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Remnant cholesterol and hypertension: how outcome definition and baseline blood pressure affect the association

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2026 and was last updated on 14 October 2026.

INTRODUCTION

Review question / Objective Review question: What is the association between remnant cholesterol (RC) levels and hypertension, and how do the outcome definition (new-onset versus prevalent hypertension) and baseline blood pressure modify this association?

Objective: This systematic review and meta-analysis aims to evaluate the association between RC and hypertension. Specifically, the review will: (1) quantify the association between elevated RC and new-onset hypertension (hazard ratios, HR) separately from prevalent hypertension (odds ratios, OR); (2) investigate how baseline blood pressure and the RC exposure scale modify the estimated association; and (3) report specific hypertension phenotypes (e.g., preeclampsia, gestational hypertension, postpartum hypertension, isolated diastolic hypertension, hypertension with diabetes)

separately, rather than as a single merged "special subtype" category.

Rationale Remnant cholesterol (RC), the cholesterol content of triglyceride-rich lipoprotein remnants, is increasingly recognised as a marker of residual cardiovascular risk. Reported associations between RC and hypertension are inconsistent, and part of this inconsistency may arise from analytic choices rather than from true population differences: whether the outcome is new-onset or prevalent hypertension, whether baseline blood pressure is adjusted for, and which RC exposure scale (per 1 mmol/L, per standard deviation, cumulative RC) is used. This protocol therefore prespecifies separate synthesis by outcome type and study design, item-level quality evaluation, and explicit registration of overlapping sources, so that the influence of these analytic choices on the estimated association can be examined transparently.

Condition being studied Therefore, this review aims to systematically evaluate the association between RC and hypertension, while examining how the outcome definition (new-onset versus prevalent hypertension) and baseline blood pressure modify this association. Specific hypertension phenotypes are reported separately rather than pooled into a unified subtype category.

METHODS

Search strategy The search strategy combines controlled vocabulary (MeSH/Emtree terms) and free-text keywords covering two concept blocks: "remnant cholesterol" (including remnant-like particle cholesterol, calculated RC, TC minus HDL-C minus LDL-C) AND "hypertension" (including high blood pressure, incident hypertension, prevalent hypertension). Reference lists of all included studies and relevant systematic reviews are manually screened. No unpublished data, grey literature, conference abstracts without sufficient full text, or trial registry records are included. The full executed search strings and record counts are documented in Supplementary File S1 (PubMed: 195 records as of 12 October 2026).

Participant or population The review includes human participants from observational studies, including general population-based cohorts and specific clinical populations. Eligible participants are adults who: underwent assessment of serum lipid profiles and RC levels; and were evaluated for hypertension status or incident hypertension. Children and adolescents are not included. Studies focusing exclusively on secondary hypertension caused by specific endocrine, renal, genetic, or pharmacological conditions are excluded.

Intervention Not applicable. This review evaluates remnant cholesterol as an exposure factor rather than an intervention. The exposure of interest is elevated RC level, assessed either through direct laboratory measurement or calculated using the formula: $RC = \text{Total cholesterol} - HDL-C - LDL-C$. Studies reporting RC as a continuous variable (e.g., per unit increase or per standard deviation increase) or categorical variable (e.g., quartiles, tertiles, clinical cut-off values) are considered eligible.

Comparator The comparator consists of participants with lower RC levels or the reference category of RC exposure. For categorical analyses, the comparator will generally be the lowest RC category, while the exposure group is the highest RC category or other predefined elevated RC categories. For continuous analyses, the

association between incremental increases in RC levels and hypertension risk is evaluated.

Study designs to be included This review will include observational studies, including: prospective cohort studies; retrospective cohort studies; analytical cross-sectional studies; and case-control studies. Cross-sectional studies evaluating prevalent hypertension are eligible as a core design. Studies must provide quantitative estimates of the association between RC and hypertension (HR, OR, RR, or sufficient data to derive these). Estimates are pooled separately by metric and are not treated as interchangeable. Randomized controlled trials, reviews, meta-analyses, case reports, case series, and conference abstracts are excluded.

Eligibility criteria Human studies investigating the association between RC levels and hypertension risk or hypertension status, in adult populations. RC assessed by direct laboratory measurement or calculated from lipid parameters (TC, HDL-C, LDL-C).

Hypertension defined according to recognized clinical guidelines or clearly described diagnostic criteria.

Quantitative effect estimates (HR, OR, RR with 95% CIs) or sufficient data for effect size calculation.

Observational designs: prospective cohort, retrospective cohort, analytical cross-sectional, and case-control studies.

Reviews, systematic reviews, meta-analyses, editorials, commentaries, letters, case reports, animal and experimental studies.

Studies lacking clear definitions or measurements of RC or hypertension.

Studies without sufficient data for quantitative synthesis or extractable effect estimates.

Reports derived from the same or overlapping source populations are managed by source-by-source registration: each overlapping source contributes at most one compatible estimate to any single pooled analysis; different reports may serve different compatible analyses (substitution or distinct questions), and sample sizes are not summed across overlapping reports.

Studies focusing exclusively on secondary hypertension.

Information sources A comprehensive literature search was conducted in PubMed, Embase, Web of Science Core Collection, and the Cochrane Library. The search period extends from database inception to 12 October 2026, without language restrictions.

Main outcome(s) The primary outcome is the association between RC level and hypertension, reported separately by metric and outcome type: New-onset hypertension (incident cases in cohort studies): HR.

Prevalent hypertension (cross-sectional and case-control studies): OR or prevalence ratio.

RC is analysed on multiple compatible scales, reported separately: per 1 mmol/L increase, per study standard deviation (SD), and cumulative RC where reported. HR, OR, and RR are pooled within their own metric and are not converted or combined across metrics. Analyses also examine how baseline blood pressure adjustment and the RC exposure scale modify the estimated association.

Additional outcome(s) Secondary outcomes include: between-study heterogeneity (Cochran's Q and I^2 , reported with study weights); prediction intervals where at least three independent sources contribute; an exploratory two-stage linear dose-response analysis; and, where reported, the incremental predictive value of RC beyond conventional lipid parameters (e.g., change in C-statistic, integrated discrimination improvement). Specific hypertension phenotypes (preeclampsia, gestational hypertension, postpartum hypertension, isolated diastolic hypertension, hypertension with diabetes) are summarised as separate analyses/narrative syntheses.

Data management Data extraction and quality evaluation are performed independently by two reviewers, with disagreements resolved through discussion or consultation with a third reviewer. For each included report, a study-model registry documents: source population and potential overlaps; design component evaluated; outcome definition (new-onset versus prevalent hypertension); RC assessment method and exposure scale; covariate adjustment (including baseline blood pressure, lipid profiles, BMI, diabetes, lipid-lowering medication, lifestyle factors); and the compatible estimate adopted in each pooled analysis. The 23 included reports correspond to 26 design-component evaluations; each overlapping source contributes at most one compatible estimate per pooled analysis, and alternative reports are retained for source-substitution and related analyses.

Quality assessment / Risk of bias analysis Cohort and case-control studies are evaluated using the Newcastle–Ottawa Scale (NOS; selection, comparability, outcome/exposure assessment), and eligible analytical cross-sectional

studies using the Joanna Briggs Institute (JBI) critical appraisal checklist. Results are reported item-by-item for each design component (23 reports; 26 design-component evaluations). A total NOS score or a ≥ 7 threshold is not used as the basis for inclusion or for grading overall certainty of evidence. Quality results are summarised and considered in the interpretation of findings.

Strategy of data synthesis Analyses were performed using STATA version 18.0 at registration; the revised re-analysis was conducted in Python (NumPy, SciPy). The association between RC and hypertension is pooled separately as HR (new-onset) and OR/RR (prevalent), with 95% confidence intervals; HR, OR, and RR are not treated as approximately comparable and are not logarithmically merged across metrics. In addition to conventional CIs, modified Hartung–Knapp intervals and — where at least three independent sources contribute — prediction intervals are reported, together with heterogeneity (Cochran's Q , I^2) and study weights. For continuous RC, separate meta-analyses are conducted per 1 mmol/L, per SD, and for cumulative RC. A random-effects model is applied; REML estimation is used in sensitivity analyses.

Subgroup analysis Prespecified subgroup analyses explore potential sources of heterogeneity by: follow-up duration (< 5 years versus ≥ 5 years); LDL-C assessment method (direct / formula / mixed); adjustment versus no adjustment for baseline blood pressure; and compatible RC exposure scale. Specific hypertension phenotypes are reported as separate narrative analyses rather than a unified subtype subgroup. Analyses based on only two studies are labelled exploratory. Differences between subgroup estimates are compared when sufficient studies are available.

Sensitivity analysis Sensitivity analyses include: (1) leave-one-out analysis by sequentially excluding individual studies; (2) REML model sensitivity; (3) two-stage linear dose-response analysis; and (4) source-substitution analysis using compatible reports for the same source population. Funnel plots and Egger's test are not performed because each compatible pooled analysis includes fewer than 10 independent sources.

Country(ies) involved China.

Other relevant information This protocol was registered with INPLASY on 25 July 2026 and updated on [amendment date] during revision of

the associated manuscript. Summary of changes: (a) population restricted to adults (children/adolescents removed); (b) outcomes split by new-onset (HR) versus prevalent (OR) hypertension and pooled separately, with specific phenotypes presented separately rather than merged; (c) analytical cross-sectional studies included as a core design; (d) HR/OR/RR no longer treated as interchangeable; (e) duplicate handling changed from "largest dataset" to source-by-source registration; (f) search extended to 12 October 2026; (g) modified Hartung–Knapp intervals, prediction intervals (≥ 3 sources), REML sensitivity, and two-stage dose-response analyses added; (h) NOS/JBI reported item-by-item instead of by total score threshold; (i) re-analysis performed in Python (NumPy, SciPy) in addition to the originally registered STATA 18. The associated review is completed but not yet published; no new numeric version number is claimed beyond this amendment record.

Keywords Remnant cholesterol; hypertension; new-onset hypertension; prevalent hypertension; systematic review; meta-analysis.

Contributions of each author

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