Apolipoprotein B Discordance with Low-Density Lipoprotein Cholesterol and Risk of Atherosclerotic Cardiovascular Events and Mortality: A Systematic Review and Meta-Analysis

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Citation : Putri, A. W., Adrya, J., Varsha, S., Ferhat, M., Pangestika, S., Eliadi, N., & Dharmasaputra, A. 2026. Apolipoprotein B Discordance with Low-Density Lipoprotein Cholesterol and Risk of Atherosclerotic Cardiovascular Events and Mortality: A Systematic Review and Meta-Analysis. *Medicinus*, 15(3), 160–172.
Keywords : apolipoprotein B; atherosclerotic cardiovascular disease; low-density lipoprotein cholesterol; meta-analysis
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Online First : 26 June 2026

Abstract

Background:
Apolipoprotein B (apoB) reflects the burden of atherogenic lipoprotein particles and may identify residual cardiovascular risk when low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol appears controlled. This review evaluated whether elevated apoB discordance is associated with cardiovascular events and mortality.

Methods:
PubMed, Scopus, ScienceDirect, and Google Scholar were searched through 23 May 2026. Eligible studies enrolled adults, assessed apoB discordance using residual-, percentile-, or median-based definitions, and reported adjusted estimates for clinical outcomes. Risk of bias was assessed using the Newcastle-Ottawa Scale. Random-effects meta-analysis used restricted maximum likelihood estimation with Hartung-Knapp-Sidik-Jonkman adjustment.

Result:
Four studies (128,103 participants) were included. In the cohort-only analysis, the pooled estimate was HR 1.28 (95% CI 0.31-5.25; I^2 = 67.7%). For all-cause mortality, the pooled estimate was HR 1.12 (95% CI 1.02-1.23; I^2 = 0%). The residual-based excess apoB-only analysis showed HR 1.11 (95% CI 1.04-1.17; I^2 = 0%).

Conclusions:
ApoB discordance may identify residual risk beyond LDL-C, with the most consistent evidence observed for all-cause mortality. Evidence for atherosclerotic cardiovascular events and cardiovascular mortality remains suggestive but limited by heterogeneity and few eligible studies.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of premature morbidity and mortality globally, accounting for a substantial proportion of preventable death across both high-income and low-to-middle-income settings.[1-2] Lipid modification occupies a central role in the prevention and management of ASCVD, and decades of genetic, epidemiological, and randomized clinical evidence have established low-density lipoprotein cholesterol (LDL-C) as the primary target of therapeutic intervention.[2-3] Mendelian randomization analyses and large statin intervention trials have consistently demonstrated that each unit reduction in LDL-C is accompanied by a proportional reduction in major cardiovascular events, supporting a causal and dose-dependent

relationship between LDL-containing particles and atherosclerotic disease progression.[2-3] Accordingly, international guideline bodies have formalized LDL-C lowering as the principal strategy for primary and secondary cardiovascular risk reduction, with increasingly ambitious targets for high- and very-high-risk populations.[4-6]

Despite its widespread clinical use, LDL-C quantifies the total cholesterol mass transported within LDL particles rather than the number of circulating atherogenic particles, a distinction that carries important clinical consequences.[1,7] Apolipoprotein B (apoB), by contrast, is present as a single molecule on each atherogenic lipoprotein particle including very-low-density lipoprotein remnants, intermediate-density lipoproteins, LDL particles, and lipoprotein(a) and therefore provides a direct quantitative index of total atherogenic particle burden.[1,8] Multiple large epidemiological studies and individual participant data meta-analyses have demonstrated that apoB predicts cardiovascular events at least as well as, and in certain populations more accurately than, LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C), independently of established risk factors.[7,9-10] The prognostic relevance of apoB over cholesterol-based measures is most apparent in clinical states characterized by altered lipoprotein composition, including type 2 diabetes mellitus, metabolic syndrome, insulin resistance, hypertriglyceridemia, obesity, and intensive pharmacologic lipid lowering, where cholesterol-depleted small dense LDL particles are prevalent and LDL-C may systematically underestimate atherogenic exposure.[1,3,8,11]

Discordance between apoB and LDL-C or non-HDL-C arises when atherogenic particle number is disproportionately high relative to the cholesterol mass those particles carry, yielding an apoB level higher than predicted from cholesterol measurement.[12-13] Emerging data have demonstrated substantial inter-individual variation in apoB across equivalent LDL-C or non-HDL-C strata, indicating that a meaningful proportion of patients with apparently controlled cholesterol levels may harbor elevated atherogenic particle burdens and consequently underappreciated residual cardiovascular risk.[12-13] Longitudinal evidence from the CARDIA study demonstrated that apoB–LDL-C discordance detectable in young adults was independently associated with subsequent development of coronary artery calcification, implicating cumulative excess particle exposure as a mechanism distinct from cholesterol burden.[14] Further analyses in statin-treated cohorts, type 2 diabetes populations, and individuals with established coronary artery disease have reported associations between apoB discordance and incident vascular events or all-cause mortality that were not fully captured by LDL-C or non-HDL-C alone.[15-20] Discordance definitions across the published literature have varied and have included residual-based excess apoB, percentile-based approaches, and median-based classifications relative to LDL-C or non-HDL-C, highlighting the need for systematic evaluation that integrates these diverse methodological approaches.[17-20]

Despite this body of prior work, a focused quantitative synthesis evaluating the clinical outcomes associated with apoB discordance across diverse study designs and populations has not previously been conducted. This evidence gap is clinically relevant because apoB measurement is increasingly recognized in contemporary lipid management guidelines and expert consensus documents from European, American, Canadian, and National Lipid Association bodies as a useful secondary marker for risk refinement, particularly among individuals with cardiometabolic risk factors, discordant lipid profiles, or residual risk during therapy.[4-6,8,11,21-22] Characterizing the direction, magnitude, and consistency of the association between apoB discordance and clinical endpoints would inform whether this phenotype captures meaningful residual risk beyond cholesterol mass alone and provide a structured evidence base to support or qualify its broader clinical adoption. Therefore, this systematic review and meta-analysis was conducted to evaluate whether elevated apoB

discordance relative to LDL-C or non-HDL-C is associated with atherosclerotic cardiovascular events, myocardial infarction, and all-cause mortality among adults with elevated cardiovascular risk.

Material and Methods

Search Strategy

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and methodological guidance from the Cochrane Handbook for Systematic Reviews of Interventions.[23-24] A systematic literature search was conducted across PubMed, Scopus, ScienceDirect, and Google Scholar electronic databases from inception through 23 May 2026. The search strategy combined controlled vocabulary, indexed terms, and free-text terms related to apolipoprotein B, LDL-C, non-HDL-C, lipid discordance, excess apoB, cardiovascular events, myocardial infarction, and all-cause mortality. Reference lists of eligible articles were also screened to identify additional relevant studies. Boolean operators were used to construct comprehensive search strings tailored to each database. Reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible publications. No language or date restrictions were applied. Study selection was performed independently by all authors, and any discrepancies were resolved through consensus discussion.

Eligibility Criteria

The eligibility criteria were structured according to the Population, Intervention or Exposure, Comparator, and Outcomes framework. The population comprised adults aged 18 years or older with elevated cardiovascular risk, including primary prevention populations with cardiometabolic risk factors, secondary prevention cohorts with established atherosclerotic cardiovascular disease, and statin-treated patients regardless of achieved LDL-C level. The exposure was elevated apoB discordance relative to LDL-C or non-HDL-C, defined as a higher atherogenic particle burden than predicted by cholesterol mass. Eligible exposure definitions included residual-based excess apoB, percentile-based discordance, and median-based discordance. The comparator was a concordant lipid phenotype, defined as low or normal apoB commensurate with LDL-C or non-HDL-C. Eligible outcomes included composite atherosclerotic cardiovascular events, myocardial infarction, and all-cause mortality. Studies were excluded if they were reviews, editorials, case reports, animal studies, in vitro studies, conference abstracts without sufficient quantitative data, duplicate reports, or studies that did not report relevant adjusted effect estimates.

Data Extraction

Data were extracted independently by all authors using a standardized form and checked for consistency with the prespecified PICO framework and discrepancies were resolved through discussion. Extracted variables included study identification, publication year, country or data source, study design, sample size, follow-up duration, population characteristics, baseline cardiovascular risk profile, statin use, lipid measurements, apoB-discordance definition, comparator category, outcome definition, adjusted effect estimate, adjustment covariates, and key methodological concerns. For reports containing analytically distinct derivation and validation cohorts, each cohort was summarized separately for outcome synthesis while preserving the report-level count for PRISMA reporting.

Risk of Bias

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational cohort and case-control studies.[25] The NOS evaluation considered selection of study groups, comparability of exposed and reference groups, ascertainment of exposure or outcome, adequacy of follow-up for cohort studies,

and response or exposure assessment for case-control evidence. Total NOS scores were summarized out of nine stars and translated into overall risk-of-bias judgments based on study design, adjustment quality, outcome ascertainment, and key methodological concerns reported in the extraction table.

Statistical Analysis

The pooled summary measure (PSM) was the adjusted relative effect estimate for each outcome. Hazard ratios, odds ratios, and risk ratios with 95% confidence intervals were extracted preferentially from the most fully adjusted multivariable models. Effect estimates were transformed to the natural logarithmic scale, and standard errors were calculated from the reported confidence intervals. Pairwise random-effects meta-analysis was performed using RStudio 4.6.0 with the metafor/meta analytical framework. Between-study variance was estimated using restricted maximum likelihood (REML), and confidence intervals for pooled estimates were calculated using the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment. Statistical heterogeneity was assessed using the I^2 statistic and τ^2. Because the number of included studies was small, publication bias testing and small-study effect assessment were not performed.

Results

A total of 308 records were identified from PubMed (n = 9), Scopus (n = 11), ScienceDirect (n = 136), and Google Scholar (n = 152). After removing duplicates, 275 records underwent title and abstract screening. The final evidence base consisted of four reports representing four eligible studies. In the PRISMA flow, 187 records were excluded during title and abstract screening, 88 reports were sought for retrieval, no reports were unavailable, and 84 full-text reports were excluded for the following reasons: Narrative review, scoping reviews, and systematic reviews (n = 52); no discordance analysis (n = 16); surrogate outcomes only (n = 12); and cross-sectional design (n = 4). Finally, 4 studies were included in the review (Figure 1).

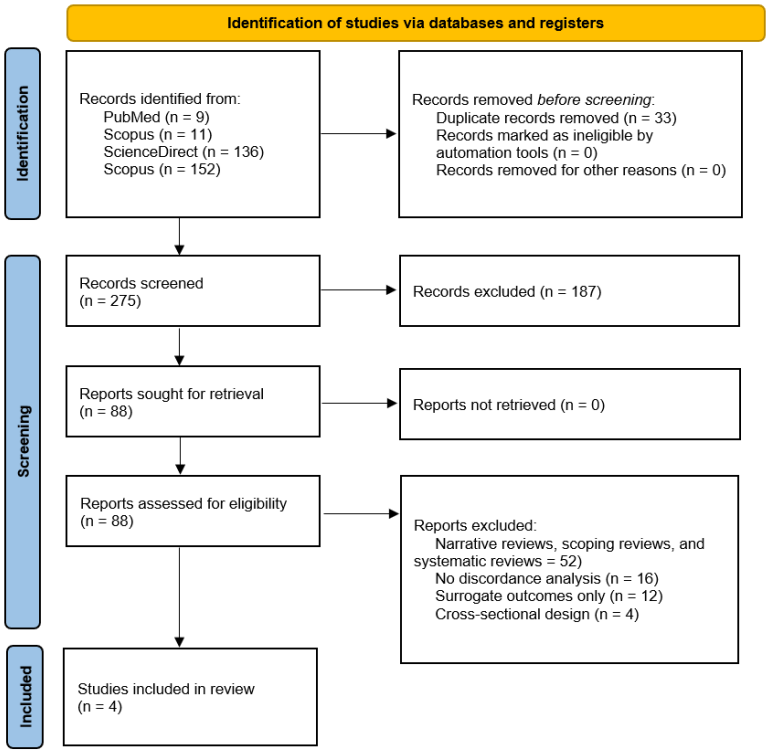

Figure 1. PRISMA flow diagram of study selection

The four included reports contributed five analytical cohorts or arms because one report included both a primary Chinese statin-treated coronary artery disease cohort and an external UK Biobank validation cohort. Study populations included adults with type 2 diabetes mellitus without baseline atherosclerotic cardiovascular disease, statin-treated patients with established coronary artery disease, statin-treated adults from a general population cohort, and a case-control population with first acute myocardial infarction. Sample size ranged from 11,918 to 68,616 in cohort-based analyses, with follow-up ranging from 5.2 years to approximately 15.4 years where applicable. ApoB discordance was defined using residual-based excess apoB, percentile-based apoB versus non-HDL-C discordance, or median-based apoB versus LDL-C discordance.

Risk of bias assessment using the NOS showed low overall risk of bias for Lyu et al., Pan et al. China primary cohort, Pan et al. UK Biobank validation cohort, and Johannesen et al., The Sniderman et al. case-control study was judged to have moderate-to-high risk of bias because of non-fasting samples, limited covariate adjustment, and case-control design limitations. Key methodological concerns across otherwise low-risk studies included single baseline lipid measurement, incomplete capture of treatment changes during follow-up, and potential mismatch when applying a prediction equation derived from one population to another.

Table 1. Demographic Characteristics of Included Studies

Author, Year	N	Age	Sex	Risk Profile	Follow-up	Statin use	Discordance Profile
Lyu et al., 2026	11,918	59.7 ± 6.6 yr	7,273 male (61.0%)	Adults with type 2 diabetes mellitus; baseline ASCVD excluded	185.3 months median	64.7%	Residual-based excess apoB predicted from LDL-C; elevated excess apoB modeled continuously and by percentile
Pan et al., 2026 China	68,616	63.1 ± 10.8 yr	49,540 male (72.2%)	Statin-treated adults with established coronary artery disease; T2DM ~34.2%; hypertension ~60.0%; CKD ~17.6%	5.2 yr median	100%	Residual-based excess apoB; highest quartile compared with lowest quartile
Pan et al., 2026 UKB	13,702	62.3 ± 5.7 yr	10,769 male (78.6%)	External UK Biobank validation cohort of statin-treated adults with established coronary artery disease	13.3 yr median	100%	Residual-based excess apoB using derivation equation from Chinese cohort
Johannesen et al., 2021	13,015	Approximately 68 yr median	Approximately 7,158 male (55%)	Statin-treated adults from the Copenhagen General Population Study; baseline ASCVD ~39.2%; T2DM ~20%	8 yr median	100%	Median/percentile-based apoB versus LDL-C discordance
Sniderman et al., 2012	20,852	57.3 ± 12.2 yr	Approximately 15,780 male (75.7%)	INTERHEART first acute myocardial infarction cases and controls from 52 countries	Not applicable	NR	Percentile-based non-HDL-C versus apoB discordance indicating cholesterol-depleted particles

Abbreviations: apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CGPS, Copenhagen General Population Study; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; NR, not reported; T2DM, type 2 diabetes mellitus; UKB, UK Biobank.

Table 2. Characteristics of Included Studies

Author, Year	Design/source	Exposure definition	Comparator	Outcome	Adjusted effect
Lyu et al., 2026	Prospective cohort; UK Biobank	Residual-based excess apoB among adults with T2DM	Lower/reference excess apoB	ASCVD events	Per-SD excess apoB HR 1.18 (1.13-1.23); ≥90th percentile HR 1.53 (1.33-1.76)
Pan et al., 2026 China	Retrospective pooled cohort; statin-treated CAD	Residual-based excess apoB quartiles	Lowest excess apoB quartile	All-cause mortality and cardiovascular mortality	All-cause mortality aHR 1.10 (1.03-1.18); cardiovascular mortality aHR 1.28 (1.17-1.40)
Pan et al., 2026 UKB	Prospective external validation cohort; statin-treated CAD	Residual-based excess apoB quartiles	Lowest excess apoB quartile	All-cause mortality and cardiovascular mortality	All-cause mortality aHR 1.11 (1.04-1.18); cardiovascular mortality aHR 1.13 (1.03-1.24)
Johannesen et al., 2021	Prospective cohort; Copenhagen General Population Study	High apoB with low LDL-C discordance in statin-treated adults	Concordant low apoB and low LDL-C	Myocardial infarction and all-cause mortality	Myocardial infarction HR 1.49 (1.15-1.93); all-cause mortality HR 1.21 (1.07-1.36)
Sniderman et al., 2012	Case-control; INTERHEART	Percentile-based apoB/non-HDL-C discordance indicating cholesterol-depleted particles	Concordant reference phenotype	First myocardial infarction	OR 1.58 (1.38-1.81) for first myocardial infarction

Abbreviations: aHR, adjusted hazard ratio; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Table 3. Newcastle-Ottawa Scale Risk of Bias Assessment

Study	Study design	NOS total (max 9)	Key concern	Overall risk of bias
Lyu et al., 2026	Prospective cohort	9/9	Single baseline measurement; treatment changes not captured	Low
Pan et al., 2026 China	Retrospective pooled cohort	8/9	Retrospective design; statin dose/adherence changes not captured over follow-up	Low
Pan et al., 2026 UKB	Prospective validation cohort	9/9	Prediction equation derived from Chinese cohort; potential equation mismatch	Low
Johannesen et al., 2021	Prospective cohort	8/9	BMI and diabetes deliberately excluded as covariates; possible regression dilution bias	Low
Sniderman et al., 2012	Case-control	4/9	Non-fasting samples; minimal covariate adjustment; case-control design	Moderate-to-high

The cohort-only analysis for atherosclerotic cardiovascular events or myocardial infarction included two cohort studies with eligible event-based outcomes. Lyu et al. reported an adjusted HR of 1.18 (95% CI 1.13–1.23) per standard deviation increase in residual-based excess apoB and an adjusted HR of 1.53 (95% CI 1.33–1.76) for participants at or above the 90th percentile of excess apoB, relative to a lower excess apoB reference group, for incident ASCVD events.[19] Johannesen et al. reported a HR of 1.49 (95% CI 1.15–1.93) for incident myocardial infarction among statin-treated adults with high apoB and low LDL-C discordance relative to a concordant low apoB and low LDL-C phenotype.[16] The Sniderman et al. case-control estimate (OR 1.58, 95% CI 1.38–1.81 for first acute myocardial infarction) was not included in the cohort-only pooled analysis because of its case-control design.[17] Between-study variance was estimated using the restricted maximum likelihood (REML) estimator, and confidence intervals were derived using the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment. The random-effects pooled estimate was HR 1.28 (95% CI 0.31–5.25; I^2 = 67.7%; τ^2 = 0.0704) (Figure 2).

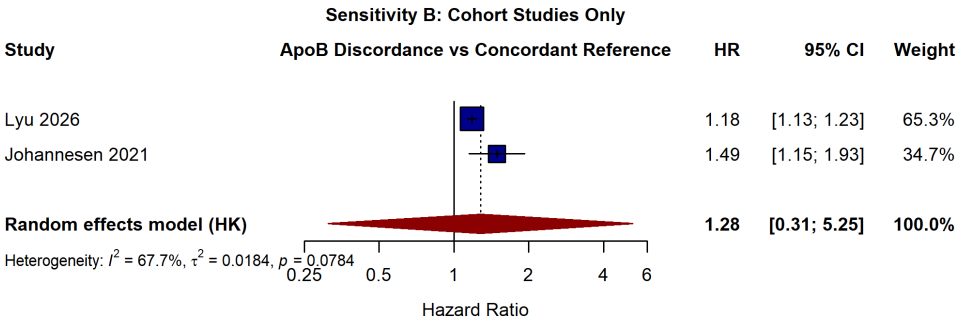

Figure 2. Cohort-only random-effects meta-analysis for atherosclerotic cardiovascular events or myocardial infarction

The all-cause mortality analysis pooled three cohort-derived effect estimates. Pan et al. (China primary cohort) reported an adjusted HR of 1.10 (95% CI 1.03–1.18) for all-cause mortality in the highest versus lowest quartile of residual-based excess apoB among 68,616 statin-treated adults with coronary artery disease over a median follow-up of 5.2 years.[20] Pan et al. (UK Biobank external validation cohort) reported an adjusted HR of 1.11 (95% CI 1.04–1.18) for all-cause mortality using the same residual-based discordance definition applied to 13,702 statin-treated adults over a median follow-up of 13.3 years.[20] Johannesen et al. reported a HR of 1.21 (95% CI 1.07–1.36) for all-cause mortality in 13,015 statin-treated adults with high apoB and low LDL-C discordance relative to a concordant reference group over a median follow-up of 8 years.[16] Between-study variance was estimated using the REML estimator with HKSJ adjustment. The random-effects pooled estimate was HR 1.12 (95% CI 1.02–1.23; I^2 = 0%; τ^2 < 0.0001) (Figure 3).

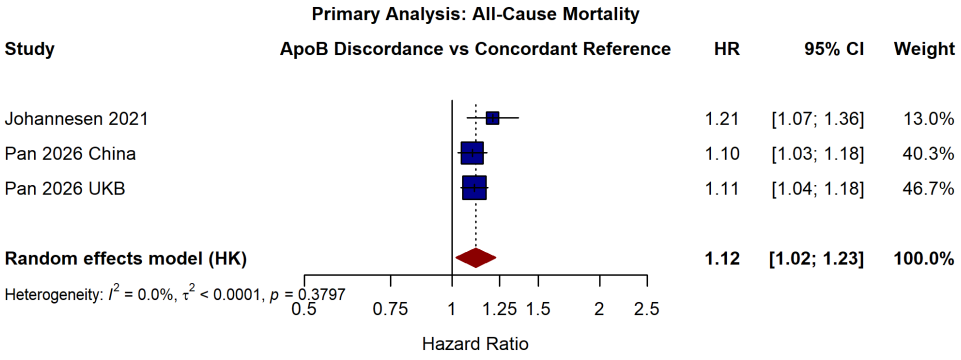

Figure 3. Random-effects meta-analysis for all-cause mortality

The sensitivity analysis restricted to studies applying residual-based excess apoB definitions included two cohort estimates contributing to the all-cause mortality outcome. Pan et al. (China primary cohort) contributed an adjusted HR of 1.10 (95% CI 1.03–1.18),20 and Pan et al. (UK Biobank validation cohort) contributed an adjusted HR of 1.11 (95% CI 1.04–1.18).[20] Johannesen et al. was excluded from this sensitivity analysis because its discordance definition relied on median- and percentile-based rather than residual-based classification.[16] Between-study variance was estimated using the REML estimator with HKSJ adjustment. The random-effects pooled estimate was HR 1.11 (95% CI 1.04–1.17; I^2 = 0%; τ^2 = 0) (Figure 4).

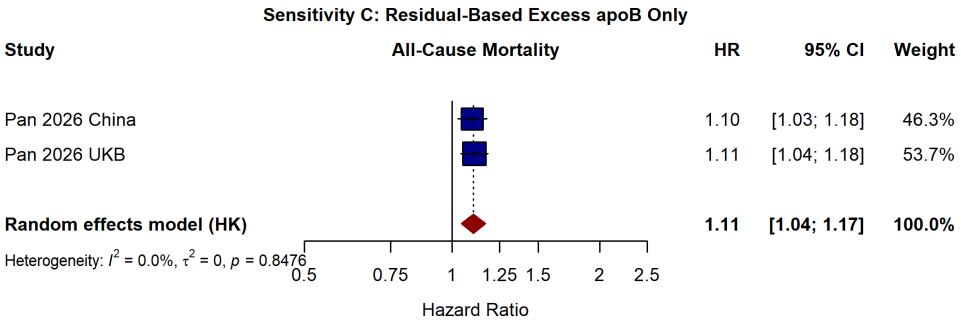

Figure 4. Residual-based excess apoB-only random-effects meta-analysis for all-cause mortality

Discussion

This systematic review and meta-analysis synthesized available evidence from four reports representing four eligible studies to evaluate the prognostic significance of apoB discordance relative to LDL-C or non-HDL-C in adults with elevated cardiovascular risk. The principal finding was that elevated apoB discordance was associated with a higher risk signal for clinical outcomes beyond cholesterol mass alone, with the strongest and most internally consistent evidence observed for all-cause mortality. In the all-cause mortality analysis, which pooled three eligible cohort-derived estimates, the summary hazard ratio was statistically significant with negligible between-study heterogeneity, and this finding was robust to a sensitivity analysis restricted to residual-based excess apoB definitions. The cohort-only analysis of atherosclerotic cardiovascular events or myocardial infarction yielded a non-significant pooled estimate with moderate-to-high heterogeneity, reflecting material differences in study design, population composition, discordance definition, outcome ascertainment, and effect measure across the included reports.[15-20] Collectively, these results are consistent with the biological framework that apoB captures atherogenic particle burden more directly than LDL-C, particularly when cholesterol content per particle varies substantially across metabolic and treatment states.[1-3,7-10]

The present findings extend and complement a broader body of literature examining the comparative prognostic value of apoB and cholesterol-based lipid indices. Large-scale epidemiological studies and collaborative meta-analyses have consistently shown that apoB is at least comparable to LDL-C and non-HDL-C as a predictor of cardiovascular events, with evidence from several analyses suggesting marginal superiority when assessed across the full range of metabolic and lipid profiles.[7,9-10] The Copenhagen General Population Study analysis by Johannesen et al. demonstrated that apoB and non-HDL-C outperformed LDL-C in reflecting residual risk among statin-treated patients, providing a direct contextual reference for the discordance-based analyses included in the present synthesis.[16] The INTERHEART case-control study contributed evidence from a multinational population evaluating first acute myocardial infarction and showed that apoB–non-HDL-C discordance was associated with incident event risk, albeit with methodological limitations related to non-fasting sampling and limited covariate adjustment.[17] The CARDIA analysis established that discordance between apoB and LDL-C identifiable in early adulthood predicts subclinical coronary atherosclerosis in later life, implicating long-term cumulative atherogenic particle exposure as a mechanism distinct from cholesterol burden alone.[14] Recent analyses in statin-treated coronary artery disease cohorts and type 2 diabetes populations further demonstrated that excess apoB relative to LDL-C predicted long-term all-cause mortality and cardiovascular events independently of achieved LDL-C levels, reinforcing the prognostic independence of the particle-based phenotype.[19-20] Taken together, the available evidence converges on the conclusion that apoB discordance identifies a clinically meaningful lipid phenotype with

prognostic signal not fully explained by cholesterol measurement.[12-13,22]

The mechanistic basis for the associations observed in the present analysis is grounded in fundamental lipoprotein biology and the pathophysiology of arterial atherogenesis. Because each atherogenic lipoprotein particle carries exactly one apoB molecule, circulating apoB concentration provides a stoichiometric measure of total atherogenic particle number that is inherently independent of particle cholesterol content.[1,8] LDL-C, by contrast, measures the mass of cholesterol within LDL particles and is therefore subject to systematic variation when particle composition is altered by elevated triglycerides, insulin resistance, obesity, diabetes mellitus, or pharmacologic lipid lowering, all of which promote the formation of smaller, cholesterol-depleted but more numerous particles.[2-3,11] When LDL-C appears within an acceptable range but apoB is elevated, the arterial wall is exposed to a larger number of atherogenic particles that retain full capacity to traverse the endothelium, bind to arterial proteoglycans, become retained within the intima, undergo oxidative and enzymatic modification, and initiate the inflammatory cascade that characterizes atherosclerotic plaque formation and progression.[2-3] Lipoprotein(a) particles, which also carry apoB and are not captured by LDL-C measurement, may additionally contribute to discordance and residual atherogenic exposure in genetically susceptible individuals.[1,8,21] This mechanistic framework explains why apoB discordance may be of particular clinical relevance in type 2 diabetes, metabolic syndrome, hypertriglyceridemia, and statin-treated states, where cholesterol mass per particle is reduced but particle number may remain elevated.[2-6,12-13]

The clinical implications of the present findings must be interpreted within the framework of established lipid management guidelines and expert consensus statements. The 2019 ESC/EAS Guidelines and the 2021 ESC cardiovascular prevention guidelines recognize apoB and non-HDL-C as secondary therapeutic targets and endorse their use for risk refinement among patients with hypertriglyceridemia, diabetes mellitus, obesity, metabolic syndrome, very low LDL-C levels, or persistent residual risk during lipid-lowering therapy.[4-5] The 2018 AHA/ACC Blood Cholesterol Guideline similarly identifies non-HDL-C and apoB as adjunctive markers that may be informative in selected patients.[6] The National Lipid Association expert consensus elaborates on the role of apoB in clinical cardiovascular risk management, recommending its consideration as an equivalent or superior target to LDL-C in circumstances where cholesterol mass may be a poor surrogate for particle burden.[8] Expert analyses have argued for broader adoption of apoB as a primary treatment target based on its mechanistic directness and superior standardization relative to LDL-C, and have emphasized that discordant lipid profiles represent a clinically actionable phenotype warranting intensified risk management.[11,21-22] The present synthesis supports these positions by demonstrating that elevated apoB discordance is associated with an identifiable excess risk signal, particularly for mortality outcomes. However, the available evidence does not yet establish a single standardized discordance definition, a validated treatment threshold, or a dedicated management algorithm for clinically identified discordance. Clinicians should therefore use apoB discordance as a complementary tool to refine risk assessment alongside established LDL-C-based targets and guideline-directed therapy, rather than as a standalone or substitute decision criterion.[4-6,11,21-22]

This review has several important limitations that must be considered when interpreting its findings. The evidence base was limited to four reports, of which one contributed two analytical cohorts, constraining statistical power and precluding formal publication bias testing or small-study effect analysis; findings from such a restricted evidence base must be considered preliminary rather than definitive.[23-24] Substantial clinical and methodological heterogeneity was present across studies with respect to population

characteristics, baseline statin exposure, applied discordance definition, comparator group, outcome type, follow-up duration, and degree of multivariable adjustment, limiting the interpretability of pooled estimates for atherosclerotic cardiovascular event outcomes.[15-20] The primary cardiovascular event analysis combined atherosclerotic cardiovascular events and myocardial infarction as related but not identical endpoints, and the inclusion of a case-control design alongside cohort studies introduced additional design-level heterogeneity that effect measure transformation only partially addressed.[17] Although the all-cause mortality analyses were statistically more stable and exhibited negligible between-study heterogeneity, residual confounding from unmeasured cardiometabolic factors, changes in statin dose or adherence over follow-up, regression dilution bias from single baseline lipid measurement, and potential equation mismatch between cohorts cannot be excluded.[18-20] The discordance definitions used across studies residual-based excess apoB, percentile-based, and median-based approaches are not fully interchangeable, and the absence of a single standardized method limits cross-study comparability and derivation of clinically applicable thresholds.[11,13,21] Future prospective studies should employ standardized apoB discordance definitions, repeated lipid measurements, harmonized cardiovascular endpoint classification systems, and prespecified multivariable adjustment frameworks to establish the incremental prognostic value of apoB discordance with greater precision and generalizability.[11,21-24]

Conclusion

In conclusion, this systematic review and meta-analysis provides evidence that apoB discordance relative to LDL-C or non-HDL-C identifies a residual-risk lipid phenotype among adults with elevated cardiovascular risk that is not fully captured by cholesterol mass measurements alone. The most consistent prognostic signal was observed for all-cause mortality outcomes, whereas the evidence for atherosclerotic cardiovascular events and myocardial infarction was constrained by between-study heterogeneity, methodological diversity, and the small number of eligible reports. These findings are mechanistically supported by the established biology of atherogenic lipoprotein particles and are aligned with contemporary guideline recognition of apoB as a clinically informative marker for risk refinement beyond LDL-C. Confirmation in larger prospective studies employing harmonized discordance definitions, standardized outcome assessment, and robust adjustment for cardiometabolic confounders is needed before apoB discordance can be integrated into routine clinical decision-making algorithms as an independently actionable treatment target.

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