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CLINICAL RESEARCH
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C-reactive protein modifies lipoprotein(a)-related risk for coronary heart disease: the BiomarCaRE project

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See the editorial comment for this article 'Lipoprotein(a) association with residual risk: what has inflammation got to do with it?', by Z.M. Farukhi and S. Mora, https://doi.org/10.1093/eurheartj/ehae045.

Abstract

Background and Aims Recent investigations have suggested an interdependence of lipoprotein(a) [Lp(a)]-related risk for cardiovascular disease with background inflammatory burden. The aim the present analysis was to investigate whether high-sensitive C-reactive protein (hsCRP) modulates the association between Lp(a) and coronary heart disease (CHD) in the general population.

Methods Data from 71 678 participants from 8 European prospective population-based cohort studies were used (65 661 without/6017 with established CHD at baseline; median follow-up 9.8/13.8 years, respectively). Fine and Gray competing risk-adjusted models were calculated according to accompanying hsCRP concentration (<2 and ≥2 mg/L).

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Results Among CHD-free individuals, increased Lp(a) levels were associated with incident CHD irrespective of hsCRP concentration: fully adjusted sub-distribution hazard ratios [sHRs (95% confidence interval)] for the highest vs. lowest fifth of Lp(a) distribution were 1.45 (1.23–1.72) and 1.48 (1.23–1.78) for a hsCRP group of <2 and ≥2 mg/L, respectively, with no interaction found between these two biomarkers on CHD risk ($P_{interaction} = 0.82$). In those with established CHD, similar associations were seen only among individuals with hsCRP ≥ 2 mg/L [1.34 (1.03–1.76)], whereas among participants with a hsCRP concentration <2 mg/L, there was no clear association between Lp(a) and future CHD events [1.29 (0.98–1.71)] (highest vs. lowest fifth, fully adjusted models; $P_{interaction} = 0.024$).

Conclusions While among CHD-free individuals Lp(a) was significantly associated with incident CHD regardless of hsCRP, in participants with CHD at baseline, Lp(a) was related to recurrent CHD events only in those with residual inflammatory risk. These findings might guide adequate selection of high-risk patients for forthcoming Lp(a)-targeting compounds.

Structured Graphical Abstract

Key Question

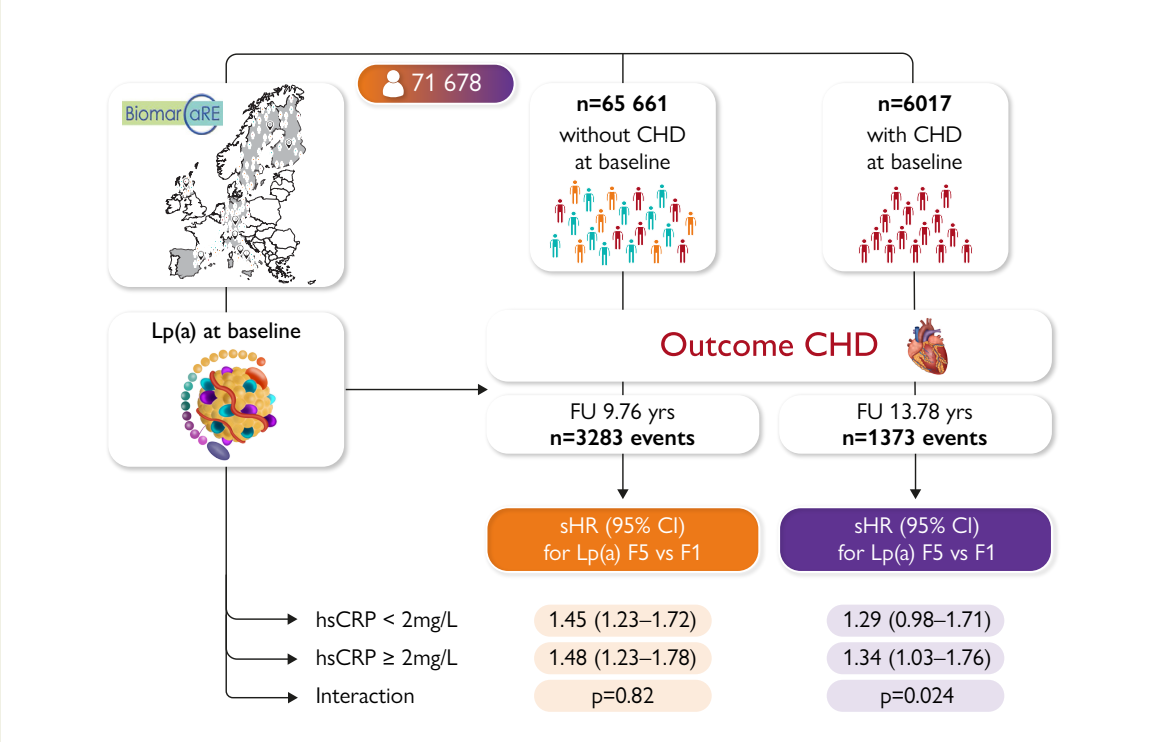
Can high-sensitive C-reactive protein (hsCRP) modulate the association between lipoprotein(a) [Lp(a)] and coronary heart disease (CHD)?

Key Finding

While among CHD-free individuals Lp(a) was significantly associated with incident CHD regardless of hsCRP, in participants with CHD at baseline, Lp(a) was related to recurrent CHD events only in those with residual inflammatory risk.

Take Home Message

These findings might guide adequate selection of high risk patients for forthcoming Lp(a)-targeting trials.



C-reactive protein as a possible modifier of lipoprotein(a)-related risk for coronary heart disease in Europe. CHD, coronary heart disease; CI, confidence interval; Lp(a), lipoprotein(a); FU, follow-up; F, fifth; hsCRP, high-sensitive C-reactive protein; sHR, sub-distribution hazard ratio.

Keywords High-sensitive C-reactive protein • Lipoprotein(a) • General population • Coronary heart disease • Epidemiology

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is recognized as a consequence of a tight interplay between lipoproteins and inflammatory processes within the arterial wall.[1,2] Oxidized lipids, due to a variety of biological actions, might trigger the local inflammatory processes within the atherosclerotic plaque.[1,2] Activation of the NLRP3 [nucleotide oligomerization domain (NOD)], leucine-rich repeat (LRR)-containing, and pyrin domain (PYD)-containing protein 3] inflammasome has been suggested as a possible underlying mechanism linking lipoproteins to vascular inflammation.[3,4] On the other hand, inflammation per se might be an important trigger or regulator of hepatic lipid metabolism, thus supporting the concept of a bidirectional relationship between cholesterol and inflammatory pathways. In addition, we have solid trial evidence that the combination of both inflammatory and lipid parameters improves our ability to predict future ASCVD events.[5]

Among the 'conventional' lipid parameters, lipoprotein(a) [Lp(a)] is very distinguishable, having a variety of unique features.[6] Being an important risk factor for ASCVD and aortic valve stenosis, Lp(a) represents a proatherogenic lipoprotein with a profound genetic background[7] which is only marginally influenced by lifestyle. It also possesses a strong pro-inflammatory potential, having higher inflammatory potency on an equimolar basis than e.g. low-density lipoproteins (LDL).[8] Such pro-inflammatory effects of Lp(a), most probably determining its atherogenicity, might be mainly attributable to an enrichment in oxidized phospholipids (oxPLs),[9] which, inter alia, might enhance cytokine expression and release, as well as increased monocyte chemotaxis.

Two recent studies in primary and secondary prevention settings[10,11] suggest that the inflammatory burden mediates the prognostic capacity of Lp(a), showing that elevated Lp(a) associates with future ASCVD risk only in individuals with residual inflammatory risk [i.e. high-sensitive C-reactive protein (hsCRP) levels >2 mg/L]. However, these results[10,11] have been either based on post-hoc analysis in a highly selected study population with very high cardiovascular disease (CVD) risk, including established ASCVD,[10] or conducted within a multi-ethnic population with significant variation in Lp(a) levels and relatively low number of CVD events.[11] In contrast, data from a community-dwelling population, including 68 090 participants of the Copenhagen General Population Study (CGPS), revealed that Lp(a) was associated with future risk of ASCVD independently of hsCRP concentration.[12]

In general, an interdependence of Lp(a) with systemic inflammation could have important clinical implications concerning the proper selection of a target population, which would benefit mostly from an ASCVD risk reduction through pharmacologic Lp(a)-lowering. However, discrepant findings on Lp(a)–hsCRP interaction for future ASCVD risk,[10–12] which might be, at least partially, reflected by the different baseline risks between studied populations, underscore the need for additional data.

Therefore, the aim of the present analysis was to investigate (i) whether the association between Lp(a) and risk of coronary heart disease (CHD) might be modulated by accompanying systemic low-grade inflammation among individuals from the general population across Europe and (ii) whether such interplay might depend on the presence or absence of CHD at baseline.

Material and methods

Study overview

The present analysis was conducted within the collaborative Biomarker for Cardiovascular Risk assessment across Europe (BiomarCaRE project; http://www.biomarcare.eu), 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.[13] Briefly, BiomarCaRE is an EU-funded initiative based on the MONICA Risk, Genetics, Archiving and Monograph (MORGAM) Project, which harmonized data from various population-based cohort studies across Europe.[14]

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. The study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Study population and outcome

A flowchart of the study population derivation is presented in *Figure 1*. In the first step, we identified 10 individual cohorts (all with harmonized endpoint and phenotypic data) with available information on hsCRP at baseline [Northern Sweden ($n = 10\,450$), FINRISK ($n = 8444$), DAN-MONICA ($n = 7582$), Scottish Heart Health Extended Cohort (SHHEC) ($n = 15\,999$), PRIME/Belfast ($n = 2745$), MONICA/KORA Augsburg (Cooperative Health Research in the Region of Augsburg) ($n = 8842$), Malattie ATerosclerotiche Istituto Superiore di Sanità (MATISS) cohort ($n = 4489$), MONICA Brianza ($n = 4932$), Moli-Sani ($n = 24\,325$), MONICA Catalonia ($n = 5505$)], resulting in a total of 93 313 individuals. Detailed cohort descriptions, including enrolment and follow-up (FU) procedures, are provided elsewhere.[13,15,16] In the second step, we excluded two cohorts from the analysis due to missing data on Lp(a) (PRIME/Belfast) or an analytical issue in Lp(a) determination [DAN-MONICA, due to significant variations in Lp(a) levels between three surveys, compared with the remaining BiomarCARE cohorts]. Finally, we excluded all participants with hsCRP values >10 mg/L [$n = 3294$ (4.39%)], as these values might reflect acute inflammation or underlying pathological immune-related disease.

The final study sample comprised 71 678 individuals. All study participants were followed up prospectively for 2.5–25 years for occurrence of CHD events, defined as fatal or non-fatal (definite or possible) myocardial infarction (MI), coronary death, unstable angina pectoris, coronary revascularization, and unclassifiable death (i.e. death with insufficient evidence of coronary origin and no competing cause). Most centres clinically validated the events using MONICA diagnostic criteria. The MORGAM manual provides further information on endpoint classifications.[14]

Data collection and risk factor definition

For detailed information on data collection and risk factor definition, please see the online supplementary material. Briefly, the following harmonized variables were available for each cohort: age, sex, body mass index (BMI), systolic and diastolic blood pressure, smoking status, alcohol, educational level, medication use, information on fasting status, family history of premature CHD, and disease history/status (arterial hypertension, diabetes). Established CHD at baseline was defined either as a history of MI and/or unstable angina pectoris and/or history of coronary revascularization and/or stable angina pectoris or CHD (all self-reported or physician-diagnosed).

Laboratory measurements

Baseline hsCRP concentration and Lp(a) mass were determined from the locally frozen stored blood samples and analysed centrally in the BiomarCaRE central laboratory in either Mainz (until 2011) or

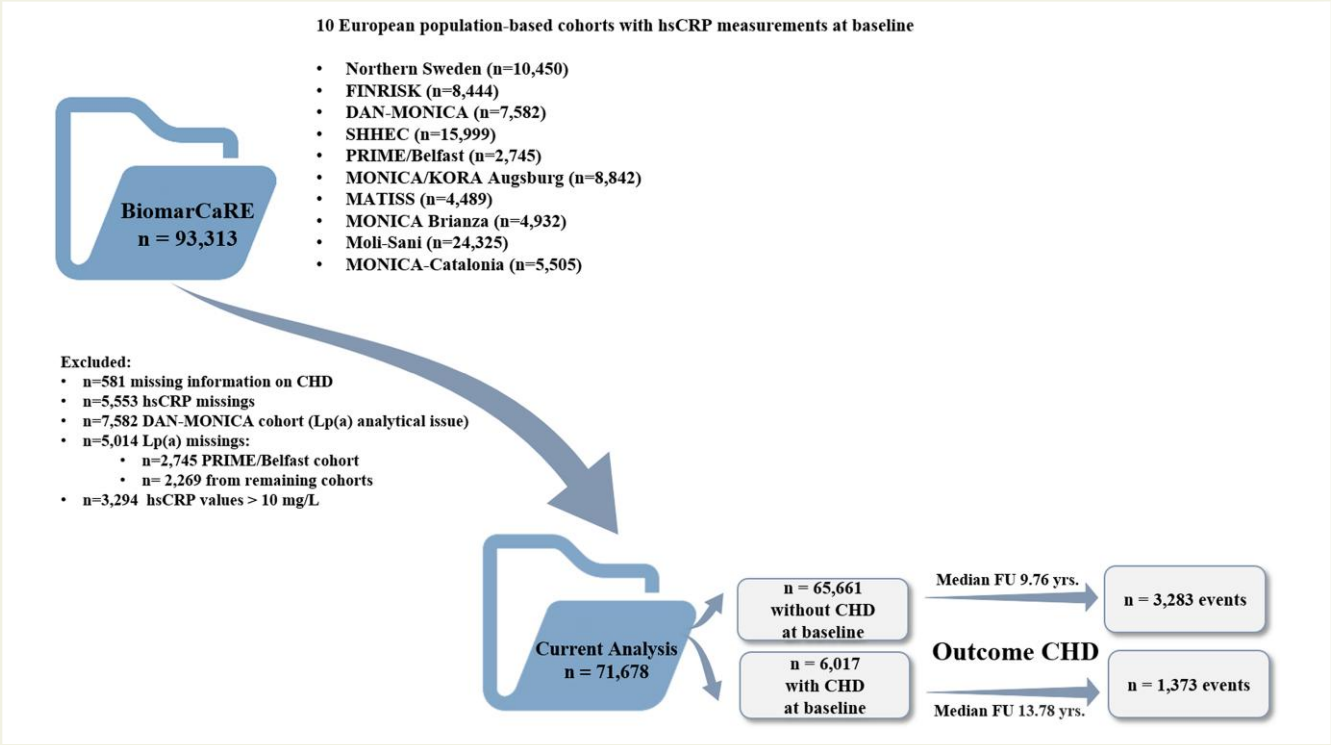


Figure 1 Flow chart of the study

Hamburg (since 2011), Germany. High-sensitive C-reactive protein was measured by latex immunoassay (Architect c8000, Abbott Labs, Rockville, MD, USA).[16] The limit of quantification for hsCRP was 0.1 mg/L. Lipoprotein(a) assessment was performed by fully automated, particle-enhanced turbidimetric immunoassay (Biokit Quantia Lp(a)-Test; Abbott Diagnostics, USA) as reported previously.[17] The limit of detection was 0.38 mg/dL with a measurement range of 1.3–90.0 mg/dL. Lipoprotein(a) values >90 mg/dL were set at 90 mg/dL. The cohort-specific intra- and interassay coefficients of variation for hsCRP and Lp(a) are provided in Supplementary data online, *Table S1*. The remaining lipid parameters [total cholesterol, high-density lipoprotein cholesterol (HDL-C) or triglycerides) were either measured locally at each participating centre by routine methods and submitted to WHO-MONICA international quality control or centrally in the BiomarCaRE central laboratory. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula without any additional hypertriglyceridaemia-related adjustments. Non–HDL-C was calculated as total cholesterol minus HDL-C.

Statistical analysis

In the present analysis, we first investigated the entire BiomarCaRE population and then divided it into a CHD-free population, including individuals without established CHD at baseline and a second group, including individuals with established CHD at baseline.

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 lower and upper quartile (interquartile range, IQR) for continuous variables.

The median FU times and event rates were estimated by the Kaplan–Meier potential FU estimator.[18] Event rates were calculated for the complete follow-up.

Lipoprotein(a) was categorized into fifths using cohort-specific quintiles (Q). The mean cut-point values for the whole population were 3.44, 6.63, 11.26, and 24.85 mg/dL, for the CHD-free population at baseline were 3.44, 6.63, 11.22, and 24.7 mg/dL, while in those with prevalent CHD the corresponding values were 3.64, 7.16, 12.66, and 28.08 mg/dL. Detailed information about the cohort-specific quintiles are shown in Supplementary data online, *Tables S3–S5*.

To assess a possible impact of hsCRP concentrations on Lp(a)-associated risk for CHD events, Fine and Gray models accounting for competing risk of death from a non-CHD cause, stratified by sex and study cohort, were calculated using individual-level data from the available cohorts. Both biomarkers were transformed prior to the analysis [hsCRP, log-transformed; Lp(a), cubic root–transformed], where needed. The data are presented as sub-distribution hazard ratios (sHRs) with their 95% confidence interval (CI).

As a first step, the models were analysed in accordance with hsCRP concentration of <2 and ≥2 mg/L for better comparability with previously published studies.[10–12] Next, we divided a hsCRP group of <2 mg/L into a hsCRP group of <1 and ≥1–<2 mg/L. For each model, several levels of adjustment were performed. Model 1 adjusted for age, and Model 2 additionally adjusted for systolic blood pressure, antihypertensive drugs, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, and highest level of education. The third (fully adjusted) model was further adjusted for lipid-lowering medication. We also performed a cubic spline regression analysis for the relationship between continuous Lp(a) and future CHD risk across the spectrum of hsCRP values [fully adjusted model (Model 3)] within the entire population and after stratification of the study population according to the presence of CHD at the time of enrolment.

We then performed an additional analysis for the association of hsCRP and Lp(a) (separately, as a sole biomarker) with future CHD

events with similar levels of adjustment. Model 1 included age, and Model 2 was additionally adjusted for systolic blood pressure, antihypertensive drugs, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, and highest level of education. Within Model 3, further adjustment for non–HDL-C (in case of hsCRP) was performed. Model 4 [or Model 3 in case of Lp(a)] was finally adjusted for lipid-lowering medication.

Because of the exploratory nature of the analysis, a significance threshold was not defined for *P*-values. R version 4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

Results

Overall, 71 678 individuals from the general population were included in the present analysis. Among them, 65 661 study participants were free of CHD at the time of enrolment (termed CHD-free cohort). The remaining 6017 participants had established CHD at baseline (CHD cohort). *Table 1* describes the baseline demographic, clinical, and biochemical characteristics of the overall population, as well as in the sub-categories of hsCRP concentration (<1; ≥1–<2, and ≥2 mg/L). In general, CHD-free individuals were slightly younger and demonstrated a more favourable risk profile than those with prevalent CHD at baseline. Considering biomarker concentrations, median Lp(a) was found to be slightly higher [9.2 mg/dL (IQR 4.2–20.4 mg/dL) vs. 8.5 mg/dL (IQR 3.6–20.1 mg/dL)] and hsCRP slightly lower [median 1.2 mg/L (IQR 0.6–2.5 mg/L) vs. 1.7 mg/L (IQR 0.8–3.4 mg/L)] among those without CHD compared with individuals with CHD at baseline. Finally, a steady increase in hsCRP concentration was associated with worsening of risk profile of participants (*Table 1*). For the baseline characteristics of each individual cohort, please see Supplementary material online (see Supplementary data online, *Tables S2–S4*).

In general, the correlation between Lp(a) and hsCRP was very low with Spearman correlation coefficients found to be 0.03 within entire population and among individuals without CHD at baseline and 0.02 among those with established CHD at baseline.

During a median FU of 9.91 (95% CI 9.86–9.95) years, overall 4656 future CHD events occurred. Among CHD-free individuals at baseline, 5.0% of them ($n = 3283$) developed an incident CHD event during a median FU of 9.76 (95% CI 9.68–9.81) years (event rate over max FU period of 25.96 years—16.8%). In the CHD cohort, 1373 events occurred over a median FU of 13.78 (95% CI 13.77–13.79) years (22.8% of cohort; event rate over the max FU period—44.42%).

If analysed separately from each other, elevated concentrations of biomarkers [Lp(a) or hsCRP] were associated with future CHD events (see Supplementary data online, *Tables S5–S7*). For instance, within the entire population as well as among those without CHD at baseline, sHRs for Lp(a) [highest vs. lowest fifth of Lp(a) distribution] were found to be 1.44 (95% 1.30–1.60) and 1.48 (95% CI 1.30–1.67) (both $P < .001$), respectively (see Supplementary data online, *Tables S5 and S6*). Within the cohort with established CHD at baseline, the fully adjusted sHRs for Lp(a) (highest vs. lowest fifth) was found to be 1.33 (95% CI 1.09–1.61; $P = .0041$) (see Supplementary data online, *Table S7*).

Similarly, an increased hsCRP concentration (≥2 vs. <1 mg/L) was associated with a 50% increased risk of incident CHD [sHR 1.50 (95% CI 1.37–1.65); $P < .001$; fully adjusted model] in entirely population and with a 41% increased risk [sHR 1.41 (95% CI 1.26–1.57); $P < .001$; fully adjusted model] in CHD-free individuals (see Supplementary data online, *Tables S5 and S6*). In those with established CHD at baseline, the corresponding sHRs were 1.43 (95% CI 1.20–1.71; $P < .001$) (for hsCRP ≥2 vs. <1 mg/L), again after multivariable adjustment for traditional cardiovascular risk factors and concomitant lipid-lowering medication use (see Supplementary data online, *Table S7*).

Next, we investigated whether baseline hsCRP concentrations might modify the association between Lp(a) levels and future CHD events. Assuming that hsCRP values ≥2 mg/L reflect a high residual inflammatory risk, as well as for better comparison with previously published data, the study population was first divided according to hsCRP concentration of <2 vs. ≥2 mg/L (*Figure 2*). Within the entire population, increased Lp(a) mass was associated with future CHD events irrespective of hsCRP concentrations at baseline, showing an sHR of 1.39 (95% CI 1.21–1.61) [highest vs. lowest fifth of the Lp(a) distribution; fully adjusted model; $P < .001$] in the group with hsCRP <2 mg/L and an sHR of 1.46 (95% CI 1.26–1.70) [highest vs. lowest fifth of Lp(a) distribution; fully adjusted model; $P < .001$] in those with a hsCRP ≥2 mg/L ($P_{interaction} = 0.62$). (*Figure 2A*; Supplementary data online, *Table S8*). Further stratification of the study population according to the absence or presence of CHD at baseline showed that in CHD-free individuals very similar results compared with the entire population were found: the magnitude of the association was almost identical between those with hsCRP concentrations <2 and ≥2 mg/L [sHR of 1.45 (95% 1.23–1.72) and of 1.48 (95% CI 1.23–1.78), respectively, for highest vs. lowest fifth of Lp(a) distribution; fully adjusted models; both $P < .001$; $P_{interaction} = 0.82$] (*Figure 2B*; Supplementary data online, *Table S9*). In contrast, in the CHD cohort, elevated Lp(a) was associated with future events among those with hsCRP concentration ≥2 mg/L [sHR 1.34 (95% CI 1.03–1.76); $P = .021$] and only borderline in those with hsCRP concentration <2 mg/L [sHR 1.29 (95% CI 0.98–1.71); $P = .071$] (both for the highest vs. lowest fifth; fully adjusted models; $P_{interaction} = 0.024$) (*Figure 2C*; Supplementary data online, Table 10). Next, we further divided the hsCRP group of <2 mg/L into those with hsCRP < 1 and ≥1–<2 mg/L. The results of such analysis are presented again for the entire population first and then after stratification according to CHD status at baseline (*Figure 3* as well as Supplementary data online, *Tables S8–S10*). Within the entire population, increased Lp(a) values were associated with future CHD events independently of accompanying hsCRP concentrations with very similar risk estimates among all three hsCRP groups. So, comparing extreme fifths of the Lp(a) distribution revealed a sHR of 1.40 [(95% CI 1.14–1.72), $P = .0011$] in these with very low hsCRP concentration of <1 mg/L and 1.36 [(95% CI 1.11–1.67), $P = .0032$] and 1.46 [(95% CI 1.25–1.70), $P < .001$] in individuals with hsCRP level of ≥1–<2 and ≥2 mg/L, respectively (fully adjusted model; $P_{interaction} = 0.93$) (*Figure 3A*; Supplementary data online, *Table S8*). Coronary heart disease–free individuals with a very low hsCRP concentration of <1 mg/L at baseline demonstrated a 56% increased risk for future CHD in the highest fifth compared with the lowest fifth of the Lp(a) distribution after multivariable adjustment [sHR 1.56 (95% CI 1.22–1.98, $P < .001$], whereas corresponding sHRs for the hsCRP group of ≥1–<2 and ≥2 mg/L were 1.32 (95% CI 1.04–1.68) ($P = .023$) and 1.47 (95% CI 1.22–1.77) ($P < .001$), respectively ($P_{interaction} = 0.89$) (*Figure 3B*; Supplementary data online, *Table S9*). Further stratification into hsCRP groups <1 and ≥1–<2 mg/L in those with established CHD at the time of enrolment, however, revealed that increased Lp(a) was associated with future coronary events in individuals having moderately elevated hsCRP concentration (≥1–<2 mg/L) [sHR 1.45 (95% CI 1.00–2.12); $P = .05$; highest vs. lowest fifth, fully adjusted model], whereas in the group with very low hsCRP of <1 mg/L, Lp(a) was not associated with future coronary events [sHR 1.14 (95% CI 0.75–1.73) highest vs. lowest fifth, fully

Table 1 Baseline demographic and clinical characteristics of the study participants

	Entire population				Subjects without CHD at baseline				Subjects with CHD at baseline			
	All	hsCRP < 1 mg/L	hsCRP ≥ 1 –<2 mg/L	hsCRP ≥ 2 mg/L	All	hsCRP < 1 mg/L	hsCRP ≥ 1 –<2 mg/L	hsCRP ≥ 2 mg/L	All	hsCRP < 1 mg/L	hsCRP ≥ 1–<2 mg/L	hsCRP ≥ 2 mg/L
n	71 678	29 339	18 164	24 175	65 661	27 531	16 596	21 534	6017	1808	1568	2641
Survey year	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010	1984–2010
Male, %	49.0	48.5	51.5	47.8	48.50	48.1	51.1	47.1	54.5	54.5	56.1	53.5
Age at baseline, years	50.4 (41.4–59.3)	46.5 (38.8–55.7)	51.7 (42.8–60.2)	54.0 (44.7–62.0)	49.5 (40.9–58.5)	46.0 (38.4–55.0)	50.9 (42.3–59.5)	53.2 (43.9–61.3)	58.6 (51.0–65.9)	56.9 (47.6–64.6)	59.0 (51.6–66.4)	59.5 (53.1–66.4)
Systolic BP, mmHg	131.0 (119.0–146.0)	126.0 (115.0–140.0)	133.0 (120.0–147.5)	137.0 (123.0–152.0)	130.5 (118.5–145.0)	126.0 (115.0–139.0)	132.0 (120.0–146.5)	136.0 (122.5–151.5)	141.0 (126.0–156.0)	137.0 (123.0–153.0)	141.0 (127.0–155.0)	143.0 (128.0–158.0)
BMI, kg/m^2	26.4 (23.7–29.4)	24.8 (22.6–27.3)	26.8 (24.4–29.5)	28.2 (25.4–31.6)	26.2 (23.6–29.2)	24.6 (22.5–27.2)	26.7 (24.3–29.4)	28.1 (25.3–31.5)	27.9 (25.2–31.1)	26.2 (23.9–29.0)	28.0 (25.5–30.9)	29.2 (26.3–32.4)
Hypertension, %	42.2	31.0	45.2	53.5	39.8	29.0	42.9	51.3	68.1	61.3	70.0	71.6
Daily smoker, %	25.2	22.6	24.8	28.8	25.6	22.9	25.3	29.2	21.7	17.7	19.2	25.9
Diabetes mellitus, %	4.3	2.9	4.2	6.1	3.7	2.5	3.5	5.3	11.2	9.1	11.3	12.5
Family history of CHD, %	42.2	31.0	45.2	53.5	17.1	16.6	17.4	17.4	33.9	33.5	31.9	35.4
Daily alcohol, g	5.0 (0–21.0)	5.0 (0–17.0)	6.0 (0–23.0)	5.0 (0–24.0)	5.0 (0–22.0)	5.0 (0–18.0)	6.0 (0–24.0)	5.0 (0–25.0)	3.0 (0–15.0)	3.0 (0–13.0)	4.0 (0–16.0)	3.0 (0–17.0)
Lipid-lowering drugs, %	3.9	3.0	4.6	4.4	2.8	2.1	3.3	3.4	15.6	17.0	18.2	13.1
Aspirin intake, %	5.3	4.1	5.7	6.6	2.7	2.1	2.9	3.4	32.6	31.8	33.7	32.6
Non–HDL-C (mmol/L)	4.2 (3.5–5.0)	4.0 (3.3–4.8)	4.3 (3.6–5.1)	4.4 (3.7–5.2)	4.2 (3.5–5.0)	4.0 (3.3–4.8)	4.3 (3.6–5.1)	4.4 (3.7–5.2)	4.5 (3.6–5.4)	4.2 (3.4–5.0)	4.5 (3.7–5.4)	4.6 (3.8–5.5)
LDL-C (mmol/L)	3.5 (2.9– 4.2)	3.4 (2.7– 4.0)	3.5 (2.9– 4.3)	3.6 (3.0– 4.3)	3.5 (2.9–4.2)	3.4 (2.7–4.0)	3.5 (2.9–4.3)	3.6 (3.0–4.3)	3.6 (2.9– 4.4)	3.4 (2.7– 4.2)	3.6 (2.9– 4.4)	3.7 (3.0– 4.5)
Lipoprotein(a) (mg/dL)	9.1 (4.2–20.3)	8.4 (3.9–19.0)	9.3 (4.3–20.1)	10.0 (4.4–21.9)	9.2 (4.2–20.4)	8.5 (3.9–19.1)	9.4 (4.3–20.3)	10.1 (4.5–21.8)	8.5 (3.6–20.1)	7.9 (3.5–18.6)	8.0 (3.5–18.8)	9.1 (3.7–22.0)
hsCRP (mg/L)	1.3 (0.6–2.6)	0.5 (0.3–0.7)	1.4 (1.2–1.7)	3.5 (2.6–5.2)	1.2 (0.6–2.5)	0.5 (0.3–0.7)	1.4 (1.2–1.7)	3.5 (2.6–5.2)	1.7 (0.8–3.4)	0.6 (0.4–0.8)	1.4 (1.2–1.7)	3.8 (2.7–5.4)

Data are presented as median with their interquartile range for continuous variables. Categorical variables are reported as frequency in percentage.
CHD, coronary heart disease; hsCRP, high-sensitive C-reactive protein; BP, blood pressure; BMI, body mass index; CV, cardiovascular; HDL, high-density lipoprotein; C, cholesterol; LDL, low-density lipoprotein.

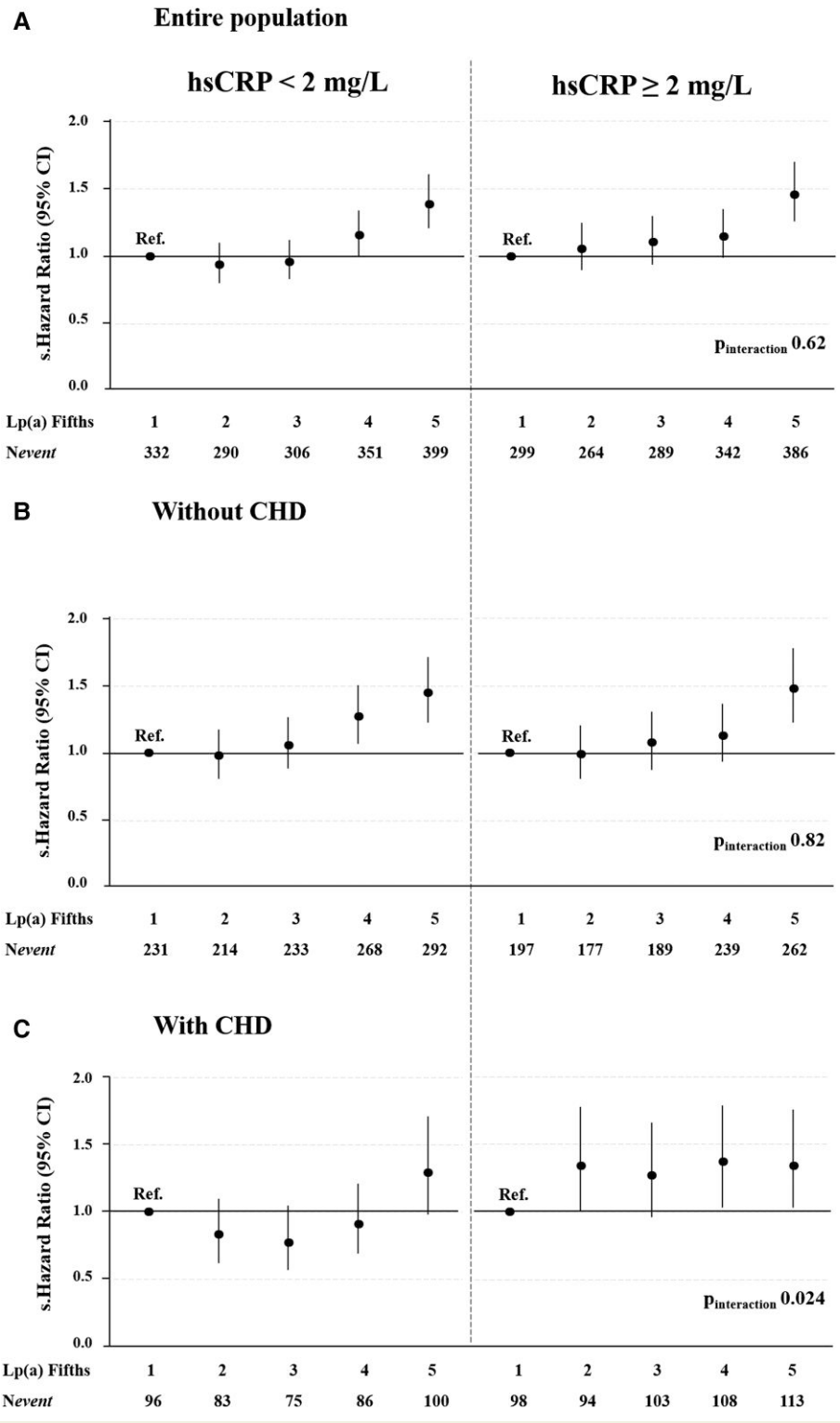


Figure 2 Risk of coronary heart disease (CHD) according to lipoprotein(a) and high-sensitive C-reactive protein (hsCRP) concentration (<2 and ≥2 mg/L). (*A*) Entire population. (*B*) In individuals without CHD at baseline. (*C*) In individuals with established CHD at baseline. Fine and Gray competing risk-adjusted models stratified by study cohort were calculated, and the data are presented as sub-distribution hazard ratios (sHRs) with their 95% CI. Biomarkers were transformed for the analysis [hsCRP, log-transformed; Lp(a), cubic root–transformed]. Fully adjusted model [adjustment for age, sex, cohort, systolic blood pressure, antihypertensive drugs, diabetes mellitus, body mass index, smoking status (daily smoker), family history of CHD, average daily alcohol consumption, highest level of education, and lipid-lowering medication]

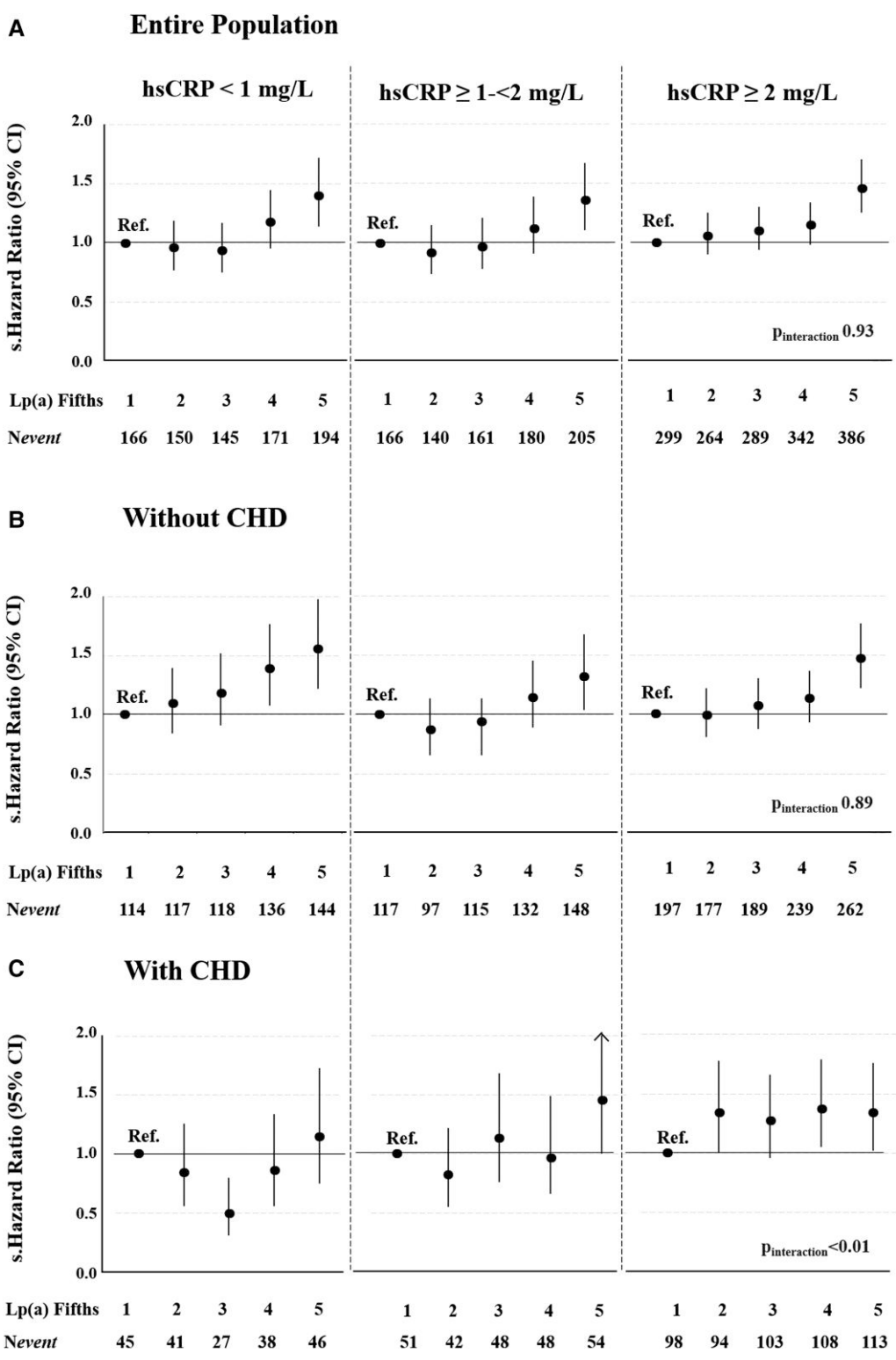


Figure 3 Risk of coronary heart disease (CHD) according to lipoprotein(a) and high-sensitive C-reactive protein (hsCRP) concentration (<1, ≥1–<2, and ≥2 mg/L). (*A*) Entire population. (*B*) In individuals without CHD at baseline. (*C*) In individuals with established CHD at baseline. Fine and Gray competing risk-adjusted models stratified by study cohort were calculated, and the data are presented as sub-distribution hazard ratios (sHRs) with their 95% CI. Biomarkers were transformed for the analysis [hsCRP, log-transformed; Lp(a), cubic root–transformed]. Fully adjusted model [adjustment for age, sex, cohort, systolic blood pressure, antihypertensive drugs, diabetes mellitus, body mass index, smoking status (daily smoker), family history of CHD, average daily alcohol consumption, highest level of education, and lipid-lowering medication]

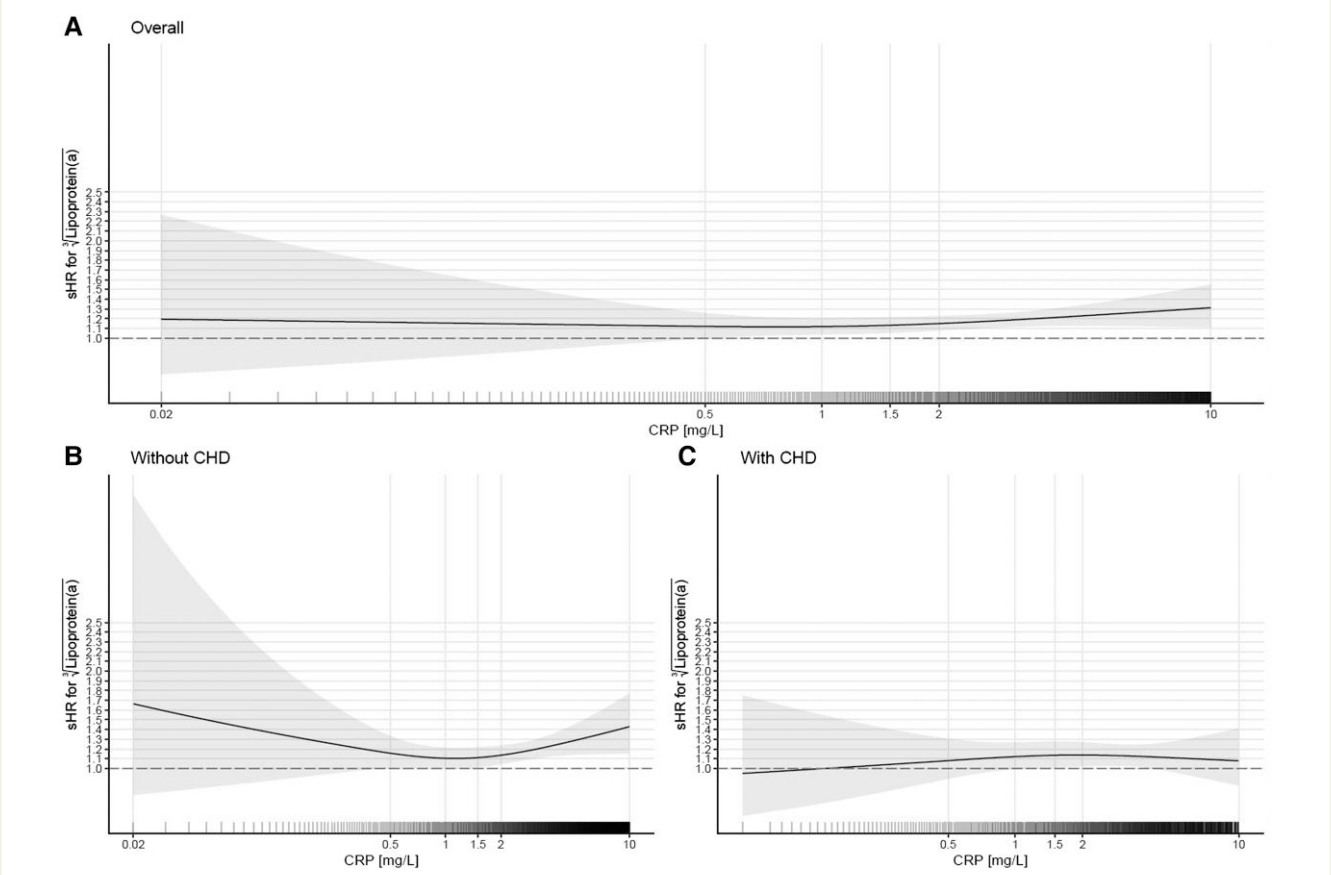


Figure 4 Cubic spline regression analysis for the relationship between continuous lipoprotein(a) and future coronary heart disease (CHD) risk across the spectrum of high-sensitive C-reactive protein (hsCRP) values. (*A*) Entire population. (*B*) In individuals without CHD at baseline. (*C*) In individuals with established CHD at baseline. Fully adjusted model [adjustment for age, sex, cohort, systolic blood pressure, antihypertensive drugs, diabetes mellitus, body mass index, smoking status (daily smoker), family history of CHD, average daily alcohol consumption, highest level of education, and lipid-lowering medication]. Per 1 unit increase of cubic root–transformed Lp(a)

adjusted model; $P = .54$; $P_{interaction} < 0.01$] (*Figure 3C*; Supplementary data online, *Table S10*).

Figure 4 shows the results of cubic spline regression analysis (fully adjusted model) for the relationship between continuous Lp(a) (per unit increase) and future CHD risk across the total spectrum of hsCRP values for all study participants (*Figure 4A*) as well after stratification of the study population according to CHD status at baseline to those without (*Figure 4B*) and with CHD (*Figure 4C*) at baseline. Interestingly, using hsCRP values as continuous traits, we observed very similar results to those obtained by using several hsCRP cut-offs. It could be shown that in CHD-free individuals, Lp(a) was associated with incident CHD across all hsCRP values and this association became even stronger with increasing hsCRP values, although the CIs at a very low hsCRP concentration were rather wide. In contrast, in individuals with manifest CHD at time of enrolment, no association between high Lp(a) and outcome was seen at extremely low hsCRP values, while the association between Lp(a) and incident CHD became meaningful only at hsCRP values of around 1 mg/L and higher.

Discussion

The present analysis of ~72 000 participants from the general population represents the largest data set so far simultaneously exploring a possible Lp(a)–hsCRP interaction for future coronary events in 2 study subgroups—in those who were free of CHD at baseline and in individuals with established CHD at the time of enrolment (*Structed Graphical Abstract*). Our major findings are that for the vast majority of study participants, hsCRP concentration does not affect the association between high Lp(a) mass and future CHD events. The only group where increased Lp(a) was not associated with outcome was the group of CHD patients with very low hsCRP levels of <1 mg/L. The results were similar if hsCRP was categorized using several cut-offs or by using it as a continuous trait. The current data, together with previously published studies, suggest that the impact of hsCRP on Lp(a)-related ASCVD/CHD risk probably might depend on the overall baseline risk.

Only a few studies so far have investigated the interdependence of Lp(a) with background hsCRP concentrations with different results.[10–12] Two studies reported very similar results, showing that higher Lp(a) levels were associated with future CVD events only in those with residual inflammatory risk (hsCRP ≥ 2 mg/L) [Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at High Risk of Vascular Outcomes[10] (ACCELERATE Trial), including 10 503 study participants at very high risk (mean FU 28 months; 714 major adverse cardiovascular events), and Multi-Ethnic Study of Atherosclerosis[11] (MESA), including 4679 individuals from the general population (mean FU 13.6 years; 684 ASCVD

events)]. In contrast to the abovementioned studies, the results from the CGPS,[12] conducted in 68 090 individuals from the general population, demonstrated similar ASCVD risk estimates for elevated Lp(a) among those with hsCRP < 2 and ≥2 mg/L over a median FU of 8.1 years ($n = 5104$ ASCVD events).

The present data on the independence of Lp(a)-related CHD risk from accompanying hsCRP concentrations among CHD-free individuals at baseline are in line with those from the CGPS, despite a much broader endpoint had been used in CGPS. However, our data are discordant with the results from MESA, potentially due to the well-known inter-racial differences in Lp(a),[19] resulting in much higher Lp(a) levels at baseline in MESA than in our populations. Moreover, the MESA cohort was older than the BiomarCARE population and had used a much broader ASCVD outcome, whereas we focused only on CHD events. Finally, the number of study participants and, more importantly, the number of achieved ASCVD endpoints was considerably lower in MESA than in the current analysis.

With regard to the interaction between Lp(a) and hsCRP, seen among patients of the CHD cohort, the present results are similar to the results from the ACCELERATE Trial, which also demonstrated no association between increased Lp(a) and CHD events in those with hsCRP concentration < 2 mg/L. However, the considerable size of our data set allowed us to extend the ACCELERATE findings, since we were able to stratify hsCRP concentrations more precisely, using an additional cut-off of 1 mg/L. More importantly, it could be shown that elevated Lp(a) mass was still associated with future coronary events even in those with hsCRP levels between 1 and 2 mg/L. Although considerable differences exist between the present study and the ACCELERATE trial attributable to population selection and design, differences in Lp(a) measurements (mass vs. molar), and possible effects of evacetrapib treatment on the studied biomarkers,[20] both investigations raise the possibility that an interaction between Lp(a) and hsCRP for ASCVD/CHD risk might be dependent on the overall baseline risk, which was much higher in participants of the ACCELERATE trial and in our study participants with CHD at baseline (both including very high-risk individuals with established ASCVD) than in CGPS or in our CHD-free participants at baseline, where Lp(a) associated risk for ASCVD/CHD was independent of the residual inflammatory risk.

Although the global burden of ASCVD has been drastically reduced within the last decades, mainly by targeting conventional risk factors and LDL-C in particular, significant residual risk remains, with low-grade inflammation being one of the strongest risk modifiers. Indeed, there is clear evidence that inhibition of an inflammatory pathway involving the NLRP3 inflammasome, in the absence of lipid lowering, results in a substantial reduction of future cardiovascular risk.[21] Furthermore, the idea that low-grade inflammation, as reflected by hsCRP levels, might affect Lp(a)-associated risk for CHD seems to be very appealing, suggesting another avenue to reduce residual risk even more successfully. Recent studies showed a solid pathophysiological background for the tight interplay between Lp(a) and systemic low-grade inflammation, where the NLRP3 inflammasome–IL-1beta/IL-6/CRP pathway might represent a mechanistic link within the Lp(a)–inflammation axis.[21] Indeed, oxPLs, which are preferentially carried on by Lp(a) in the circulation,[22] might act as danger-associated molecular patterns, thereby activating the NLRP3 inflammasome with subsequent IL-1beta/IL-6/CRP release.[21,23] So, individuals with elevated Lp(a) exhibit increased inflammatory activity in the arterial wall, as demonstrated by positron emission tomography/computed tomography.[9] Furthermore, subsequent lowering of Lp(a) by antisense oligonucleotide led to attenuation of a pro-inflammatory state of circulating monocytes on the transcriptional and functional level.[24] On the other hand, Lp(a) might also be considered as an acute phase reactant,[25] most probably due to the presence of an IL-6 response element within the *LPA* gene.[26] Further evidence for the specificity of the IL-6 pathway in regulating Lp(a) production comes from experimental studies, showing that monoclonal antibodies directed against the IL-6 receptor (e.g. tocilizumab or sarilumab) reduced Lp(a) levels by 30%–40%, whereas anti-TNF-α monoclonal antibodies (adalimumab) failed to lower Lp(a) level substantially.[27–29] More recently, the results of the RESCUE trial, investigating ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand, in a very high-risk population with hsCRP ≥ 2 mg/L, showed a dose-dependent reduction of Lp(a) from baseline of up to 25% and of hsCRP up to 92%. Interestingly, no changes in other lipid parameters were seen, thereby suggesting an important role of the IL-6 pathway for Lp(a) regulation.[30] Despite those data, the final evidence whether inflammation increases Lp(a) or Lp(a) promotes low-grade inflammation should come from randomized clinical trials or at least from Mendelian randomization studies, evaluating the Lp(a)–inflammation interdependency.

Our findings in individuals with a very low hsCRP concentration (<1 mg/L) merit particular consideration. Although in the group of CHD-free study participants with a hsCRP values <1 mg/L at baseline, Lp(a)-associated risk estimates were similar to those in the two remaining hsCRP groups, the association between Lp(a) and future coronary events among those with established CHD and very low hsCRP level (<1 mg/L) at baseline seems to be more complex. We found that individuals within the third fifth of the Lp(a) distribution revealed rather unexpectedly a reduced CHD risk compared with the first one, whereas no differences in CHD risk were observed between extreme fifths [highest vs. lowest fifth of Lp(a)] after multivariable adjustment. Interestingly, 1 recently published study, conducted among 851 consecutive MI patients, demonstrated a U-shaped relationship between Lp(a) level and overall mortality and recurrent cardiovascular events during a median FU of 19 months with even higher risk estimates in patients with very low (<7 nmol/L) Lp(a) concentrations compared with those with high Lp(a) (≥125 nmol/L).[31] Surprisingly, very low Lp(a) concentrations were also associated with higher odds of glycoprotein IIb/IIIa inhibitor use, suggesting a higher procoagulatory state in those patients. Although very intriguing, our finding on the predictive role of Lp(a) in CHD patients with very low hsCRP concentration of <1 mg/L should be interpreted with caution, because of the small number of events in each Lp(a) fifth, and needs to be replicated in larger populations. In addition, a pathophysiologic basis for such interaction has still to be established, presuming that our findings are not subject to type I error. To this end, first evidence from targeted proteomics is available suggesting the involvement of differential regulatory pathways in those with residual inflammatory risk but low baseline hsCRP in a secondary prevention setting.[32]

Several limitations of our study merit consideration. First, the present data may not be extrapolated to other ethnic populations or age groups, since only populations from Europe were included in this analysis. Second, 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.[33] However, the Lp(a) assay used in the BiomarCaRE population is not affected by apo(a) isoforms.[34] Furthermore, the studied biomarkers were measured at only one time-point and therefore the results could be subject to regression dilution bias. In addition, CHD assessment at baseline mainly relied on medical reviews or was self-reported, which might have led to misclassification. Finally, no data on IL-6 are available within

the present analysis, which probably would provide much deeper insight into the Lp(a)–inflammation axis.

The current study has also several strengths. The present analysis is based on the largest data set with long-term FU investigating Lp(a)–hsCRP interdependency so far. Moreover, similar risk factor data collection procedures, thorough FU for endpoints and careful data harmonization, led to a high-quality combined data set from eight European general population-based studies. Furthermore, centralized measurements of studied biomarkers by the same assay minimize analytical imprecision in Lp(a) measurements between individual BiomarCaRE cohorts.

In conclusion, in participants, who were free of CHD at baseline, systemic inflammation has no effect on Lp(a)-associated risk for CHD, since increased Lp(a) was robustly associated with CHD events across all hsCRP strata in the present analysis. These data, together with data from CGPS, including more than 150 000 individuals from the general population in Europe, provide clear evidence of no Lp(a)–hsCRP interaction in the primary prevention setting. In contrast, in those at very high risk (i.e. in those with prevalent CHD), the interplay of Lp(a) with inflammation seems to be more complex. A better understanding of such interaction might result in better identification and more personalized treatment of the target population who might benefit most from Lp(a)-lowering therapies. Nonetheless, various questions still need to be adequately addressed, especially in light of forthcoming Lp(a)-lowering trials, where proper criteria for patient selection might be a key element for successful Lp(a)-mediated CHD risk reduction.[35]

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors have completed the International Committee of Medical Journal Editors (ICJME) disclosure of potential conflicts of interest (COI) form at www.icmje.org/coi_disclosure.pdf and declare the following: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work. Outside the scope of the present work, N.A. reports grant and personal fees from Novartis; S.B. reports grants and personal fees from Abbott Diagnostics, Bayer, SIEMENS Healthineers, and AMGEN, grants from Singulex, consulting fees from Thermo Fisher, and personal fees from AstraZeneca, Medtronic, Pfizer, Roche, and Novartis; V.S. reports personal fees from Sanofi and grants from Bayer AG; St.S. reports grants and personal fees from Actelion Ltd; R.B.S. reports personal fees from BMS/Pfizer; C.W. reports lecture fees from AstraZeneca. W.K. reports receiving consulting fees and lecture fees from AstraZeneca, Novartis, and Amgen; consulting fees from Pfizer, The Medicines Company, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, Esperion, Genentech, OMEICOS, Novo Nordisk, LIB Therapeutics, TenSixteen Bio, New Amsterdam Pharma, and Daiichi Sankyo; lecture fees from Berlin-Chemie, Bristol-Myers Squibb, and Sanofi; and grant support and provision of reagents from Singulex, Abbott, Roche Diagnostics, and Dr Beckmann Pharma. All other authors declare no conflict of interest.

Data Availability

The data are not available in a public repository. Access to the data is dependent upon ethics approval and restricted by the legislation of the European Union and the countries providing data to the study. Furthermore, approval by the principal investigator of each cohort study and the MORGAM/ BiomarCaRE Steering Group is required to release 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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Ethical Approval

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. The study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Pre-registered Clinical Trial Number

None supplied.

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