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ORIGINAL RESEARCH

Association of Lipoprotein(a) With Major Adverse Cardiovascular Events Across hs-CRP

A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND Lipoprotein(a) [Lp(a)] is an independent risk factor for atherosclerotic cardiovascular disease. The relationship between Lp(a) and major adverse cardiovascular events (MACE) in the context of high-sensitivity C-reactive protein (hs-CRP) levels remains controversial due to conflicting results from previous studies.

OBJECTIVES This systematic review and meta-analysis aimed to clarify the association between Lp(a) and risk of MACE across different hs-CRP levels in both primary and secondary prevention settings.

METHODS We performed a systematic review by searching MEDLINE (PubMed), Embase (Ovid), Cochrane CENTRAL (Wiley), and Web of Science (Clarivate) from their inception to February 2024. Eligible studies reported the association of Lp(a) with MACE stratified by hs-CRP level. Data extraction and quality assessment were systematically conducted. Meta-analyses used random-effects models to compute pooled HRs for individuals with low (<2 mg/L) and high (≥2 mg/L) hs-CRP levels. Subgroup analyses were performed in primary and secondary prevention populations.

RESULTS Nine publications encompassing 11 studies that involved 562,301 participants met the inclusion criteria. The mean proportion of females was 39.9% and the weighted mean age for the entire cohort was 61.2 years. Elevated Lp(a) was significantly associated with MACE risk in both low and high hs-CRP groups, with pooled HR of 1.26 (95% CI: 1.11-1.42) and 1.33 (95% CI: 1.20-1.47), respectively. In the primary prevention group, the pooled HR for low and high hs-CRP groups was 1.33 (95% CI: 1.06-1.66) and 1.43 (95% CI: 1.13-1.82), respectively (subgroup difference, $P = 0.65$). The corresponding HRs for the secondary prevention population were 1.13 (95% CI: 1.00-1.27) and 1.31 (95% CI: 1.12-1.52), respectively (subgroup difference $P = 0.13$).

CONCLUSION Elevated Lp(a) is associated with an increased risk of MACE independent of hs-CRP levels in both primary and secondary prevention populations. (JACC Adv. 2024;3:101409) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

hs-CRP = high-sensitivity C-reactive protein

IL = interleukin

Lp(a) = Lipoprotein(a)

MACE = major adverse cardiovascular events

RCT = randomized controlled trial

Lipoprotein(a) [Lp(a)] has been increasingly recognized as an independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD).[1] Lp(a) is proinflammatory and a potent atherogenic lipoprotein present in elevated levels in approximately 20% of individuals.[2] Since its discovery nearly 6 decades ago, the focus of research has expanded to elucidate its role in atherosclerosis, particularly its complex relationship with systemic inflammation, a key factor in the progression of atherosclerotic plaque.[3] Interleukin-6 (IL-6) is suggested to upregulate the *LPA* gene by binding to the promoter region, influencing apolipoprotein(a) synthesis, and ultimately circulating Lp(a) concentration.[4,5] Oxidized phospholipids, known to bind preferentially to Lp(a) in the plasma, are central to its pathogenicity and promote inflammation and exacerbate endothelial damage.[6]

High-sensitivity C-reactive protein (hs-CRP) is a widely recognized biomarker of systemic inflammation, often used in clinical settings to assess inflammatory status as well as inflammation-related ASCVD risk.[7] Multiple recent studies have evaluated the association of Lp(a) with the risk of major adverse cardiovascular events (MACE) in the context of hs-CRP levels. These studies have been conducted in both primary and secondary prevention populations, have dichotomized hs-CRP levels using the cut-off of 2 mg/L, and have yielded conflicting results. Evidence from large primary prevention studies such as the UK Biobank,[8] BiomaCARE,[9] and Copenhagen General Population Study[10] suggests that elevated Lp(a) levels correlate with increased ASCVD risk, seemingly independent of hs-CRP levels. Similar findings have been reported in secondary prevention populations from the FOURIER-TIMI 59 (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk - Thrombolysis In Myocardial Infarction 59) and SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) trials.[8] Conversely, data from the Multiethnic Study of Atherosclerosis[11] primary prevention cohort and multiple secondary prevention cohorts, including studies from BiomaCARE,[9] the ACCELERATE trial,[12] and Chinese cohorts from Fuwai Hospital,[13,14] report no significant association between Lp(a) and ASCVD risk in individuals with low hs-CRP (<2 mg/L).

These discrepancies highlight the variability in outcomes and the complexity of the interactions between Lp(a), systemic inflammation, and cardiovascular risk. Given these conflicting results, a systematic review and meta-analysis is essential to synthesize these diverse findings and evaluate the role of Lp(a) in cardiovascular risk across different hs-CRP levels. This approach leverages the increased statistical power of pooled data to provide a more definitive understanding of how Lp(a)-related cardiovascular risk varies with systemic inflammation, thereby addressing a critical knowledge gap.

METHODS

PROTOCOL REGISTRATION. This systematic review and meta-analysis adheres to the guidelines outlined in The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[15] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is presented in Supplemental Table 1 The comprehensive protocol for this study was prospectively registered on PROSPERO (CRD4202345109), ensuring transparency and adherence to planned methodological processes before data collection and analysis began. The meta-analysis was conducted using data from previously published studies, so ethical approval and/or informed consent from patients was not required.

ELIGIBILITY CRITERIA. Our study included original prospective and retrospective cohort studies as well as randomized clinical trials that investigated the association of lipoprotein(a) [Lp(a)] with incident MACE across varying levels of hs-CRP. Eligible studies needed to focus on adult populations (aged 18 years and above) and were required to report both Lp(a) and hs-CRP levels as concurrent exposures. Only studies that provided HRs for the association of Lp(a) with MACE, categorized by levels of hs-CRP, were considered. We excluded case reports, case-control, and cross-sectional studies to avoid design-related biases. Furthermore, studies that assessed

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Lp(a) and hs-CRP independently or only reported on one of these biomarkers were also excluded to ensure a consistent analytical focus on the association of Lp(a) with cardiovascular outcomes across hs-CRP levels.

SEARCH STRATEGY. We conducted a comprehensive electronic search of the following databases from their inception to February 28, 2024: MEDLINE (PubMed), Embase (Ovid), Cochrane CENTRAL (Wiley), and Web of Science (Clarivate). Our search strategy, detailed in the Supplemental Appendix, utilized a combination of controlled vocabulary and keywords targeting atherosclerotic cardiovascular disease, Lp(a), and hs-CRP. The complete search strategies for each database are presented in Supplemental Table 2. We imposed no restrictions on follow-up time, language, or publication format. To broaden our search and potentially reduce publication bias, we included conference abstracts and preprint articles. Additionally, we conducted a hand search of references from included articles to identify further studies. The search results and the study selection process are depicted in **Figure 1**. Where necessary, we contacted the authors of the included studies to request additional relevant data to ensure consistency in data analysis.

DATA COLLECTION. The search results were managed using the Covidence systematic review platform, where screening was performed by 3 independent reviewers (P.A., C.Y.P., and G.K.). Any disagreements regarding study inclusion were resolved by a final reviewer (A.M.). The software automatically removed duplicate entries. Following initial screening, data extraction was independently conducted by 2 reviewers (P.A. and K.H.).

DATA ITEMS. Data extracted included author names, publication year, study design, country of origin, follow-up duration, assays used for Lp(a) and hs-CRP, age, gender, and race/ethnicity. The primary endpoint was the time to occurrence of MACE, expressed as HRs. The definition of MACE varied across studies (**Table 1**). For studies presenting multiple statistical models, data from the most comprehensive model were extracted. We also noted whether the study was from a primary or secondary prevention cohort. Studies with both primary and secondary prevention cohorts were treated as separate entries to allow stratification in the analysis. The included studies utilized different assays for Lp(a) quantification and varied in their definitions of high and low Lp(a) levels, as detailed in **Table 1**. Data will be made available by the corresponding author upon reasonable request.

QUALITY ASSESSMENT. The quality of each study was assessed using the Newcastle-Ottawa Scale for nonrandomized studies in meta-analyses.[19] This scale includes 8 items divided among a selection of study groups, comparability of groups, and outcome assessment. Studies scoring ≥7 were considered of good quality, those scoring 2-6 were deemed fair, and scores ≤1 were rated as poor. Quality assessments were conducted by 2 investigators (PA and KH), with any discrepancies resolved through discussion to reach consensus.

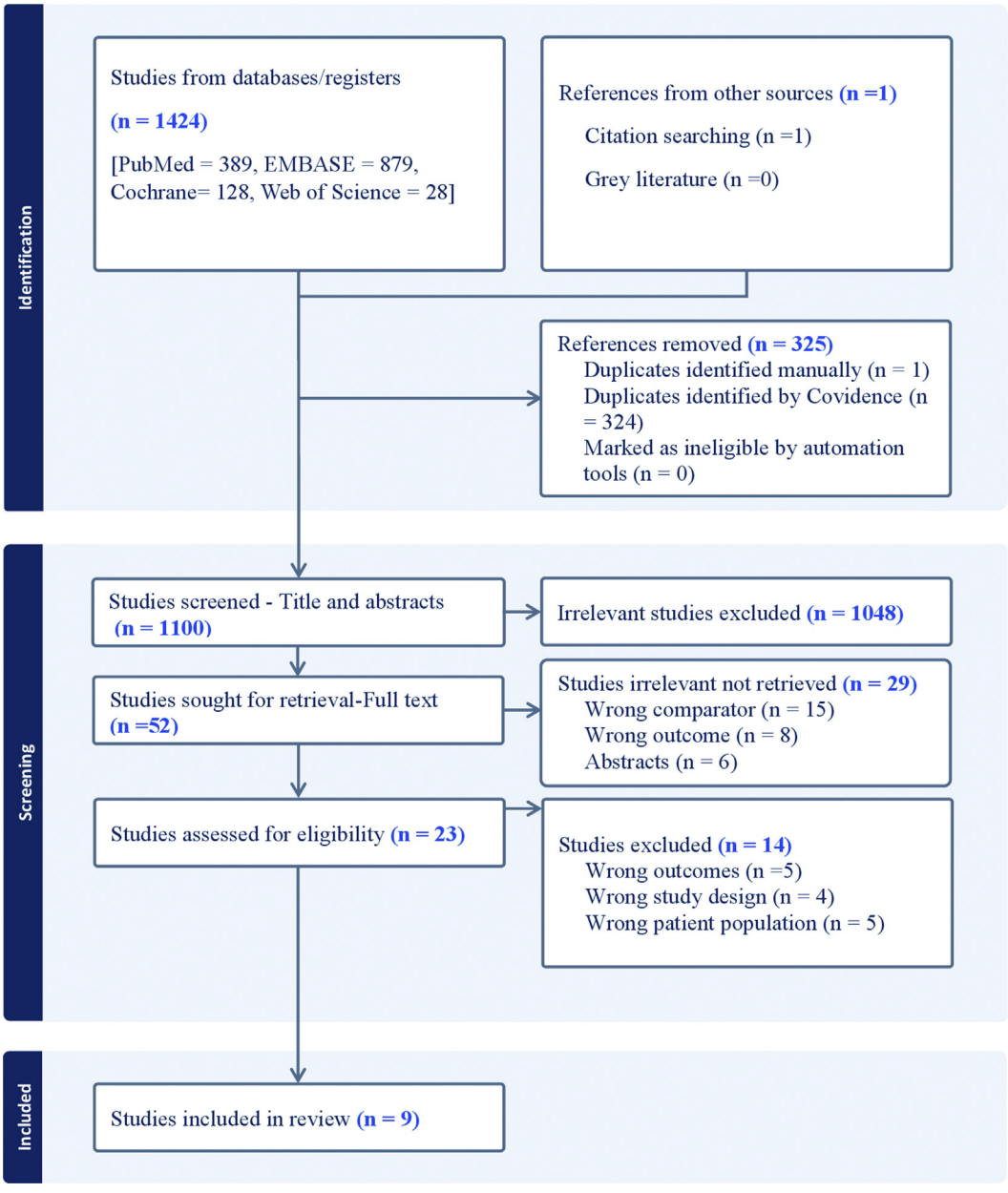
STATISTICAL ANALYSIS. The primary outcome, the association of elevated Lp(a) levels with MACE, was quantified using HRs derived from Cox proportional hazards regression models. These results were stratified by levels of hs-CRP, categorized as low (<2 mg/L) and high (≥2 mg/L). For studies that did not report HRs corresponding to the dichotomized Lp(a) level above or below 125 nmol/L, we converted the reported estimates to match this threshold. Details of the conversion method are provided in the supplementary material.

The meta-analysis employed a random-effects model using the Mantel-Haenszel method to accommodate the large study sizes and the relatively common nature of the outcome. Graphical representation of the results was achieved through forest plots. To quantify heterogeneity among the included studies, we used Tau^2, estimated via the DerSimonian-Laird method, along with the Cochran Q test and the I^2 statistic. Furthermore, the analysis was stratified by cohort type, distinguishing between primary and secondary prevention cohorts to elucidate differences in the impact of Lp(a) levels on cardiovascular outcomes. Publication bias was initially assessed visually using a funnel plot, while a more rigorous evaluation was conducted using Eger's test within a mixed-effects meta-regression model to explore funnel plot asymmetry. Sensitivity analyses included the recalculated pooled estimates following the exclusion of influential studies and randomized controlled trials to test the robustness of our findings. All statistical analyses were conducted using R software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), utilizing the Meta package. Significance was established at a 2-tailed P value of <0.05.

RESULTS

Our comprehensive literature search initially identified 1,425 studies. After removing duplicates,

FIGURE 1 PRISMA Flow Diagram for Study Selection Process



This PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram outlines the study selection process for our systematic review and meta-analysis assessing the association between Lipoprotein(a) [Lp(a)] and major adverse cardiovascular events (MACE) across varying levels of high-sensitivity C-reactive protein (hs-CRP). Initially, 1,425 studies were identified from databases including PubMed, Embase, Cochrane, and Web of Science. After rigorous screening and eligibility assessment, eleven studies from nine publications comprising 562,301 participants were included in the final analysis. Names of the databases searched: PubMed, Embase, Cochrane, Web of Science. hs-CRP = high-sensitivity C-reactive protein; Lp(a): lipoprotein(a); MACE = major adverse cardiovascular events; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

screening, and full-text review, we included 9 publications encompassing 11 distinct studies in our meta-analysis (**Figure 1**).[8-14,17,18] These studies, which collectively involved 562,301 individuals, consistently met our quality criteria (Supplemental Table 3). The included cohort was 39.86% female with a weighted mean age of 61.7 years. In terms of race/ethnic composition, 3 cohorts were predominantly White

TABLE 1 Summary of the Population Characteristics, Methods Used for Quantifying Lp(a) and hs-CRP, Outcome Definitions and Assessments in the Eleven Cohorts Included

Cohort Name (First Author, Year) N Follow-Up Time	[a]Lipoprotein(a) and hs-CRP Quantification (Exposure Assessment)	Cardiovascular Events (Outcome Assessment)	Confounders Assessed
BiomarCARE-Harmonized data from various population-based cohort studies across Europe (Arnold et al,[1] 2024) 71,678 individuals Median follow up 9.8 y (primary prevention), 13 y (secondary prevention)	Hs-CRP and Lp(a) mass were determined from the locally frozen stored blood samples and analyzed centrally in the BiomarCaRE central laboratory in either Mainz (until 2011) or Hamburg (since 2011), Germany. Lp(a) mass assessed with a particle-enhanced turbidimetric immunoassay (Biokit Quantia Lp(a)-Test; Abbott Diagnostics, USA). The limit of detection was 0.38 mg/dL with a measurement range of 1.3-90.0 mg/dL. Lp(a) values >90 mg/dL were set at 90 mg/dL. Hs-CRP was measured by latex immunoassay (Architect c8000, Abbott Labs, Rockville, MD, USA).16 The limit of quantification for hsCRP was 0.1 mg/L. Lp(a) was categorized using cohort-specific quintiles(Q). Low Lp(a) defined as <3.44 mg/dL. High Lp(a) defined as >24.7 mg/dL.	Primary outcome was defined as CHD, a composite of fatal or non-fatal, myocardial infarction, coronary death, unstable angina pectoris, coronary revascularization, and unclassifiable death (i.e. death with insufficient evidence of coronary origin and no competing cause).	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 use.
Copenhagen General Population Study (Thomas et al,[2] 2022) 68,090 individuals Median follow up 8.1 y	Lp(a) mass (mg/dl) was measured turbidimetrically using an assay from Denka on a KONE (KONE Corporation, Finland) or Cobas (Roche Professional Diagnostics, Switzerland) platform while 8.3% was measured using an assay from DiaSys on a KONE platform; both assays are largely independent of apolipoprotein(a) isoform size. In total, 43,855 (64%) individuals were measured consecutively using fresh samples, while 24,235 (36%) individuals were measured using frozen samples stored at −80 °C (median storage time: 7.2 years). Hs-CRP was measured on fresh samples using standard hospital assays. Lp (a) was categorized into percentiles. Low Lp(a) defined as ≤9 nmol/L. High Lp(a) defined as ≥147 nmol/L.	Primary outcome was defined as ASCVD, a composite of myocardial infarction, coronary heart disease death, ischemic stroke, coronary artery bypass graft and percutaneous coronary intervention using ICD codes.	Age, sex, non-HDL cholesterol corrected for Lp(a) cholesterol, systolic blood pressure, smoking status, years of education, month of blood sampling, Charlson Comorbidity Index, menopause status, and hormone replacement therapy.
MESA (Multiethnic Study of Atherosclerosis) (Zhang et al,[16] 2021) 4,679 individuals Mean follow-up 13.6 y	Lp(a) mass (mg/dL) was determined in plasma using a latex-enhanced turbidimetric immunoassay (Denka Seiken) at Health Diagnostics Laboratory. Hs-CRP was measured by a BNII nephelometer using a particle-enhanced immunonephelometric assay (N High Sensitivity CRP, Dade Behring Inc). Lp(a) was examined as a categorical variable by commonly used clinical cut points (50 and 100 mg/dL). Low Lp(a) defined as <50 mg/dL. High Lp(a) defined as ≥50 mg/dL.	Primary outcome was defined as CV events, which comprised of myocardial infarction, fatal and nonfatal coronary heart disease (CHD), definite angina, and probable angina if followed by revascularization, resuscitated cardiac arrest, fatal and nonfatal stroke, and other atherosclerotic or CVD death. Data gathered through telephone interviews, interim hospitalizations, outpatient cardiovascular procedures and diagnoses, medical record abstractions, and obituaries.	Age, sex, race/ethnicity, hypertension, use of hypertension medications, diabetes, smoking status, high-density lipoprotein cholesterol, triglycerides, total cholesterol, and renal function (estimated glomerular filtration rate).
ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes) (Puri et al,[3] 2020) 10,503 individuals Median follow-up 2.4 y	Lp(a) was measured by the Randox assay in nmol/L. Hs-CRP was measured by the Roche Modular Turbidimetric method. Lp (a) was categorized into percentiles. Low Lp(a) defined as <8.2 nmol/L. High Lp(a) defined as ≥183.4 nmol/L.	Primary outcome was MACE, defined as cardiovascular death, MI, or stroke. An independent clinical-events committee, whose members were unaware of the trial-group assignments, adjudicated the end points.	Adjusted for age, sex, race/ethnicity, region, diabetes, smoking, baseline low-density lipoprotein cholesterol, baseline high-density lipoprotein cholesterol, and randomized treatment group.

Continued on the next page

TABLE 1 Continued

Cohort Name (First Author, Year) N Follow-Up Time	[a]Lipoprotein(a) and hs-CRP Quantification (Exposure Assessment)	Cardiovascular Events (Outcome Assessment)	Confounders Assessed
National tertiary care institute cohort (Fuwai Hospital, Beijing) (Yuan et al,[4] 2022) 10,724 patients Mean follow-up 5 y	Lp(a) was measured using the immunoturbidimetry method [LASAY Lipoprotein(a) auto; SHIMA laboratories Co, Ltd] The latex beads were coated with polyclonal anti-human Lp(a) antibodies (goat) to react with Lp(a). The assay was calibrated by Lp(a) protein-validated lyophilized methods with a 5-point calibrator and expressed in mg/dL. Hs-CRP was measured using immunoturbidimetry (Beckmann Assay, Bera, California). Lp (a) was stratified into 3 groups. Low Lp(a) defined as <15 mg/dL. High Lp(a) defined as ≥30 mg/dL.	Primary outcome was defined as MACE, a composite of all-cause death, myocardial infarction (MI), unplanned revascularization and ischemic stroke. All events were adjudicated by independent cardiologists, and disagreement was resolved by consensus.	Adjusted for age, sex, diabetes mellitus, hypertension and current/former smoker, LDL-C and eGFR.
Fuwai Hospital in Beijing, China Patients with STEMI undergoing emergent coronary angiography and PCI (Wang et al,[5] 2021) 3,177 patients Mean follow up 2.5 y	Lp(a) was measured by an immunoturbidimetry method (LASAY lipoprotein(a) auto; SHIMA Laboratories Co, Ltd, Tokyo, Japan) expressed in mg/dL. The level of hs-CRP was measured using immunoturbidimetry (Beckmann Assay, Bera, California). Lp (a) was categorized into tertiles. Low Lp(a) defined as <6.3 mg/dL. High Lp(a) defined as ≥48.3 mg/dL.	Primary outcome was defined as MACE, a composite of all-cause death, recurrence of myocardial infarction or stroke. Outcome data were collected by outpatient visits or telephone interviews.	Age, sex, hypertension, diabetes mellitus, total cholesterol, triglyceride, low-density-lipoprotein cholesterol and high-density lipoprotein-cholesterol.
UK Biobank (Small et al,[8] 2024) 357,220 individuals Median follow up 11 y	Lp(a) was measured by immunoturbidimetry with the Randox AU5800 assay expressed in nmol/L. Hs-CRP was measured by immunoturbidimetry with Beckman Coulter AU5800 assay. Lp (a) was categorized into 2 groups. Low Lp(a) defined as <125 nmol/L. High Lp(a) defined as ≥125 nmol/L.	Primary outcome was defined as MACE, a composite of cardiovascular death, myocardial infarction, or ischemic stroke. Each diagnosis was designated using ICD 9/10 codes. Prevalent disease was defined as a first coding instance occurring at or prior to a patient's enrollment date. Incident cardiovascular disease was defined as a first coding instance occurring after a patient's enrollment date.	Age, sex, hypertension, type 2 diabetes, body mass index, statin use, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and estimated glomerular filtration rate.
FOURIER [TIMI 59] (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk) (Small et al,[8] 2024) 34,020 combined TIMI studies Median follow up 2.2 y	Lp(a) was measured based on the Denka Seiken reagents (Denka Seiken, Ltd; Polymedco) using an immunoturbidometric assay (Polymedco) with a Beckman AU series analyzer (Olympus, Beckman Coulter Instruments). Lp(a) was reported in nmol/L. Hs-CRP was measured using the Cobas particle-enhanced immunologic agglutination assay (Roche Diagnostics). Lp (a) was reported as a continuous variable which was later categorized into 2 groups for data harmonization for the meta-analysis. Low Lp(a) defined as <125 nmol/L. High Lp(a) defined as ≥125 nmol/L.	Primary outcome was defined as MACE, a composite of MI, ischemic stroke, and cardiovascular death. A blinded clinical endpoints committee adjudicated outcome.	Age, sex, hypertension, type 2 diabetes, body mass index, statin use, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate.
SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) (Small et al.[8] 2024) Median follow up 2.1 y	Both Lp(a) and hs-CRP levels were measured using a Roche (cobas) assay. Lp(a) was reported in nmol/L. Lp (a) was reported as a continuous variable which was later categorized into 2 groups for data harmonization for the meta-analysis. Low Lp(a) defined as <125 nmol/L. High Lp(a) defined as ≥125 nmol/L.	Primary outcome was defined as MACE, a composite of MI, ischemic stroke, and cardiovascular death. A blinded clinical endpoints committee adjudicated outcome.	Age, sex, hypertension, type 2 diabetes, body mass index, statin use, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate.
REGARDS (Reasons for Geographic and Racial Differences in Stroke) study (Colantonio et al,[17] 2022) 1,948 individuals Follow up time from 2003 to 2017	Lp(a) molar concentration was measured using a particle-enhanced turbidimetric immunoassay (Tina-quant; Roche, Basel, Switzerland). Lp(a) was reported in nmol/L. Lp (a) was reported as a continuous variable which was later categorized into 2 groups for data harmonization for the meta-analysis. Low Lp(a) defined as <125 nmol/L. High Lp(a) defined as ≥125 nmol/L. Hs-CRP was measured by particle-enhanced immune-nephelometry.	Primary outcome was coronary heart disease defined as myocardial infarction. Events were reviewed independently by 2 study clinicians.	Age, sex, residence, education, income, physical activity, BMI, alcohol use, smoking, systolic blood pressure, history of CHD, diabetes, chronic kidney disease, high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, statin, and non-Lp(a) apolipoprotein B.

Continued on the next page

TABLE 1 Continued

Cohort Name (First Author, Year) N Follow-Up Time	[a]Lipoprotein(a) and hs-CRP Quantification (Exposure Assessment)	Cardiovascular Events (Outcome Assessment)	Confounders Assessed
CRIC (The Chronic Renal Insufficiency Cohort) study (Poudel et al,[18] 2023) 1,439 individuals Median follow up 6.6 y	Lp(a) mass concentration was measured using latex-enhanced immunoturbidimetric assay (Pointe Scientific). Lp(a) was reported in mg/dl. Lp (a) was reported as a continuous variable which was later categorized into 2 groups for data harmonization for the meta-analysis. Low Lp(a) defined as <125 nmol/L. High Lp(a) defined as ≥125 nmol/L.	Cardiovascular events include myocardial infarction hospitalization, ischemic stroke hospitalization, PAD hospitalization, CHD death, or ischemic stroke death. Medical records were retrieved and adjudicated by at least 2 study clinicians to confirm the occurrence of study outcomes.	Age, sex, race, CKD, study center, education, income, smoking status, physical activity, BMI, diabetes, SBP, antihypertensive use, eGFR, HDL-C, triglycerides, albumin-creatinine ratio, fibroblast growth factor 23, homocysteine, use of aspirin and statins, and non-Lp(a) LDL cholesterol.

[a]In all studies low and high hs-CRP was defined as <2 mg/L and ≥2 mg/L respectively.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; CKD = chronic renal disease; EDTA = ethylenediaminetetraacetic acid; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ICD= International Classification of Disease; IS = ischemic stroke; MACE = major adverse cardiovascular events; MI = myocardial infarction; PAD = peripheral artery disease; SBP = systolic blood pressure.

Europeans,[8-10] 2 cohorts were Chinese,[13,14] 4 cohorts comprised multiple race/ethnic groups[11,12,17,18] and 2 did not report race/ethnic distribution.[8]

In the overall analysis, elevated Lp(a) had a significant association with MACE risk across both low and high hs-CRP groups, with pooled HRs of 1.26 (95% CI: 1.11-1.42, I^2 = 85%) and 1.33 (95% CI: 1.20-1.47, I^2 = 81%), respectively, as shown in **Figure 2**. There was no evidence of publication bias using Eger's regression test for funnel plot asymmetry in the low hs-CRP group (t = 1.29; df = 10; P = 0.23). However, there was evidence of study bias in the high hs-CRP group (t = 3.97; df = 10; P = 0.003) (Supplemental Figure 1). Our influential analysis revealed that omitting Thomas et al. study[10] had the greatest impact on heterogeneity; I^2 decreased from 81.0% to 52.9% in the low-hs-CRP group and 81.0% to 73.90% in the high hs-CRP group.

SUBGROUP ANALYSIS. In the primary prevention population, the pooled HR for the low and high hs-CRP groups were 1.33 (95% CI: 1.06-1.66) and 1.43 (95% CI: 1.13-1.82), respectively, with a nonsignificant subgroup difference (P = 0.65). The corresponding HR for the secondary prevention population was 1.13 (95% CI: 1.00-1.27) and 1.31 (95% CI: 1.12-1.52), respectively, with a nonsignificant subgroup difference (P = 0.13) (**Figure 3**).

SENSITIVITY ANALYSIS. Due to the high heterogeneity observed (I^2 = 85.0% and 81.0% in the low and high hs-CRP groups, respectively), further sensitivity analysis excluding the influential Thomas et al.[10] study recalibrated the pooled HRs to 1.16 (95% CI: 1.07-1.23; I^2 = 52.9%) for low hs-CRP and 1.28 (95% CI: 1.16-1.41; I^2 = 73.9%) for high hs-CRP group.

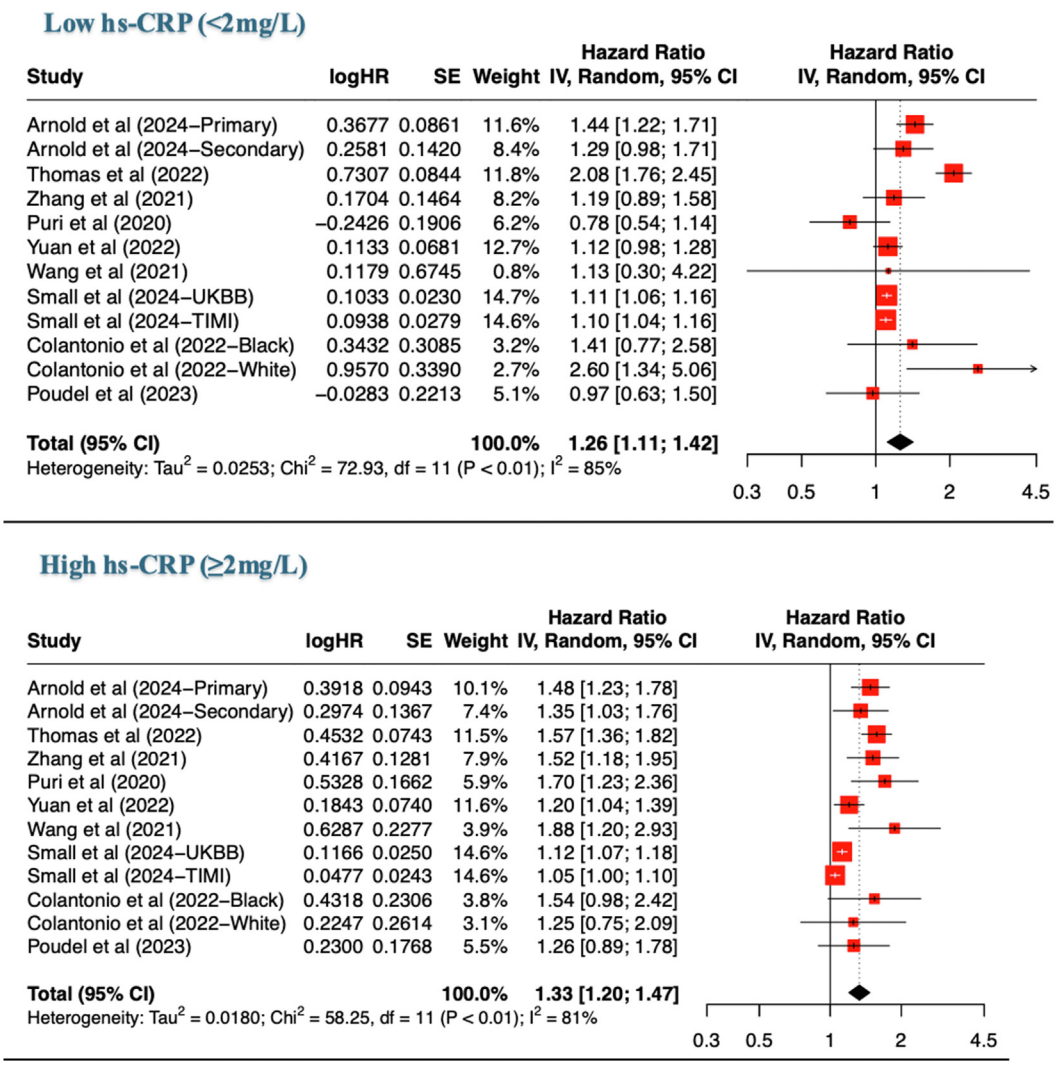
Some of the included studies were randomized controlled trials (RCTs)[8,12] and given the potential for trial interventions to influence MACE outcomes and biomarkers such as Lp(a) and hs-CRP, we performed a sensitivity analysis excluding all RCTs. The pooled HRs remained consistent with those from the primary analysis, which included all studies. The results of this sensitivity analysis are presented in Supplemental Figure 2.

DISCUSSION

This is the first systematic review and meta-analysis to synthesize findings on the association between Lp(a) and MACE risk in the context of hs-CRP levels. Our study provides compelling evidence that elevated Lp(a) is significantly associated with an increased risk of MACE across varying levels of hs-CRP. Specifically, we observed that the association persists both in contexts of low (<2 mg/L) and high (≥2 mg/L) hs-CRP, with pooled HRs of 1.24 and 1.33, respectively. These results were consistent across primary and secondary prevention populations, underscoring the robustness of Lp(a) as an independent risk factor for MACE, regardless of inflammatory status as indexed by hs-CRP (**Central Illustration**).

Previous studies have shown mixed results regarding the interaction between Lp(a) and hs-CRP for the association with MACE risk in primary and secondary prevention populations. Our systematic review and meta-analysis provides a more nuanced understanding, indicating that while high hs-CRP may enhance the risk posed by Lp(a), the impact of Lp(a) on cardiovascular risk is substantial and independent of inflammation.[1] This consistent association of elevated Lp(a) with increased cardiovascular risk, irrespective of hs-CRP levels, demonstrates that Lp(a) exerts its atherogenic effects through multiple pathways. The apolipoprotein B-100 component of Lp(a) is directly atherogenic,[20] and the apolipoprotein(a)

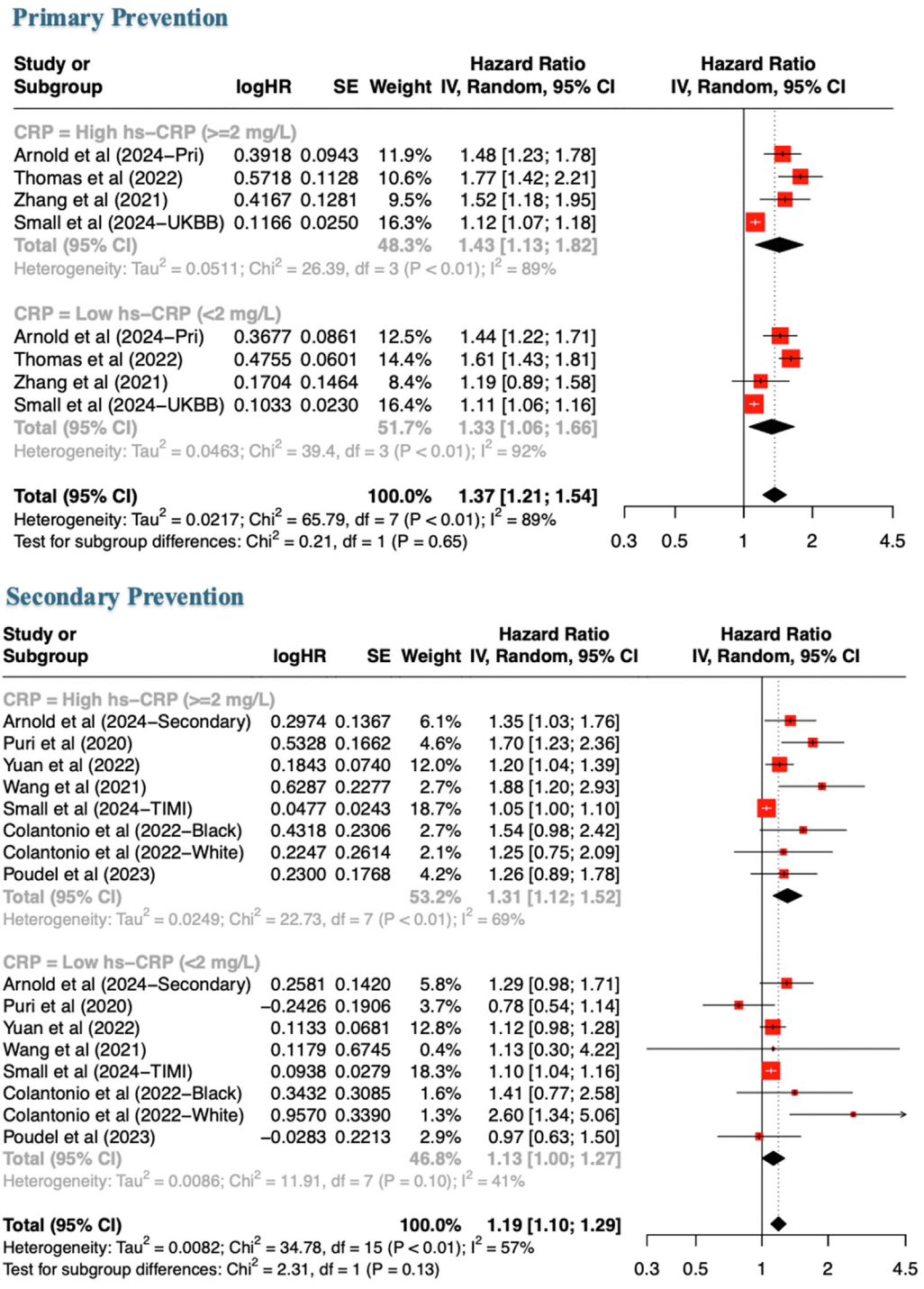
FIGURE 2 Pooled HRs for the Association Between Lipoprotein(a) and MACE Across Low and High hs-CRP Groups



Forest plots illustrating the pooled HRs for the association between elevated Lipoprotein(a) [Lp(a)] levels and major adverse cardiovascular events (MACE) in both low hs-CRP (<2 mg/L) and high hs-CRP (≥2 mg/L) groups. This meta-analysis includes data from eleven studies with various populations, reflecting significant heterogeneity ($I^2 = 88\%$ for low hs-CRP and $I^2 = 86\%$ for high hs-CRP). The HRs are stratified by hs-CRP levels to demonstrate the differential impact of inflammation on the cardiovascular risk posed by elevated Lp(a) levels. Elevated Lp(a) was significantly associated with MACE risk across low and high hs-CRP groups, with pooled HR of 1.26 (95% CI: 1.11–1.42) and 1.33 (95% CI: 1.20–1.47), respectively. hs-CRP = high-sensitivity C-reactive protein; IV = inverse variance; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular events; SE = standard error.

component closely resembles plasminogen, allowing it to potentially interfere with fibrinolysis, promoting thrombogenesis.[21] Additionally, Lp(a) carries oxidized phospholipids that contribute to oxidative stress and endothelial dysfunction, further exacerbating arterial plaque formation.[16,22] Thus, the association with MACE across low and high hs-CRP levels could be attributed to these direct atherogenic actions, which do not rely solely on inflammation-mediated pathways. However, it is important to note that the absence of a differential association with MACE based on hs-CRP levels in this analysis does not imply the lack of a synergistic association of Lp(a) and inflammation with MACE risk.[23] A recent study of participants from the Women's Health Study revealed that, similar to LDL-C, both Lp(a) and hs-

FIGURE 3 Pooled HRs for the Association Between Lipoprotein(a) and MACE Stratified by hs-CRP Levels in Primary and Secondary Prevention Populations



The pooled HRs demonstrating the association of lipoprotein(a) [Lp(a)] with major adverse cardiovascular events (MACE) across different hs-CRP levels, categorized into primary and secondary prevention groups. The forest plots show HRs for low (<2 mg/L) and high (≥2 mg/L) hs-CRP conditions in primary and secondary prevention settings. In the primary prevention group, the pooled HR for low and high hs-CRP groups was 1.33 (95% CI: 1.06–1.66) and 1.43 (95% CI: 1.13–1.82), respectively (subgroup difference, p = 0.65). The corresponding HRs for the secondary prevention population was 1.13 (95% CI: 1.00–1.27) and 1.31 (95% CI: 1.12–1.52), respectively (subgroup difference p = 0.13). There was no significant difference between primary and secondary prevention populations, indicating a consistent influence of Lp(a) across various clinical contexts. hs-CRP = high-sensitivity C-reactive protein; IV = inverse variance; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular events.

CRP predict ASCVD events over 30 years of follow-up. Moreover, the combination of these biomarkers was associated with a higher risk compared to individual estimates.[24] Additionally current evidence suggests that Lp(a) activates the endothelium,[25] recruits monocytes, and enhances chemotaxis,[22] leading to arterial wall inflammation. Likewise, oxidized phospholipids on Lp(a) serve as damage-associated molecular patterns triggering sterile inflammation.[26] Furthermore, inflammatory indicators like IL-1β, IL-6, and IL-8 might affect the association of Lp(a) with MACE risk as compared to a downstream marker like hs-CRP.[26,27]

CLINICAL IMPLICATIONS. The identification of Lp(a) as a significant risk factor for MACE, independent of hs-CRP has important clinical implications for potential Lp(a) therapeutics, as these results suggest that they may be effective in all patients with elevated Lp(a), not only those with high Lp(a) and high hs-CRP. Elevated Lp(a) level (≥50 mg/dL or ≥125 nmol/L) and high hs-CRP (≥2 mg/L) are both recognized as risk-enhancing factors by the ACC/AHA primary prevention guidelines.[28] As Lp(a) becomes integrated into clinical practice for cardiovascular risk assessment, our findings support its independent association with MACE in primary prevention regardless of hs-CRP status.

Multiple emerging therapies can significantly reduce Lp(a) synthesis in the liver by employing distinct pathways including antisense oligonucleotide (pelacarsen),[29] small interfering RNA (olpasiran, lepodisiran, zerlasiran),[30-32] and stereotactic inhibition of apolipoprotein B-100 and apolipoprotein(a) interaction (muvalaplin).[33] Among these therapies, pelacarsen and olpasiran are currently being studied in phase III randomized clinical trials and might offer a novel preventive and risk mitigation strategy in high-risk secondary prevention populations. Given the consistent association of elevated Lp(a) with MACE risk across hs-CRP levels, our study indicates that patients may benefit from these therapies regardless of their "residual inflammatory" risk.[34]

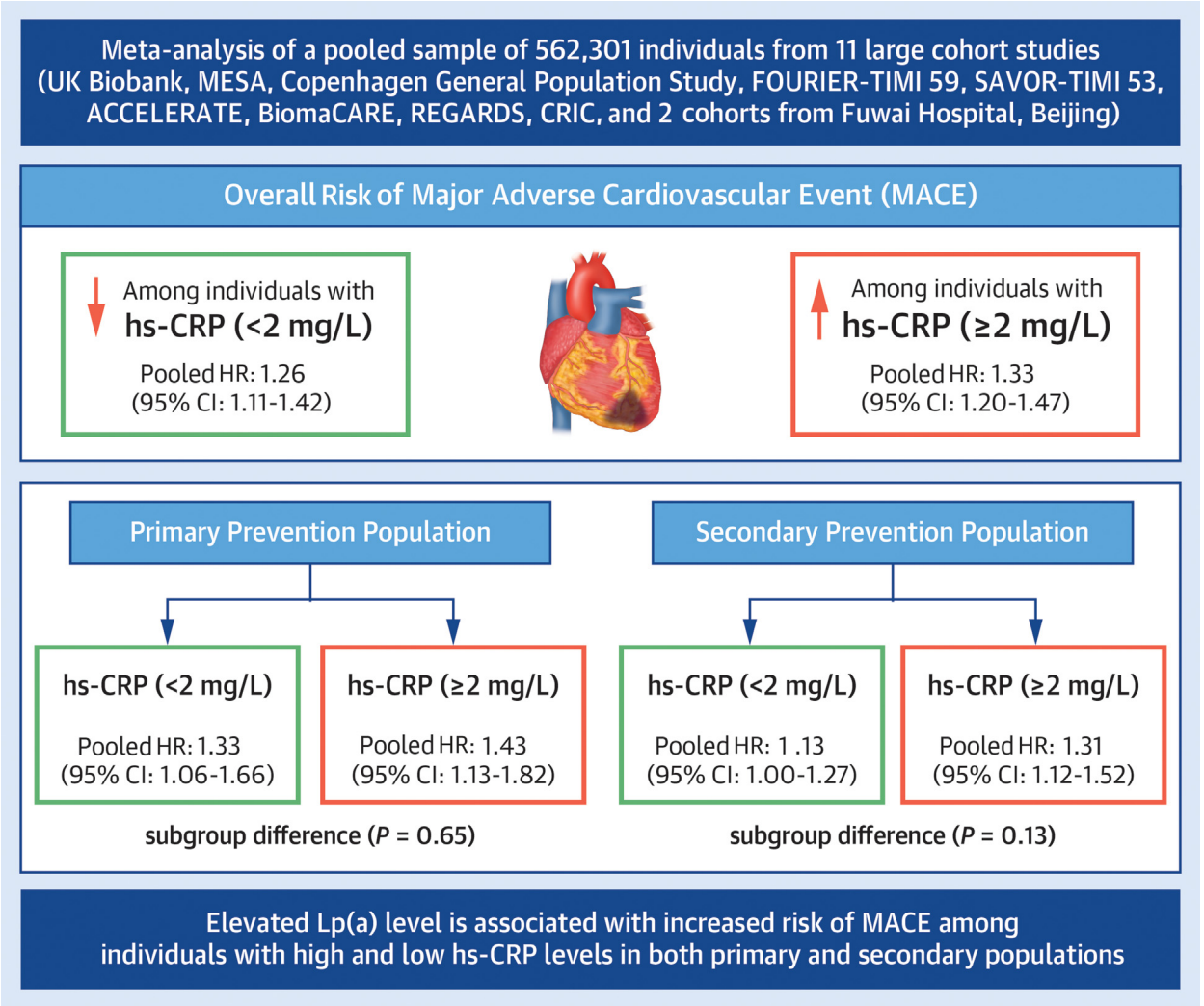
STRENGTHS AND LIMITATIONS. Our study benefits from the large sample size, a rigorous methodological approach, including a comprehensive search strategy and robust statistical analysis, lending confidence to our findings. However, our findings should be interpreted in the context of several limitations. First, Lp(a) was measured using different assays across studies and there was variability in the cutoff values used for defining elevated Lp(a), in addition, the definition of MACE varied across studies, these limit direct comparisons across studies. Second, in 4 cohorts[8,17,18] where HRs were reported for Lp(a) as a continuous variable, we converted them to dichotomized values, which could have biased our estimates towards the null. Third, we could not assess the impact of race/ethnicity on the differential association of Lp(a) risk across hs-CRP levels. It is well established that individuals of African ancestry typically exhibit higher levels of Lp(a) compared to other racial groups. However, the papers included in the meta-analysis lacked racial diversity, which may limit the generalizability of our findings. Fourth, while there was consistency in defining hs-CRP categories, some studies did not indicate if individuals with extremely high hs-CRP levels were excluded, which often indicates acute illnesses or an active rheumatologic condition. Also, the distribution of Lp(a) is rightly skewed, hence the majority of participants in the studies included in our meta-analysis have low Lp(a) levels. Consequently, the analysis of pooled HRs may obscure any potential effects in the clinically significant high Lp(a) subgroup. This limitation suggests that a potential modification of Lp(a) function by an inflammatory milieu might not be adequately captured in our pooled analysis. Furthermore, IL-1β, IL-6, and oxidized phospholipids, which are closely linked to Lp(a) in the inflammatory cascade, were not assessed in these studies. Fifth, the use of study-level data rather than individual-level data limits our ability to perform subgroup analysis and may introduce potential bias. Sixth, although RCTs provide superior internal validity, their interventions may confound the association between Lp(a) and MACE, potentially reducing the generalizability of our findings. To address this, we conducted a sensitivity analysis excluding RCT's and the results remained consistent with the primary analysis. Seventh, the high heterogeneity of studies indicates substantial variability, which potentially reduces the reliability in the pooled estimates.

Finally, there is a potential for publication bias, as suggested by the asymmetry in the funnel plot for the high hs-CRP group. This may potentially lead to overestimation of the true effect size due to the disproportionate influence of published studies.

CONCLUSIONS

Our study demonstrates that elevated Lp(a) level is associated with MACE risk across hs-CRP categories in both primary and secondary prevention

CENTRAL ILLUSTRATION **Association of Lipoprotein(a) Levels on Major Adverse Cardiovascular Events Across hs-CRP Levels**



Alebna PL, et al. JACC Adv. 2024;3(12):101409.

The pooled HRs for the association between elevated Lipoprotein(a) [Lp(a)] levels and the risk of major adverse cardiovascular events (MACE) stratified by high-sensitivity C-reactive protein (hs-CRP) levels are illustrated. Data were pooled from 562,301 individuals participating in eleven large studies including primary and secondary prevention cohorts. The figure shows that elevated Lp(a) levels are associated with an increased risk of MACE across both low (<2 mg/L) and high (≥2 mg/L) hs-CRP levels. Subgroup analyses in primary and secondary prevention populations further detail the consistent risk elevation across different hs-CRP strata. Studies: UK Biobank, MESA(Multi-Ethnic Study of Atherosclerosis), Copenhagen General Population Study, FOURIER-TIMI 59 (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk), SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus), ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes), BiomaCARE (Biomarker for Cardiovascular Risk Assessment in Europe), REGARDS (REasons for Geographic and Racial Differences in Stroke), CRIC (The Chronic Renal Insufficiency Cohort) and 2 cohorts from Fuwai Hospital, Beijing, China. IV = inverse variance; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular events.

populations. This underscores the importance of Lp(a) as an important independent risk factor for cardiovascular events across different populations. The findings advocate for a more inclusive approach to cardiovascular risk assessment, one that considers Lp(a) levels alongside traditional markers such as hs-CRP. They also highlight the need for broader clinical recognition and targeted management strategies that could potentially include novel Lp(a)-lowering therapies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This systematic review and meta-analysis clarifies that elevated Lp(a) level is associated with major adverse cardiovascular events (MACE) independent of hs-CRP levels in both primary and secondary prevention populations.

TRANSLATIONAL OUTLOOK: This study underscores the translational potential of integrating Lp(a) measurement into clinical practice for cardiovascular risk stratification and management of ASCVD, including the potential use of Lp(a) targeting therapies in clinical practice.

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KEY WORDS **cardiovascular outcomes, inflammation, Lp(a)**

APPENDIX **For a conversion of hazard ratios to dichotomized values as well as supplemental tables and figures, please see the online version of this paper.**