipidemia, other risk factors should be treated not only more aggressively but also as early as possible.[1] Our current findings provide additional evidence in this context. In the present analysis, conducted in the general population among individuals free of prevalent CHD at the time of enrollment, it could be demonstrated that increased Lp(a) concentrations (i.e. being ≥ 90th pctl. of Lp(a) distribution) were associated with incident CHD independently of absolute baseline risk. The main finding of the present analysis was that Lp(a)-related relative risk of future CHD was similar between individuals at very low absolute risk, having no or only one CVRF at baseline and those at elevated absolute risk with two or more traditional modifiable CVRFs.

To date, there is sufficient evidence to support the assumption, that ASCVD risk related to high Lp(a) needs to be interpreted in the context of other CVRFs/overall CVD risk, rather than according to Lp(a) levels

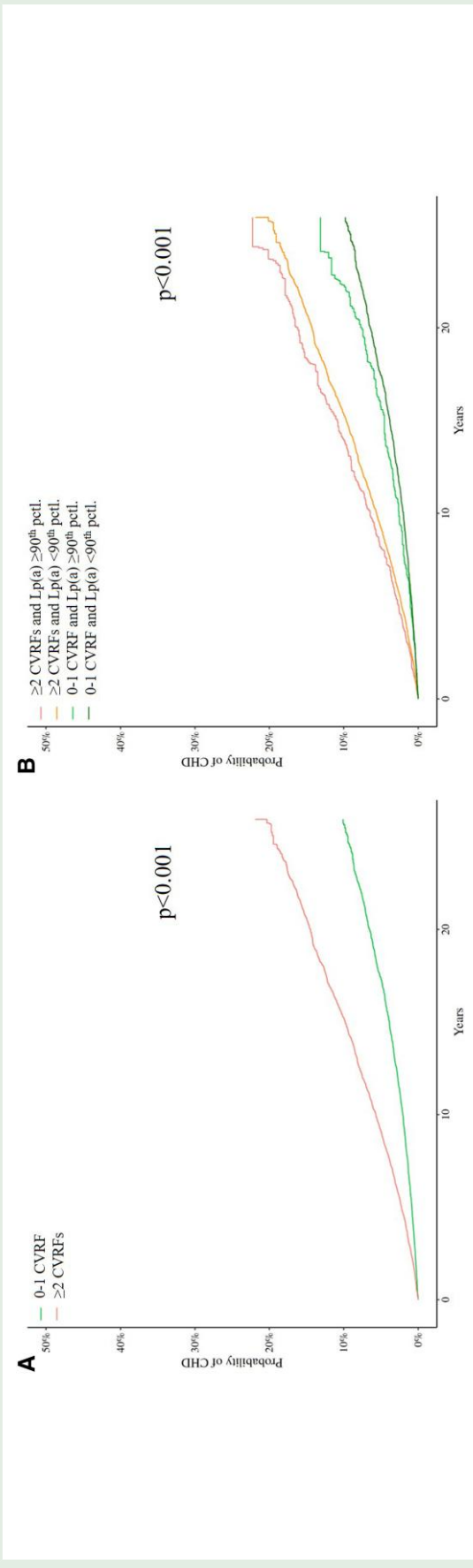


Figure 1 Cumulative incidence curves for CHD. (*A*) Entire population; (*B*) After stratification by Lp(a) values. Data from 66 495 individuals from eight European prospective population-based cohorts were analysed. During a median follow up of 9.7 years 3467 CHD events occurred (1191 events in 0/1 CVRF group; 2 276 events in ≥ 2 CVRFs group). Lp(a), lipoprotein (a); CVRF, cardiovascular risk factors; CHD, coronary heart disease; pctl., percentile.

Table 2 Association between lipoprotein (a) and risk of incident CHD in accordance with the presence of traditional cardiovascular risk factors

		0–1 CVRF				≥ 2 CVRFs				P_{inter}*	0–1 CVRF	≥ 2 CVRFs
		$N_{overall}$	N_{events}	sHR (95% CI)	*P*-value	$N_{overall}$	N_{events}	sHR (95% CI)	*P*-value		Events/1000 person-years	
Cut-off Analysis												
Model 1	< 90th pctl.	33 291	882	1.0 [REF.]		19 781	1707	1.0 [REF.]			2.4 (2.2–2.5)	8.2 (7.8–8.6)
	≥ 90th pctl.	3304	119	1.42 (1.18–1.71)	<0.001	2628	254	1.21 (1.07–1.39)	0.0037	0.17	3.2 (2.7–3.9)	9.2 (8.1–10.3)
Model 2	< 90th pctl.	33 206	877	1.0 [REF.]		19 724	1703	1.0 [REF.]			2.4 (2.2–2.5)	8.2 (7.8–8.6)
	≥ 90th pctl.	3292	118	1.47 (1.22–1.78)	<0.001	2619	254	1.27 (1.11–1.45)	<0.001	0.20	3.2 (2.7–3.8)	9.2 (8.1–10.4)
Model 3	< 90th pctl.	25 835	743	1.0 [REF.]		15 224	1450	1.0 [REF.]			2.4 (2.3–2.6)	8.4 (7.9–8.8)
	≥ 90th pctl.	2565	94	1.38 (1.12–1.71)	0.0025	2022	220	1.27 (1.10–1.46)	0.0011	0.50	3.1 (2.5–3.8)	9.6 (8.4–10.9)
Per SD increase												
Model 1		36 595	1001	1.15 (1.09–1.23)	<0.001	22 409	1961	1.11 (1.06–1.16)	<0.001	0.30	2.4 (2.3–2.6)	8.3 (7.9–8.7)
Model 2		36 498	995	1.17 (1.10–1.24)	<0.001	22 343	1957	1.13 (1.09–1.18)	<0.001	0.42	2.4 (2.3–2.6)	8.3 (7.9–8.7)
Model 3		28 400	837	1.16 (1.08–1.24)	<0.001	17 246	1670	1.13 (1.08–1.18)	<0.001	0.51	2.5 (2.3–2.7)	8.5 (8.1–8.9)

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). *P_{inter} = *P* for interaction across CVRF categories.
90th percentile of Lp(a) is 43.2 mg/dL (cohort-specific). Cubic root transformed Lp(a)1 SD = 0.84.
Model 1: Adjusted for examination age, fasting status and male sex.
Model 2: Additionally adjusted for systolic blood pressure, diabetes mellitus, BMI, daily smoking.
Model 3: Additionally adjusted for family history of CHD.
CHD, coronary heart disease; CVRF, cardiovascular risk factors; pctl., percentile; SD, standard deviation.

alone.[1,9,17,18] The concept of a sufficient reduction of traditional CVRF burden to decrease Lp(a)-associated risk came initially from the EPIC-Norfolk study[9] and was subsequently confirmed by several additional investigations.[17,19] So, the EPIC-Norfolk study, including 14 051 participants, prospectively followed for 11.5 years[9] revealed that subjects with increased Lp(a) levels (≥50 mg/dL) but with a favorable CVD health profile had a two-thirds lower relative risk of an ASCVD event (HR (95% CI) 0.33 (0.17–0.63); $P = 0.001$) compared with participants with similar Lp(a) elevations and an unhealthy lifestyle (e.g. smoking, obesity, diabetes, hypertension, high cholesterol, physical inactivity and poor diet). Furthermore, the contribution of Lp(a) to the overall risk was also demonstrated within the UK Biobank (UKBB) in individuals without baseline ASCVD.[1] Dividing the UKBB population of 415 274 participants of European ancestry in accordance with their baseline estimated lifetime risk (using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm) into low, i.e. 5% baseline risk (reflecting no or a low number of traditional CVRFs), intermediate (i.e. 15% risk with a medium number of CVRFs) and high risk (i.e. 25% with a high number of modifiable CVRFs), the authors showed that subjects with low baseline risk, but increased Lp(a) mass (50 or150 mg/dL) still have a lower baseline estimated lifetime risk than subjects with normal Lp(a) but increased baseline risk (i.e. by having more CVRFs).[1]

Aiming to evaluate Lp(a)-related risk of future CHD depending on baseline risk, we chose a simplified strategy of absolute risk assessment based on the numbers of four traditional CVRFs at the time of enrollment as an easy and more practical solution for routine clinical assessment. However, our results may raise more questions than answers. Although representing a straightforward analysis, our finding that an increased Lp(a) level was significantly associated with incident CHD even among individuals with no or only one CVRF might have important clinical implications. While we still lack therapeutic options for high Lp(a), targeting modifiable CVRFs would definitely lower CHD risk, as shown by the EPIC-Norfolk and other studies.[9,17,19] But how should one mitigate Lp(a)-related risk in those who are already at very low risk, especially in individuals without any of the four traditional modifiable CVRFs, if the only way to do it (i.e. reduction of CVRFs) is not applicable? We also should keep in mind that after their approval, forthcoming Lp(a)-targeted drugs will be initially used only in a secondary prevention setting, due to lack of randomized clinical trials in primary prevention to date. So, perhaps for years to come, the reduction of overall CV risk would remain 'the only' option to mitigate the risk in Lp(a)-hyperlipidemic individuals. This strategy would only concern those at increased absolute CVD risk, leaving individuals at very low risk, who, however, posess the same Lp(a)-related relative risk, untreated. Thus, our current data underscore the importance of upcoming Lp(a)-targeting therapy for the primary prevention setting if current ongoing trials in patients with manifest ASCVD are promising.

Another central question, which unfortunately remains unanswered by the present analysis due to lack of statistical power is whether we would see any differences in the association between elevated Lp(a) and incident CHD between individuals without any of the four major CVRFs (i.e. CVRF-less subjects) and individuals with only one traditional risk factor. Due to the extremely low number of events in the healthiest group of study participants, we could not conduct such analysis and decided to combine both very low risk groups (i.e. 0 and 1 CVRF). Interestingly, the preliminary results from the UKBB Study, presented recently, revealed that among individuals from the general population without standard modifiable risk factors, elevated Lp(a) was an independent predictor for CHD, but not for stroke, all-cause mortality or major adverse cardiovascular events. The corresponding HR (95% CI) for developing CHD was 2.2 (1.1–4.4) ($P = 0.021$) in those with Lp(a) > 150 nmol/L and 1.8 (1.1–3.1) ($P = 0.028$) in those with Lp(a) > 120 nmol/L.[20]

We believe that the results of the present analysis should also raise awareness in the research community that even in individuals at very low absolute CV risk, increased Lp(a) levels still represent an important risk factor for adverse outcomes, which however might be potentially modifiable.

Several limitations of our study merit consideration. The present data may not be extrapolated to other ethnic populations or age groups, since only populations from Europe were included in this analysis. A further shortcoming of this analysis is that risk has been only assessed at a single point in time and we were unable to follow the trajectory of risk. More specifically, no data were available on physical activity, dietary modifications, adoption of new medications or on how well controlled traditional risk factors were in this particular population. Furthermore, Lp(a) was only assessed at baseline and we had no data on serial Lp(a) measurements. However, unlike LDL, most of the current guidelines/statements[1–3] recommend that for risk assessment, Lp(a) should be measured at least once in a life-time. Moreover, one recent investigation revealed that Lp(a) levels were generally stable over time.[21] Finally, Lp(a) was assessed in mass units (mg/dL), whereas Lp(a) measurement in molar terms is more desirable due to existing complexity related to apo(a) particle heterogeneity.[22]

The current study has also several strengths. Our analysis is based on the largest dataset so far with long-term follow-up investigating the impact of the interrelationship between CVRF and Lp(a) on CHD outcome. We used the 90th percentile of Lp(a), which was 43.2 mg/dL and thus very close to the high risk cut off of 50 mg/dL, proposed by latest EAS[1] and AHA[2] Lp(a) statements as well as by the National Lipid Association.[3] Moreover, common risk factor data collection procedures, thorough follow-up for endpoints and careful data harmonization led to a high-quality combined dataset from eight European general population-based studies. Furthermore, centralized measurements of studied biomarkers by the same assay minimizes analytical imprecision in Lp(a) measurements between individual BiomarCaRE cohorts.

In conclusion, in participants who were at very low absolute CV risk at the time of enrollment (without or only one CVRF) Lp(a)-associated relative risk for CHD seemed to be similar to that, observed among individuals with higher absolute risk, having e.g. two or more CVRFs at baseline. Our findings not only underline the fact that high Lp(a) levels influence outcomes (in our case—incident CHD) independently of absolute overall CVD risk, but they also highlight the unmet need for upcoming Lp(a)-targeting compounds in a primary prevention setting.

Supplementary material

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

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Author's contribution

N.A., A.G., C.W., W.K., V.S., F.K., K.K., H.T-.P. contributed to the conception or design of the work; N.A., A.G., B.B., J.W., C.B., F.J.B., M.M.F. P.B., G.C.,

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Data availability

The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval by the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data.

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