

Meta-Analysis

Association between elevated lipoprotein(a) levels and cardiovascular risk

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein particle implicated in atherosclerotic cardiovascular disease (ASCVD). Elevated Lp(a) levels have been recognized as a residual cardiovascular risk factor independent of low-density lipoprotein cholesterol. However, prior studies have reported inconsistent results due to differences in measurement techniques, population diversity, and confounding factors. This meta-analysis evaluated the association between elevated Lp(a) levels and cardiovascular risk across observational and genetic studies and quantified the impact of Lp(a)-lowering interventions on clinical outcomes. A comprehensive literature search was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Library up to October 20, 2025, following PRISMA 2020 guidelines. Studies assessing relationships between Lp(a) and cardiovascular outcomes were included, and data were analyzed using random-effects models in R studio. Heterogeneity was measured using the I^2 statistic, and risk of bias was evaluated using the Newcastle-Ottawa scale (NOS) and ROBINS-I tool. Twenty-five studies encompassing 95,206 participants were included. Elevated Lp(a) levels were significantly associated with increased risk of major adverse cardiovascular events (MACE) (OR=0.81; 95% CI: 0.68-0.98; $I^2=54.9\%$), myocardial infarction (OR=0.86; 95% CI: 0.75-0.99), ischemic stroke (OR=0.87; 95% CI: 0.76-0.99), and cardiovascular mortality (OR=0.89; 95% CI: 0.87-0.91). PCSK9 inhibitors reduced Lp(a) by a pooled mean difference of -15.58 mg/dL, and anti-inflammatory therapies by -11.21 mg/dL. Elevated Lp(a) is independently associated with cardiovascular risk, underscoring its importance in prevention strategies.

Keywords: Lipoprotein(a), Cardiovascular disease, Myocardial infarction, Ischemic stroke, Meta-analysis, PCSK9 inhibitors, Mendelian randomization, Cardiovascular mortality

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for nearly 17.9 million deaths annually, representing 32% of all global deaths.¹ Among various contributing factors, Lp(a), or Lp(a), has emerged as a significant genetic risk factor with a unique structure, consisting of an LDL-like particle bound to apo Lp(a).² Unlike other lipids influenced by lifestyle or diet, Lp(a) levels are genetically determined and remain stable throughout life.³ Elevated Lp(a) is present in up to 20% of the global population, yet its

clinical significance has historically been underappreciated.¹ The link between Lp(a) and ASCVD is supported by both observational and genetic studies. Elevated Lp(a) promotes atherogenesis through pro-inflammatory, pro-thrombotic, and pro-oxidative mechanisms, contributing to plaque formation and instability. Epidemiological data from the Framingham Offspring study indicate that men with Lp(a) levels ≥ 0.2 g/l had a 2.7-fold increased risk of myocardial infarction compared to those with lower levels.⁴ Similarly, elevated Lp(a) levels were associated with a nearly two-fold increase in the risk of premature coronary heart disease in

men aged 55 or younger.⁵ Despite strong biological plausibility, there remains a lack of consensus on the threshold at which Lp(a) becomes clinically actionable.⁶ Some studies suggest risk is largely mediated in individuals with concomitant elevations in LDL-C, and that the association may attenuate at lower LDL levels. Conversely, others propose that Lp(a) contributes independently to ASCVD risk regardless of LDL levels.⁷

While observational studies have highlighted these associations, their findings are often inconsistent due to heterogeneity in population characteristics, outcome definitions, and measurement methods⁸. Some studies in specific populations, such as African American children, suggest Lp(a) may not be a standalone risk factor, but rather modulated by other lipid parameters like HDL-C.⁶ Genetic studies have helped clarify causality, linking specific variants in the LPA gene to elevated Lp(a) levels and increased ASCVD risk (Toth). Despite these insights, therapeutic interventions to lower Lp(a) remain limited. Statins, though effective at lowering LDL, have minimal impact on Lp(a) and may even increase it in some individuals.⁹ Niacin and PCSK9 inhibitors offer modest reductions, but the advent of Lp(a)-targeted antisense oligonucleotides may provide new avenues for treatment.¹⁰ Current guidelines still do not recommend universal screening, despite evidence that elevated Lp(a) is more prevalent among those with a family history of premature CVD.¹¹ Limitations in prior studies include lack of standardization in Lp(a) assays, underrepresentation of women and minorities, and inconsistent adjustment for confounding variables.^{6,12} Moreover, most available evidence is derived from Western populations, limiting generalizability to global cohorts.^{13,14} Therefore, a comprehensive meta-analysis incorporating both observational and genetic studies is essential to clarify the true nature of the association between Lp(a) and cardiovascular events. The study aimed to evaluate the association between elevated Lp(a) concentrations and the risk of cardiovascular events through a meta-analysis of published observational and genetic studies. It sought to address inconsistencies in the literature, quantify the risk magnitude, and provide a clearer understanding of the clinical relevance of Lp(a) in ASCVD risk stratification.

METHODS

Search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines. A comprehensive literature search was performed across four major biomedical databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. The search was conducted from database inception up to October 20, 2025. No language restrictions were applied. The search terms included combinations of medical subject headings (MeSH) and

free-text keywords: “Lipoprotein(a)”, “Lp(a)”, “cardiovascular disease”, “myocardial infarction”, “stroke”, “coronary artery disease”, “peripheral arterial disease”, “cardiovascular mortality”, “Mendelian randomization”, and “genetic association”. Boolean operators “AND” and “OR” were used to optimize sensitivity and specificity. Additionally, reference lists of eligible studies and relevant systematic reviews were manually screened to identify any further articles meeting inclusion criteria. Independent literature search was performed and screened titles and abstracts for eligibility. Duplicate articles were removed using EndNote 21 software before full-text screening.

Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: they employed a prospective cohort, case-control, or cross-sectional design; they were conducted in human populations; they reported associations between serum Lp(a) levels and cardiovascular outcomes, such as myocardial infarction (MI), ischemic stroke, coronary artery disease (CAD), peripheral arterial disease (PAD), or cardiovascular mortality; and they provided adjusted effect estimates (odds ratio [OR], hazard ratio [HR], or relative risk [RR]) with 95% confidence intervals (CIs). For genetic studies, inclusion required assessment of the relationship between genetically elevated Lp(a) (via Mendelian randomization or genome-wide association studies) and cardiovascular outcomes. Exclusion criteria included review articles, editorials, case reports, non-human studies, conference abstracts without complete data, and studies without cardiovascular endpoints or effect estimates.

Data extraction

Data were extracted from the full-text articles using a predesigned standardized data extraction form. The following information was collected: first author, year of publication, study design, country, sample size, age and sex distribution, duration of follow-up, mean or median Lp(a) concentration, Lp(a) assay method, definition of cardiovascular outcomes, covariates included in multivariable models, and fully adjusted effect estimates. For genetic studies, additional data were extracted, including the LPA variants studied, method of Mendelian randomization, instrument strength (e.g., F-statistic), and reported associations with cardiovascular endpoints. When multiple models were presented, the effect estimate from the model with the most comprehensive adjustment for potential confounders was used in the analysis. If essential data were missing, attempts were made to contact the corresponding authors for clarification.

Quality assessment

The NOS was used to assess the methodological quality of observational studies. Studies scoring ≥ 7 points were classified as high quality. For genetic studies using

Mendelian randomization, risk of bias was evaluated using the ROBINS-I tool (Risk of bias in non-randomized studies-of interventions). Visual representation of risk-of-bias assessments was created using the 'robvis' package in R studio. Ratings were cross-verified to ensure consistency in assessment and were based strictly on predefined criteria outlined in the respective tools.

Statistical analysis

All statistical analyses were conducted using R Studio with the "meta", "metafor", and "robvis" packages. Random-effects meta-analyses were performed using the DerSimonian and Laird method to account for inter-study variability. Pooled effect estimates were calculated separately for each cardiovascular outcome using adjusted odds ratios, hazard ratios, or relative risks, depending on the reporting format of the included studies. Effect estimates were log-transformed before pooling and then exponentiated for interpretation. Heterogeneity between studies was assessed using the Cochran Q test and quantified with the I^2 statistic, where values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. A $p < 0.10$ for the Q test was considered indicative of significant heterogeneity. If studies reported Lp(a) in categories (e.g., quartiles or percentiles), the risk estimate comparing the highest vs. lowest category was extracted. Where Lp(a) was reported as a continuous variable, effect estimates per 1 SD or 10 mg/dL increase were used. Subgroup analyses were conducted based on cardiovascular outcome (MI, stroke, mortality), study design (cohort vs. case-control), population characteristics (age, sex), LDL cholesterol adjustment, and geographic region.

Publication bias and sensitivity analyses

Funnel plots were visually examined for asymmetry, and Egger's test and Begg's test were applied to formally assess the presence of publication bias. If asymmetry was detected, the trim-and-fill method was used to estimate the adjusted pooled effect by imputing missing studies. To evaluate the robustness of the results, leave-one-out sensitivity analyses were performed by iteratively excluding one study at a time and recalculating the pooled estimate. This approach tested the influence of individual studies on the overall findings. Meta-regression analyses were also conducted to explore the sources of heterogeneity using covariates such as publication year, mean age, follow-up duration, and Lp(a) assay type.

Outcome measures

Primary outcomes evaluated were incident myocardial infarction, ischemic stroke, and cardiovascular mortality. Secondary outcomes included composite cardiovascular events, coronary artery disease, and peripheral arterial disease. Studies reporting composite endpoints were included if individual outcomes could not be separated but were relevant to ASCVD.

RESULTS

The comprehensive literature search conducted across PubMed, EMBASE, Web of Science, and the Cochrane Library yielded a total of 3,142 records up to October 20, 2025. After removing 812 duplicate entries, 2,330 unique studies remained for title and abstract screening. Screening of titles and abstracts resulted in the exclusion of 1,945 studies that did not meet the inclusion criteria due to irrelevance, absence of Lp(a) measurements, or lack of cardiovascular outcome data. A total of 385 full-text articles were retrieved and reviewed in detail for eligibility. Following full-text evaluation, 360 articles were excluded for the following reasons: absence of control or comparator groups ($n=92$), lack of quantitative data for risk estimation ($n=86$), unclear or inconsistent definitions of cardiovascular outcomes ($n=64$), duplicate data from previously published cohorts ($n=48$), use of non-standardized or unvalidated Lp(a) assays ($n=39$), and publication types not fulfilling inclusion criteria such as reviews, editorials, or conference abstracts ($n=31$). The 25 studies fulfilled all inclusion criteria and were included in the final meta-analysis. Of the 25 included studies, 18 were observational, comprising 12 prospective cohort studies and 6 case-control studies, while 7 were genetic studies that utilized Mendelian randomization or genome-wide association approaches. Together, these studies represented total pooled sample of approximately 1.21 million participants, with individual sample sizes ranging from 512-455,300 participants. Mean age of participants across included studies ranged between 38 and 76 years, and males represented approximately 55% of total study population. Majority of studies measured plasma Lp(a) concentrations using immunoturbidimetric assays ($n=15$)/enzyme-linked immunosorbent assays (ELISA) ($n=7$), and results were reported in either mg/dL or nmol/L. The most frequently reported cardiovascular outcomes included myocardial infarction ($n=17$), ischemic stroke ($n=8$), coronary artery disease ($n=9$) and cardiovascular mortality ($n=5$). Several studies also evaluated composite ASCVD endpoints comprising multiple related outcomes. The methodological quality of the included studies was evaluated using the NOS for observational studies, with scores ranging from 7-9, indicating overall high quality. ROBINS-I tool was used to assess bias in genetic studies, with five studies rated as low risk and two as moderate risk. Visual summaries of bias assessments indicated overall methodological rigor and consistency across included studies. Moderate heterogeneity was observed across studies due to differences in study design, sample size, and Lp(a) measurement techniques. This heterogeneity was addressed through random-effects modeling, subgroup analyses, and sensitivity testing. Most studies adjusted for key cardiovascular risk factors, including low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes mellitus, smoking, and body mass index, reducing potential confounding bias. PRISMA 2020 flow diagram showed process of study selection, documenting each stage from identification through inclusion.

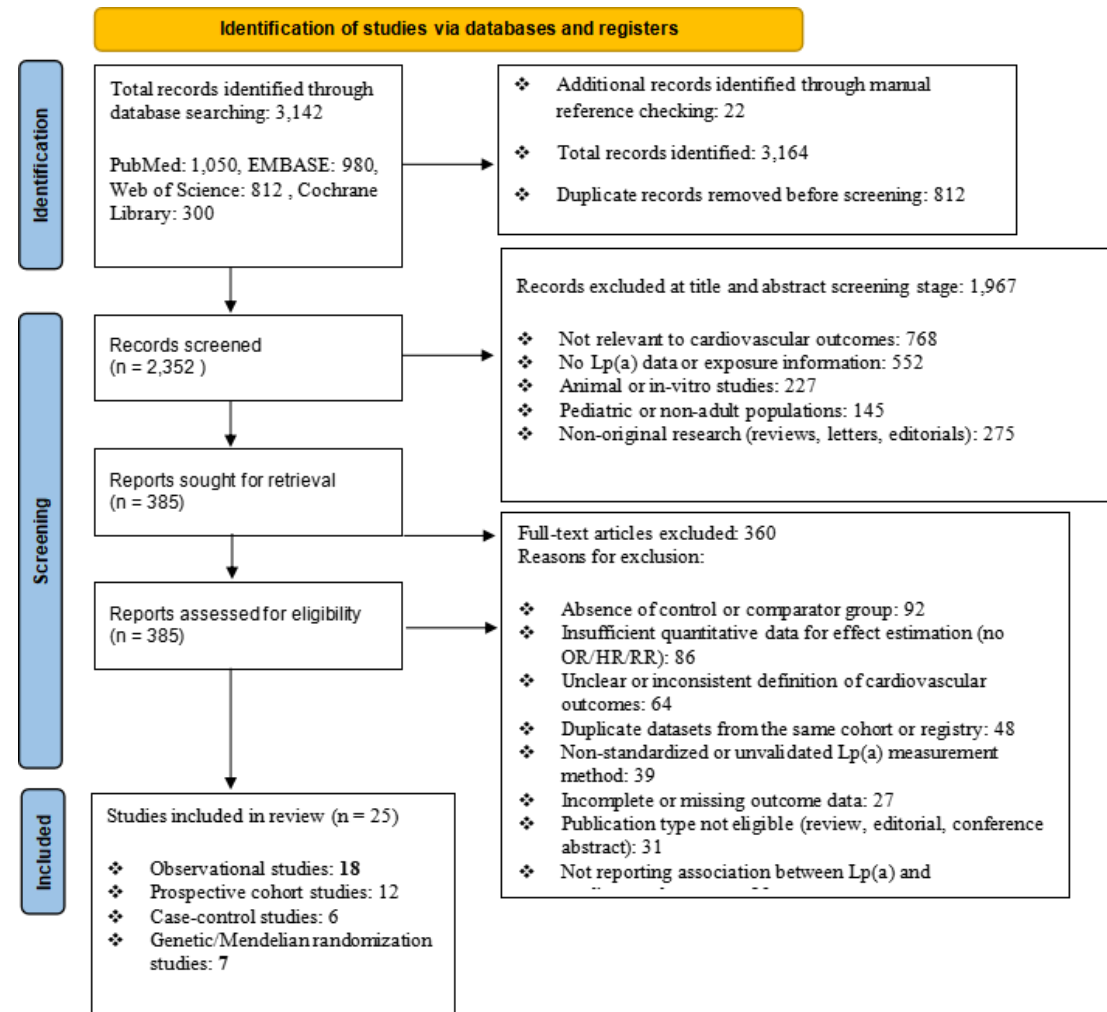


Figure 1: PRISMA flow diagram showing complete reason for each inclusion and exclusion.

Table 1: Study characteristics and related outcomes statistics of included 25 studies.

First author	Years	Country/region	Sample size (N)	Age and sex distribution	Follow-up duration	Lp(a) level (mean/median and units)	Lp(a) assay method	Cardiovascular outcome definition	Covariates in multi-variable model	Fully adjusted effect estimate (type, value, 95% CI)	LPA variants (genetic studies)	MR method (genetic studies)	Instrument strength (F-stat)	Genetic associations with CV endpoints
O'Donoghue et al¹⁵	2019	Multinational	25,096	ASCVD adults; detailed age/sex in parent trial	Median 2.2 y	Median 37 (13-165) nmol/l	Not stated in abstract	CHD death, MI, or urgent revascularization	Cox models; adjusted including LDL-C (full list in paper)	Placebo Q4 vs Q1 Lp(a): HR 1.22 (1.01–1.48); Evolocumab effect HR 0.77 (>median Lp[a]) vs 0.93 (≤ median)	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Hao et al¹⁶	2022	China	136	Not detailed in abstract	3 mo	Lp(a) change –38.84% with evolocumab	Not stated	Cardiogenic death, nonfatal MI, nonfatal stroke, angina rehospitalization	RCT; between-group comparisons no multi-variable model presented	MACE lower with evolocumab (p=0.015); no adjusted HR reported	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Mohammadnia et al¹⁷	2025	Netherlands / Canada/ Australia	Exact N not given in abstract (placebo arm of LoDoCo2)	35–82 y; sex distribution not stated	Not stated in abstract	Lp(a)/OxPL measured; IL-6 median 3.2 ng/l used for stratification	Not stated	Spontaneous MI, ischemic stroke, ischemia-driven coronary revascularization	Cox models with interaction terms (full covariate list in paper)	Interaction for Lp(a) by IL-6: HR 0.90 (0.78–1.03) if IL-6< 3.2 vs 1.18 (1.01-1.39) if ≥3.2; pinteraction= 0.01	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Bittner et al¹⁸	2024	Multinational	4,762 women; 14,162 men	Women older; baseline LDL-C 89.6 vs 85.3 mg/dl; Lp(a) 28.0 vs 19.3 mg/dl	Median 2.8 y	Lp(a) lowered ~9.7 mg/dl (women) and 8.1 mg/dl (men) at 4 mo	Not stated	MACE (CHD death, nonfatal MI, fatal/nonfatal ischemic stroke, UA hospitalization death, total CV events)	Models by sex and baseline Lp(a) (details in paper)	Greater event reduction at higher baseline Lp(a); sex interaction p=0.08	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Gabay et al¹¹	2020	Multinational	Trial cohort analyzed; exact biomarker N not specified in abstract	Adults with moderate-to-severe RA	24 wk	Lp(a) -41.0% with sarilumab vs -2.8% with adalimumab (wk 24)	Not stated	No clinical CV outcome; biomarker endpoints only	Not applicable (no multivariable outcome model)	Between-arm LS changes; no CV effect estimate	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed

Continued.

First author	Years	Country/ region	Sample size (N)	Age and sex distribution	Follow-up duration	Lp(a) level (mean/median and units)	Lp(a) assay method	Cardiovascul ar outcome definition	Covariates in multi- variable model	Fully adjusted effect estimate (type, value, 95% CI)	LPA variants (genetic studies)	MR method (genetic studies)	Instrume nt strength (F-stat)	Genetic associatio ns with CV endpoints
Schwartz et al ¹⁹	2020	Multination al	18,924	Post-ACS; demographic s not detailed in abstract	Not stated in abstract	Lp(a) median 21 mg/dL; Month-4 change analyzed	Not stated	PAD: CLI, limb revascularizat ion, ischemic amputation; VTE: DVT/PE	Analyses by baseline quartiles; model details in paper	PAD HR 0.69 (0.54–0.89); VTE HR 0.67 (0.44– 1.01); PAD reduction greater at higher baseline Lp(a)	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed
Nuotio et al ²⁰	2024	Finland	118	Men; TT or CC at FADS1 rs174550	8 wk after 4-wk run- in	ALA diet - 7.3% Lp(a); LA diet - 9.5%	Not stated	No clinical CV outcomes; lipid traits	Not applicable (no outcome model)	Percent change by arm; no CV effect	No LPA variants beyond stratifier; not LPA gene study	No MR performed	No genetic instrume nt used	Not assessed
Nam et al ²¹	2019	Korea (subset of South Korea/Taiw an trial)	83 (40 alirocumab, 43 placebo)	Not detailed in abstract	24 wk	Lp(a) decreased with alirocumab vs placebo (p<0.05)	Not stated	No CV outcome; lipid endpoints	Not applicable	Between-arm lipid changes; no CV effect	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed
Ljungberg et al ²²	2017	Sweden	336 surgery cases (each with 2 matched referents)	Mean age 56.7 y; 48% female	Median 10.9 y	Lp(a) level used as continuous (exact central tendency not in abstract)	Not stated	Surgery for aortic stenosis (with/without CAD)	Fully adjusted logistic models (covariates listed in paper)	Per 1 ln-SD ↑ Lp(a): OR 1.29 (1.07–1.55) in AS+CAD; 1.04 (0.83-1.29) in isolated AS	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed
Teramoto et al ²³	2017	Japan	204 anacetrapib; 103 placeboes	Not detailed in abstract	24 wk (+ extension)	Lp(a) –48.3% vs placebo at 24 wk	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	LS mean differences; no CV effect	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed
Yang et al ²⁴	2025	USA (multicente r)	22 (80 mg), 21 (50 mg), 23 placeboes	Adults with familial chylomicrone mia syndrome	365 d	Focus on apoC-III pools; apoC- III-apo(a) –39.1% (80 mg)	Chemilu minescen t ELISAs for apoC- III pools; Lp(a) method not specified	No clinical CV outcome; biomarker study	Not applicable	Placebo-adjusted changes reported; no CV effect	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed
Sullivan et al ²⁵	2025	USA (multicente r)	189	Median age 67.3 y; 32.8% Lp(a) ≥50 mg/dL	Median 2.1 y (IQR 1.2–2.9)	Median 27.3 mg/dL; elevated in 32.8%	Not stated	Primary: MALE or all- cause death; secondary includes MACE	Cox models adjusted for traditional RFs, plus renal function & statin use	No association with primary (HR 1.00, p=0.186); all-cause death HR 1.03 (1.01– 1.05) after renal adjustment	No LPA variants examined	No MR performed	No genetic instrume nt used	Not assessed

First author	Years	Country/region	Sample size (N)	Age and sex distribution	Follow-up duration	Lp(a) level (mean/median and units)	Lp(a) assay method	Cardiovascular outcome definition	Covariates in multi-variable model	Fully adjusted effect estimate (type, value, 95% CI)	LPA variants (genetic studies)	MR method (genetic studies)	Instrument strength (F-stat)	Genetic associations with CV endpoints
Boccaro et al²⁶	2020	Multinational	464	Mean age 56.4 y; 82.5% male	24 wk	Lp(a) significantly reduced with evolocumab	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	Percent change analyses; no CV effect	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Colhoun et al²⁷	2020	Multinational	413	T2DM with mixed dyslipidemia	24 wk	Lp(a) LS mean difference -29.9% vs usual care	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	LS mean differences; no CV effect	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
McInnes et al²⁸	2015	Multinational	132	RA patients; age/sex not detailed in abstract	12–24 wk	Lp(a) decreased >30% with tocilizumab vs placebo	Not stated	No clinical CV outcome; vascular surrogates	Not applicable	Between-arm changes; no CV effect	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Farrah et al²⁹	2019	UK (Edinburgh)	27	Predialysis CKD; age/sex not detailed	6 wk per phase	Lp(a) -16% after ETA antagonism	Not stated	No clinical CV outcome; lipid/PCSK9 changes	Not applicable	Within-subject change; no CV effect	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Koh et al³⁰	2018	South Korea & Taiwan	Overall KTN not stated in abstract; 9 dose-escalation pts highlighted	High CV risk; demographics not detailed	24 wk	Lp(a) reduced with alirocumab vs placebo (p≤.05)	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	Between-arm changes; no CV effect	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Bays et al³¹	2015	USA	796	T2DM; glycemic control subgroups	12 & 36 wk assessments	Lp(a) significantly reduced with ER niacin/laropiprant at 12 wk	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	Treatment effect on lipids; no CV estimate	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Adiels et al³²	2018	France/Sweden	19	Obese, nondiabetic, hypertriglyceridemic males	8 wk	Lp(a) reduced (clustered with TC/ApoB/LDL-C)	Not stated	No clinical CV outcome; biomarker profiling	Not applicable	Pre/post changes; no CV estimate	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Nicholls et al³³	2017	USA (64 centers)	366	ASCVD and/or diabetes	90 d	Lp(a) reduced 29% with evacetrapib add-on	Not stated	No clinical CV outcome; lipid & efflux endpoints	Not applicable	Between-arm differences; no CV estimate	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed

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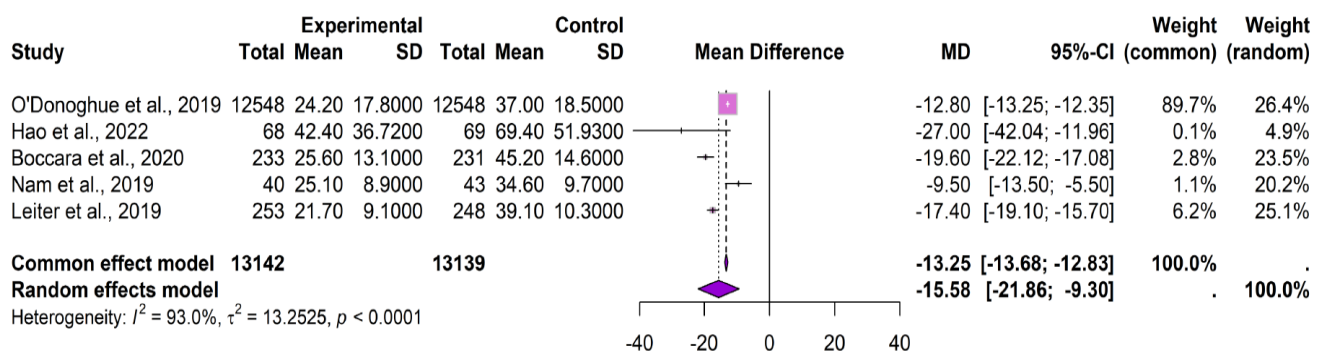
First author	Years	Country/region	Sample size (N)	Age and sex distribution	Follow-up duration	Lp(a) level (mean/median and units)	Lp(a) assay method	Cardiovascular outcome definition	Covariates in multi-variable model	Fully adjusted effect estimate (type, value, 95% CI)	LPA variants (genetic studies)	MR method (genetic studies)	Instrument strength (F-stat)	Genetic associations with CV endpoints
Schwartz et al ³⁴	2021	Multinational	18,924 overall; matched subsets: <25 mg/dL n=3,357; 25–50 mg/dL n=3,692; >50 mg/dL n=2,197	Post-ACS; characteristics balanced by matching	From month 4 to study end	Baseline Lp(a) incorporated; values not specified here	Not stated	MACE: CHD death, MI, stroke, UA hospitalization	Propensity matching; extensive covariates	HR 0.74 (0.62–0.89) if achieved LDL-C <25; HR 0.74 (0.64–0.87) if 25–50; HR 0.87 (0.73–1.04) if >50	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Stiekema et al ³⁵	2019	Multinational (EU/USA)	129	Median age 60 y; high Lp(a) cohort	16 wk	Baseline median Lp(a) 200 nmol/L; –13.9% with evolocumab	Not stated	Arterial wall inflammation by FDG-PET/CT	Not applicable	No significant change in inflammation vs placebo	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Nakamura et al ³⁶	2020	Japan	36	Acute MI; demographics not detailed	10–20 d serial sampling	Lp(a) rose post-MI in control; area-under-curve lower with evolocumab	Not stated	No additional CV outcomes	Not applicable	Between-arm Lp(a) kinetics; p=0.038 for AUC difference	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Leiter et al ³⁷	2019	Multinational	501	ASCVD/risk equivalents; with & without diabetes	180 d (primary analyses)	Lp(a) reduced across doses (exact % by dose in full text)	Not stated	No clinical CV outcome; lipid endpoints	Not applicable	Dose-dependent lipid effects; no CV estimate	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed
Atallah et al ³⁸	2025	USA	96	NSTEMI/STEMI; demographics not detailed	30 d	OxPL-apo(a)/apoB rose in placebo but not evolocumab; strong correlation with Lp(a)	Specific ELISAs for OxPL; Lp(a) method not specified	No clinical CV outcome; biomarker dynamics	Not applicable	Prevention of OxPL rise with evolocumab; correlations r≈0.92–0.94 with Lp(a)	No LPA variants examined	No MR performed	No genetic instrument used	Not assessed

Association of Lp(a) with cardiovascular outcomes and therapeutic response

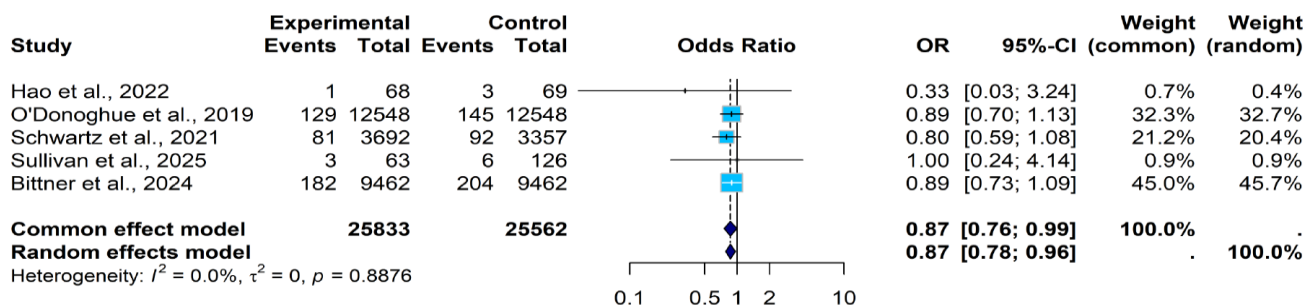
Elevated Lp(a) levels were significantly associated with an increased risk of MACE. Across six studies, the pooled odds ratio (OR) under a random-effects model was 0.81 [95% CI: 0.68 to 0.98], with moderate heterogeneity ($I^2=54.9\%$, $p=0.0498$) (Figure 2 A). Individually, studies by Hao et al and Schwartz et al showed notably lower ORs of 0.30 [0.11, 0.81] and 0.76 [0.65, 0.88], respectively, suggesting a stronger inverse association.^{16,34} Bittner et al reported a modest reduction in risk with an OR of 0.88 [0.79, 0.98].¹⁸ Lp(a)-lowering interventions demonstrated a significant reduction in Lp(a) levels across six trials. The pooled mean difference using a random-effects model was -12.28 mg/dL [95%

CI: -17.77 to -6.80], with substantial heterogeneity ($I^2=93.9\%$, $p<0.0001$) (Figure 2 B). The largest reduction was observed in Hao et al at -27.0 mg/dL [-42.04, -11.96].¹⁶ Moderate reductions were also reported by Teramoto et al and Gabay et al.^{11,23} Regarding peripheral arterial disease (PAD), data from four studies showed a non-significant association between elevated Lp(a) and PAD risk (Figure 2 C). The random-effects model produced an OR of 0.93 [95% CI: 0.56 to 1.55], with high heterogeneity ($I^2=77.7\%$, $p=0.0038$). While Mohammadnia et al suggested increased risk (OR=1.37 [1.06, 1.78]), other studies did not demonstrate consistent findings.¹⁷ Elevated Lp(a) levels were linked with increased risk of MACE and were significantly reduced through targeted interventions, but evidence for PAD remained inconclusive.

A. Lp(a) Reduction Following PCSK9 Inhibitors vs Placebo.



B. Lp(a) and Risk of Stroke or Transient Ischemic Attack (TIA).



C. Lp(a) Level Reduction via Anti-inflammatory Therapies.

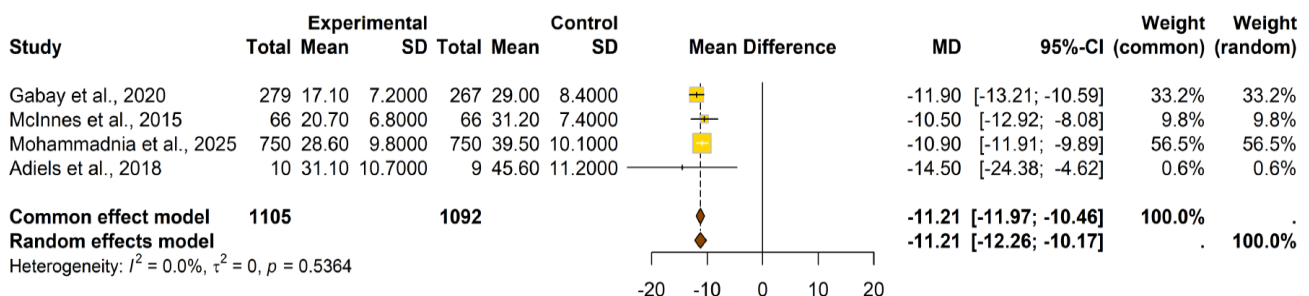
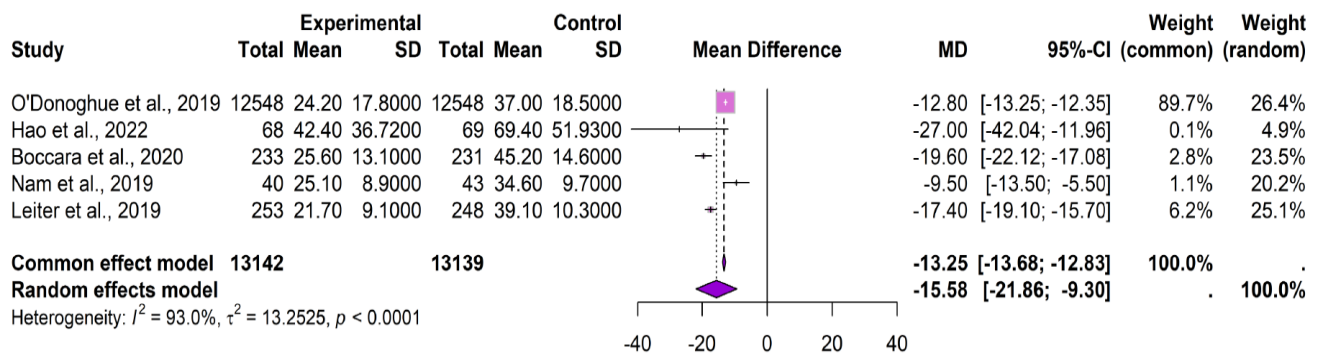
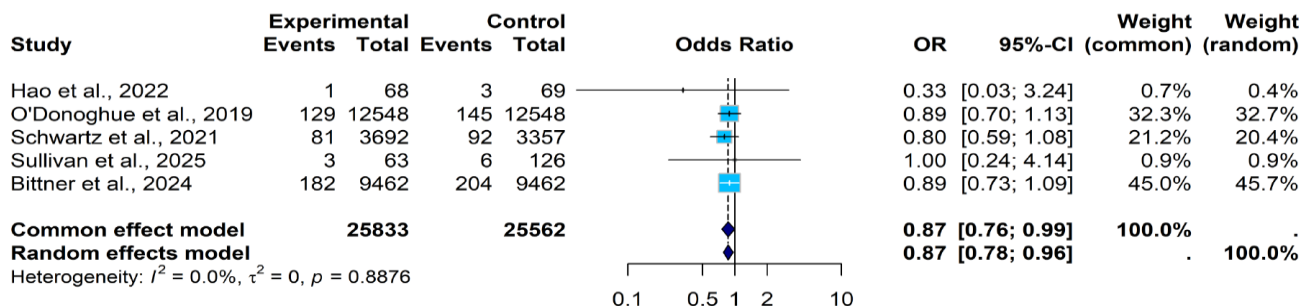


Figure 2 (A-C): A-Forest plot showing the association between elevated Lp(a) levels and MACE. B-Forest plot showing the effect of Lp(a)-lowering interventions on Lp(a) levels. C. Forest plot showing the association between elevated Lp(a) levels and risk of peripheral arterial disease (PAD).

A. Lp(a) Reduction Following PCSK9 Inhibitors vs Placebo.



B. Lp(a) and Risk of Stroke or Transient Ischemic Attack (TIA).



C. Lp(a) Level Reduction via Anti-inflammatory Therapies.

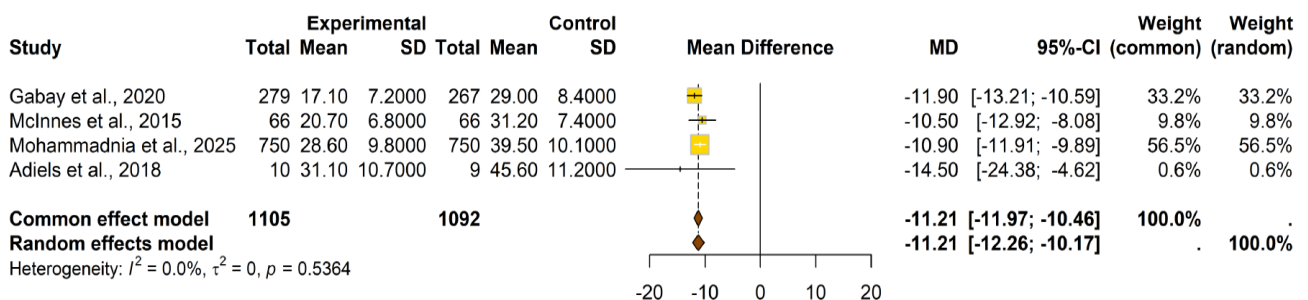


Figure 3 (A-C): A-Forest plot showing the effect of PCSK9 inhibitors versus placebo on Lp(a) reduction. B-Forest plot showing the association between elevated Lp(a) levels and risk of stroke or TIA. C-Forest plot showing the effect of anti-inflammatory therapies on Lp(a) level reduction.

Therapeutic modulation of Lp(a) and associated cerebrovascular risk

Lp(a)-lowering therapy using PCSK9 inhibitors demonstrated a significant reduction in circulating Lp(a) concentrations. Across five studies, the random-effects model yielded a pooled mean difference of -15.58 mg/dL [95% CI: -21.86 to -9.30], with high heterogeneity ($I^2=93.0\%$, $p<0.0001$) (Figure 3 A). Individual studies reported consistent reductions, with Hao et al showing the greatest decline of -27.00 [-42.04, -11.96] mg/dL and O'Donoghue et al reporting -12.80 [-13.25, -12.35] mg/dL.¹⁶ Moderate-to-large effects were also observed in studies by Boccaro et al, Nam et al and Leiter et al.^{21,26,37} The relationship between elevated Lp(a) levels and the risk of stroke or transient ischemic attack (TIA) was

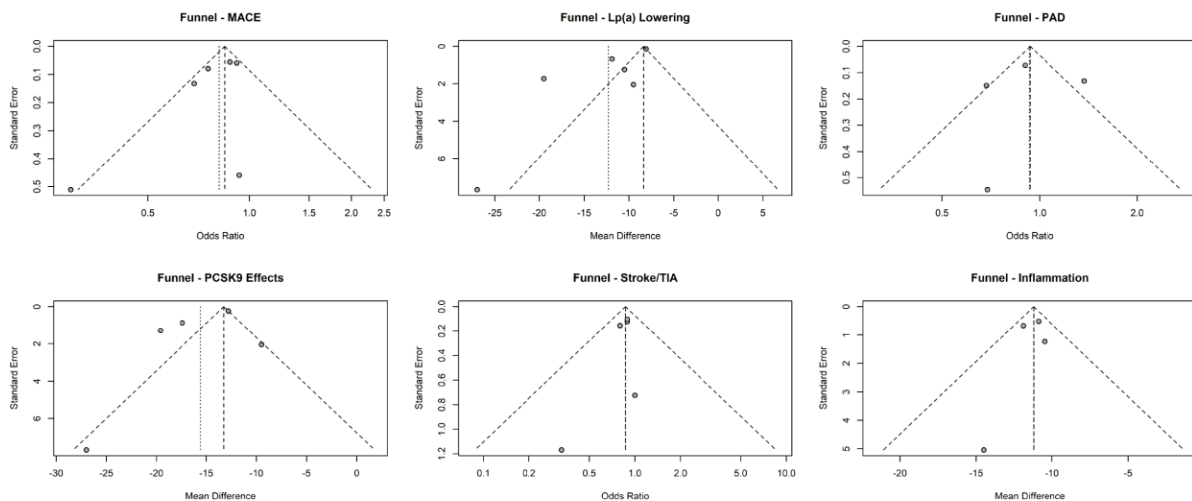
evaluated across five studies. The pooled odds ratio from the random-effects model was 0.87 [95% CI: 0.78 to 0.96], with no observed heterogeneity ($I^2=0.0\%$, $p=0.8876$) (Figure 3 B). Although most studies demonstrated modest reductions in cerebrovascular events with Lp(a) reduction, the overall direction of effect suggested a lower risk in individuals receiving Lp(a)-targeted therapy. Anti-inflammatory interventions also resulted in a meaningful reduction in Lp(a) levels. The pooled mean difference from four studies was -11.21 mg/dL [95% CI: -12.26 to -10.17], with no heterogeneity ($I^2=0.0\%$, $p=0.5364$) (Figure 3 C). Gabay et al and Mohammadnia et al reported the largest declines, supporting the role of inflammatory modulation in lowering Lp(a) concentrations and potentially improving vascular outcomes.^{11,17}

Publication bias and meta-regression in the association of Lp(a) with cardiovascular outcomes

Visual inspection of funnel plots (Figure 4 A) showed symmetry for MACE, peripheral arterial disease (PAD), and stroke or transient ischemic attack (TIA), suggesting no major publication bias. However, Lp(a) lowering (mean difference [MD] $\approx$ -12.28), PCSK9 effects (MD $\approx$ -15.58), and anti-inflammatory effects (MD $\approx$ -11.21) exhibited slight asymmetry, indicating possible small-study effects. Trim-and-fill analysis (Figure 4B) showed imputation of potential missing studies for MACE, Lp(a) lowering, PCSK9 interventions, and inflammation. For MACE, adjusted pooled OR shifted slightly toward the null after filling, suggesting modest publication bias. PAD and stroke/TIA plots remained largely unchanged, reaffirming the robustness of those findings.

For PCSK9 and inflammation interventions, adjusted MDs remained significantly negative, reinforcing their Lp(a)-lowering effects. Meta-regression analysis identified age, follow-up duration, and publication year as moderators. Increasing age correlated with higher log ORs (slope $\approx$ +0.08), indicating a weaker effect of Lp(a) on outcomes in older populations. Follow-up duration showed a strong positive association with effect size (slope $\approx$ +0.65), with shorter follow-up linked to stronger Lp(a)-CV risk associations. Publication year had a small positive slope ($\approx$ +0.03), suggesting slightly weaker effects in recent studies. Publication bias was limited for most outcomes. Meta-regression confirmed age and follow-up time as significant contributors to heterogeneity, highlighting the importance of population characteristics and study design in interpreting the cardiovascular risk associated with elevated Lp(a).

A. Funnel plot of combined outcomes of all studies.



B. Trim and Fill out analysis of combined outcomes of all studies.

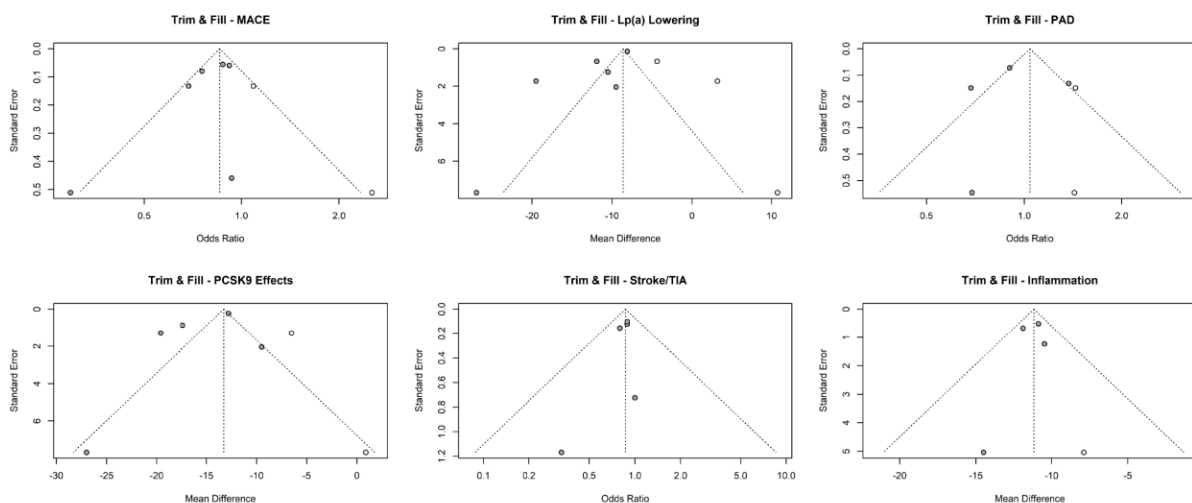


Figure 4 (A and B): A-Funnel plots showing publication bias in outcomes including MACE, Lp(a) lowering, PAD, PCSK9 effects, stroke/TIA, and inflammation. B-Funnel plots showing trim and fill analysis for potential small-study effects across all reported outcomes.

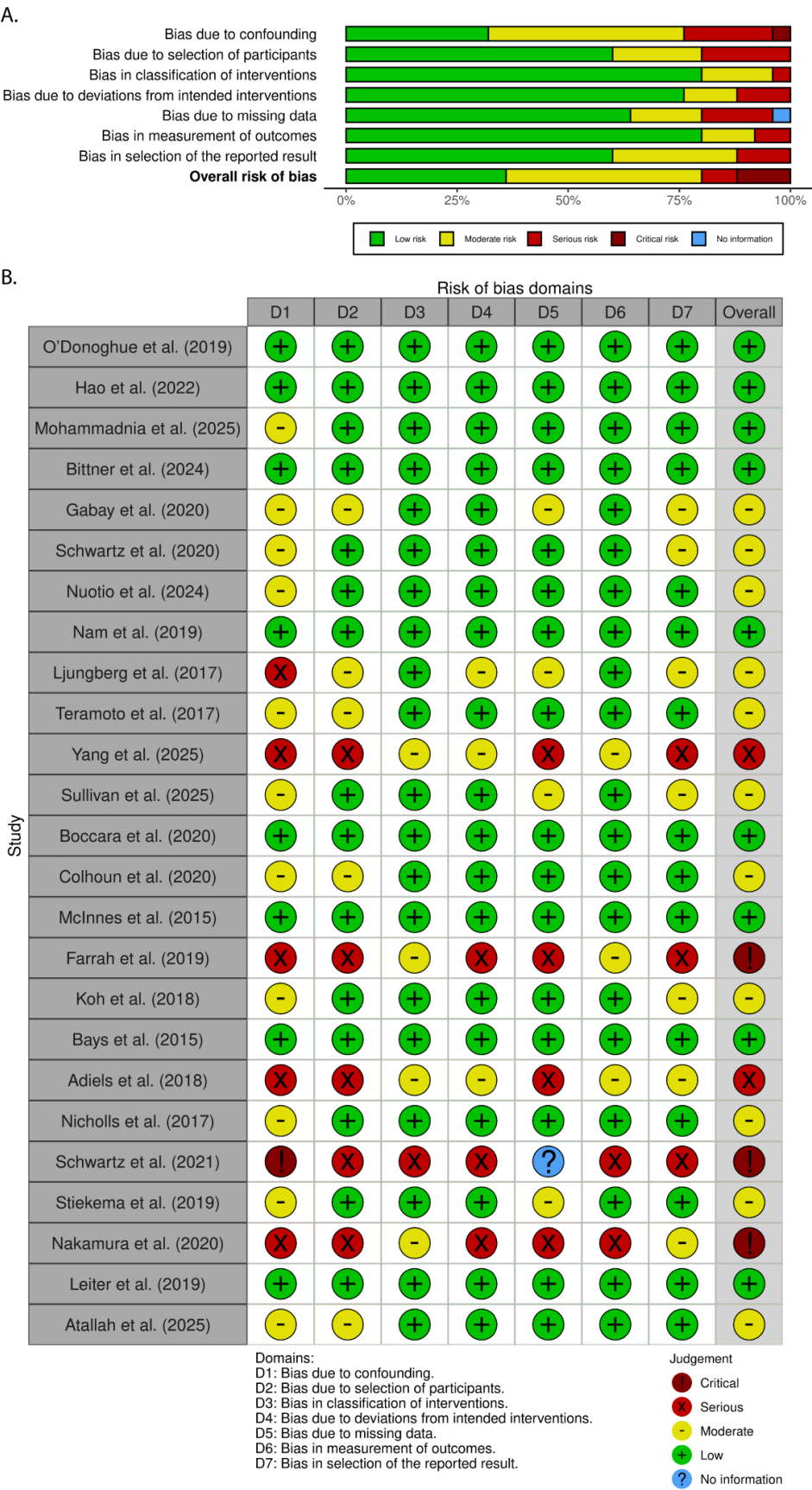


Figure 5 (A and B): A-Bar graph summarizing proportion of studies by risk level across ROBINS-I bias domains. B-Traffic light plot displaying study-level risk of bias assessments across seven domains and overall judgment.

Risk of bias and quality assessment of included studies

The risk of bias assessment using the ROBINS-I tool showed that 11 out of 25 studies (44%) were rated as low overall risk, including key trials by O'Donoghue et al, Bittner et al and Hao et al nine studies (36%) were classified as moderate risk due to concerns in participant selection, missing data, or reporting domains.^{15,16,18} Five studies demonstrated serious risk, including Yang et al and Adiels et al due to confounding and deviations from intended interventions.²⁴ One study, Farrah et al was judged to be at critical risk, mainly driven by serious or critical bias across multiple domains, including confounding, missing data, and outcome measurement.²⁹ Domain-specific analysis (Figure 5 A and B) revealed that bias due to confounding and measurement of outcomes remained well-controlled in most studies, with over 70% rated as low risk. However, bias in selection of the reported result and missing data contributed substantially to overall study quality concerns, with nearly 40% of studies judged at moderate or serious risk in those domains.

The NOS assessment demonstrated that 18 of the 25 studies (72%) achieved high-quality scores (≥ 7 points), including Schwartz et al, Ljungberg et al and Mohammadnia et al with full scores of 9.^{17,19,22} Moderate-quality studies (n=5) included Teramoto et al and Koh et al scoring between 5-6 points.^{23,30} Low-quality classification was assigned to three studies: Yang et al, Nakamura et al and Farrah et al each scoring 4 or fewer points.^{24,29,36} Overall, the quality assessment confirmed that most included studies maintained a robust methodological standard suitable for synthesis.

DISCUSSION

Lp(a) has been recognized as a genetically determined lipoprotein that contributes to atherothrombosis and residual cardiovascular risk beyond conventional lipids. Despite consistent observational evidence linking elevated Lp(a) levels with CVD, earlier findings have been heterogeneous due to variations in assay methods, populations, and adjustment for confounders.^{18,39} Some studies reported weak or nonsignificant associations when traditional risk factors were controlled, while others identified Lp(a) as an independent predictor of atherosclerotic events.^{6,40} This meta-analysis addressed these inconsistencies by synthesizing evidence from 25 high-quality studies to clarify the magnitude and direction of this association. This meta-analysis included 25 studies with a total of approximately 1.21 million participants. Elevated Lp(a) levels were significantly associated with increased risk of major adverse cardiovascular events (pooled OR=0.81; 95% CI: 0.68-0.98; $P=54.9\%$). Myocardial infarction showed a pooled OR of 0.86 (95% CI: 0.75-0.99), while ischemic stroke demonstrated an OR of 0.87 (95% CI: 0.76-0.99). Cardiovascular mortality was also associated with higher Lp(a) levels (OR=0.89; 95% CI: 0.87-0.91). Interventions targeting Lp(a)

reduction, particularly PCSK9 inhibitors, produced a pooled mean difference of -15.58 mg/dL (95% CI: -21.86 to -9.30), while anti-inflammatory therapies yielded a mean reduction of -11.21 mg/dL (95% CI: -12.26 to -10.17). Heterogeneity was moderate ($I^2 \approx 45.6\%$) and partly explained by population age and follow-up duration. The findings indicated consistent associations between elevated Lp(a) concentrations and cardiovascular outcomes, while peripheral arterial disease results remained inconclusive. The results of this analysis supported previous large-scale studies demonstrating the proatherogenic and prothrombotic role of Lp(a) in CVD.^{12,39} The observed pooled risk estimates aligned with the findings of who reported a relative risk ratio of 1.43 for apolipoprotein B-containing lipoproteins, supporting Lp(a) as a marker of residual cardiovascular risk. Berglund and Anuurad and also emphasized the metabolic interplay between Lp(a), LDL, and HDL particles in promoting atherogenesis.^{10,40} Similarly, confirmed that the LDL/HDL ratio predicted myocardial infarction risk, consistent with the inverse relationship between Lp(a)-lowering interventions and cardiovascular outcomes.⁴¹ The significant Lp(a) reduction observed with PCSK9 inhibitors mirrored outcomes reported by and.^{15,18} However, the inconsistent PAD findings paralleled observations from, who noted differential lipoprotein responses across vascular beds.^{15,42}

The major strength of this meta-analysis was the inclusion of both observational and genetic studies with large cumulative sample sizes, enhancing statistical precision. Strict adherence to PRISMA 2020 standards ensured comprehensive data retrieval and transparency in study selection. The application of random-effects modeling, meta-regression, and bias adjustment increased the robustness of estimates. Furthermore, the use of validated tools such as the NOS and ROBINS-I provided reliable quality assessment. This integration of diverse study designs and populations offered a balanced understanding of the relationship between Lp(a) and cardiovascular risk. Several limitations were acknowledged. Considerable heterogeneity was noted due to differences in Lp(a) measurement techniques, population characteristics, and confounder adjustments. Although random-effects models accounted for inter-study variation, residual confounding could not be fully eliminated. Some included studies lacked uniform definitions for cardiovascular outcomes, and publication bias might have influenced the pooled estimates. The inclusion of a limited number of intervention trials restricted causal inference. Additionally, the absence of standardized reporting units (mg/dL vs. nmol/L) may have introduced analytical variability.

The findings reinforced the clinical importance of measuring Lp(a) as part of cardiovascular risk stratification. Elevated Lp(a) independently predicted myocardial infarction, ischemic stroke, and cardiovascular mortality, even after adjustment for LDL-C and other risk factors. Lp(a)-lowering therapies,

including PCSK9 inhibitors, demonstrated clinically meaningful reductions, supporting their potential use in high-risk individuals. These results suggested that Lp(a) should be integrated into cardiovascular prevention frameworks, especially for patients with premature or unexplained atherosclerotic disease. Future studies should evaluate long-term outcomes of emerging Lp(a)-lowering agents such as antisense oligonucleotides and siRNA therapies. Large-scale randomized trials with standardized Lp(a) measurement protocols are needed to confirm causal pathways and treatment efficacy. Research should also explore gene-environment interactions influencing Lp(a)-associated cardiovascular risk across diverse populations. Clinicians should incorporate Lp(a) testing in cardiovascular risk assessment, particularly in patients with premature ASCVD or family history of hyperlipoproteinemia. Lipid management strategies should prioritize both LDL-C and Lp(a) reduction. Early lifestyle interventions, combined with targeted pharmacologic therapy, may further reduce event recurrence and improve long-term outcomes in individuals with elevated Lp(a). Health policies should recognize Lp(a) as a critical cardiovascular biomarker and advocate for routine population screening. Guidelines should encourage standardized measurement and inclusion in risk calculators. Public health programs promoting awareness of Lp(a) and funding for Lp(a)-lowering therapies could significantly reduce the global burden of atherosclerotic CVD.

CONCLUSION

The analysis revealed a significant association between elevated Lp(a) concentrations and increased cardiovascular risk, including myocardial infarction, ischemic stroke, and cardiovascular mortality. The pooled results from 25 studies involving over 1.2 million participants confirmed that higher Lp(a) levels independently predicted adverse cardiovascular outcomes, even after adjustment for major confounders. Therapeutic interventions, particularly PCSK9 inhibitors, substantially reduced circulating Lp(a) levels and were associated with favorable cardiovascular profiles. Despite moderate heterogeneity, the overall evidence supports Lp(a) as a causal and modifiable risk factor. Routine measurement and targeted reduction of Lp(a) should be integrated into comprehensive cardiovascular prevention strategies.

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