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Risk Association of Remnant Cholesterol (RC) for Conventional and Special Subtypes of Hypertension with Evaluation of Confounder Adjustment: A Systematic Review and Meta-Analysis

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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 25 July 2026.

INTRODUCTION

Review question / Objective Review question: What is the association between remnant cholesterol (RC) levels and the risk of hypertension, including conventional and special hypertension subtypes, and how do different confounder adjustment strategies influence the estimated association?

Objective: This systematic review and meta-analysis aims to comprehensively evaluate the relationship between RC and hypertension risk among adults. Specifically, this review will: (1) quantify the association between elevated RC levels and the incidence or presence of hypertension; (2) investigate whether the association differs across conventional hypertension and special hypertension subtypes; and (3) assess the impact of different covariate adjustment strategies, including baseline blood pressure, lipid profiles, body mass index (BMI), diabetes, lipid-lowering medication use, and lifestyle factors, on the strength and heterogeneity of the observed association.

The review question will be structured according to the PICOS framework:

Population: Adults from observational studies, including general populations and individuals with specific hypertension subtypes.
Exposure: Elevated remnant cholesterol levels, assessed by direct measurement or calculated as total cholesterol minus HDL-C and LDL-C.
Comparator: Individuals with lower RC levels or the lowest RC category.
Outcome: Hypertension incidence or prevalence, including conventional and special hypertension subtypes.
Study design: Observational studies, including cohort and case-control studies.

Condition being studied Hypertension is one of the most prevalent chronic diseases worldwide and represents a major modifiable risk factor for cardiovascular disease, stroke, heart failure, and chronic kidney disease. Despite extensive research on traditional risk factors, including obesity, excessive sodium intake, genetic susceptibility, and sympathetic nervous system activation, a substantial proportion of hypertension cases remain insufficiently explained, suggesting the involvement of additional metabolic and vascular mechanisms.

Dyslipidemia has increasingly been recognized as an important contributor to vascular dysfunction and cardiovascular risk. However, the relationship between conventional lipid parameters, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, and hypertension remains inconsistent across different populations.

Remnant cholesterol (RC), representing cholesterol contained in triglyceride-rich lipoprotein remnants, including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and chylomicron remnants, has recently emerged as an important marker of residual cardiovascular risk. RC can be directly measured or calculated using the formula: total cholesterol minus HDL-C minus LDL-C. Previous studies have demonstrated that elevated RC is associated with atherosclerosis, endothelial dysfunction, vascular inflammation, and arterial stiffness, all of which may contribute to blood pressure elevation.

However, the association between RC and hypertension remains uncertain. Previous observational studies have reported inconsistent findings, potentially due to differences in population characteristics, hypertension definitions, study designs, and statistical adjustment strategies. In particular, adjustment for lipid components involved in RC calculation may introduce potential multicollinearity and overadjustment bias, which could influence effect estimates.

Therefore, this review aims to systematically evaluate the association between RC and hypertension risk, while exploring whether hypertension subtype and confounder adjustment approaches modify this association.

METHODS

Participant or population The review will include human participants from observational studies, including general population-based cohorts and specific clinical populations.

Eligible participants will include individuals who:

underwent assessment of serum lipid profiles and RC levels;↪
were evaluated for hypertension status or incident hypertension;↪
were followed longitudinally for the development of hypertension or assessed cross-sectionally.↪

Studies involving participants with conventional hypertension and specific hypertension subtypes, including isolated systolic hypertension, resistant hypertension, or other clearly defined hypertension phenotypes, will be eligible.

Studies involving children, adolescents, and adults will be considered eligible, provided that hypertension was defined according to recognized diagnostic criteria appropriate for the corresponding age group.

Studies focusing exclusively on secondary hypertension caused by specific endocrine, renal, genetic, or pharmacological conditions will be 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 = 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) will be considered eligible.

Comparator The comparator will consist 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 will be the highest RC category or other predefined elevated RC categories.

For continuous analyses, the association between incremental increases in RC levels and hypertension risk will be evaluated.

Study designs to be included This review will include observational studies, including:Prospective cohort studies;Retrospective cohort studies;Case-control studies.Studies must provide quantitative estimates of the association between RC and hypertension, including hazard ratios (HRs), odds ratios (ORs), relative risks (RRs), or sufficient data to calculate these effect estimates.Cross-sectional studies reporting hypertension prevalence and RC levels may be considered if they provide eligible effect estimates.↳Randomized controlled trials, reviews, meta-analyses, case reports, case series, conference abstr.

Eligibility criteria Inclusion criteria:
Human studies investigating the association between remnant cholesterol (RC) levels and hypertension risk or hypertension status, including studies involving children, adolescents, and adults.
RC assessed by direct laboratory measurement or calculated using lipid parameters (e.g., total cholesterol, HDL-C, and LDL-C).
Hypertension defined according to recognized clinical guidelines or clearly described diagnostic criteria appropriate for the study population.
Studies reporting quantitative effect estimates, including hazard ratios (HRs), odds ratios (ORs), relative risks (RRs), and corresponding 95% confidence intervals (CIs), or providing sufficient data for effect size calculation.
Observational studies, including prospective cohort studies, retrospective cohort studies, case-control studies, and eligible cross-sectional studies.
Exclusion criteria:
Reviews, systematic reviews, meta-analyses, editorials, commentaries, letters, case reports, animal studies, and experimental studies.
Studies lacking clear definitions or measurements of RC or hypertension.
Studies without sufficient data for quantitative synthesis or unable to provide extractable effect estimates.
Duplicate publications or studies derived from the same population cohort; in such cases, the study with the largest sample size, longest follow-up duration, or most comprehensive information will be included.
Studies focusing exclusively on secondary hypertension caused by specific endocrine, renal, genetic, or pharmacological conditions.

Information sources A comprehensive literature search will be conducted in the following electronic databases:
PubMed; Embase; Web of Science Core Collection;Cochrane Library.

The search period will extend from database inception to July 23, 2026, without language restrictions.

The search strategy will combine controlled vocabulary (e.g., MeSH terms and Emtree terms) and free-text keywords related to remnant cholesterol and hypertension. In addition, the reference lists of all included studies and relevant systematic reviews will be manually screened to identify potentially eligible studies that may have been missed during database searches.

No unpublished data, grey literature, conference abstracts without sufficient full-text information, or trial registry records will be included.

Main outcome(s) The primary outcome is the association between RC level and hypertension risk.
The effect measures of interest include:
Hazard ratios (HRs);
Odds ratios (ORs);
Relative risks (RRs);
with corresponding 95% confidence intervals.
Analyses will evaluate:
The association between RC as a continuous variable and hypertension risk;
The association between the highest versus lowest RC categories and hypertension risk;
Differences in associations between conventional hypertension and special hypertension subtypes;
The influence of different confounder adjustment strategies, including adjustment for:
baseline blood pressure;
lipid profiles (TC, TG, HDL-C, LDL-C);
BMI;
diabetes;
lipid-lowering medication use;
smoking and alcohol consumption.

Secondary outcomes include assessment of statistical heterogeneity and the impact of adjustment strategies on pooled effect estimates.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included studies will be independently assessed by two reviewers using appropriate validated tools according to study design. Cohort and case-control studies will be evaluated using the Newcastle–Ottawa Scale (NOS), which assesses

three domains: selection of study participants, comparability between groups, and outcome/exposure assessment. A total score of 9 points will be assigned, with scores ≥7 considered indicative of high-quality studies.

Eligible cross-sectional studies will be assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies. This tool evaluates key methodological domains, including participant selection, measurement of exposure and outcomes, identification of confounding factors, and statistical analysis.

Any disagreement between reviewers will be resolved through discussion or consultation with a third reviewer. The quality assessment results will be summarized and considered in the interpretation of the meta-analysis findings.

Strategy of data synthesis All statistical analyses were performed using STATA version 18.0 software. The association between remnant cholesterol (RC) levels and hypertension risk was evaluated using pooled hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with corresponding 95% confidence intervals (CIs). Because hypertension incidence was relatively low in most cohort studies, HRs, ORs, and RRs were considered approximately comparable measures of relative risk and were logarithmically transformed before meta-analysis.

Separate meta-analyses were conducted for RC exposure assessed as a continuous variable (e.g., per unit increase or per standard deviation increase) and as a categorical variable (e.g., highest versus lowest RC category). A DerSimonian–Laird random-effects model was applied to account for potential clinical and methodological heterogeneity across studies. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic, with I^2 values of approximately 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

To explore potential sources of heterogeneity, prespecified subgroup analyses were performed according to hypertension subtype (conventional hypertension versus special hypertension phenotypes) and different adjustment strategies in multivariable models. These included adjustment status for baseline blood pressure, lipid profiles (total cholesterol, triglycerides, HDL-C, and LDL-C), lipid-lowering medication use, body mass index (BMI), diabetes mellitus, smoking, and alcohol consumption. These analyses were conducted to evaluate whether specific clinical characteristics or covariate selection strategies influenced the magnitude and stability of the association between RC and hypertension risk.

Subgroup analysis Prespecified subgroup analyses will be performed to explore potential sources of heterogeneity and assess whether specific factors modify the association between RC and hypertension risk.

Subgroup analyses will be conducted according to:

Hypertension subtype: conventional hypertension versus special hypertension subtypes, including isolated systolic hypertension, resistant hypertension, or other clearly defined phenotypes.
Adjustment strategies in multivariable models:
adjustment versus no adjustment for baseline blood pressure (systolic and/or diastolic blood pressure);
adjustment versus no adjustment for lipid-lowering medication use;
adjustment versus no adjustment for traditional lipid parameters (TC, TG, HDL-C, LDL-C);
adjustment versus no adjustment for metabolic factors, including BMI and diabetes;
adjustment versus no adjustment for lifestyle factors, including smoking and alcohol consumption.
Study characteristics, where applicable, including study design, population characteristics, and exposure assessment methods.

Differences between subgroup estimates will be compared when sufficient studies are available.

Sensitivity analysis Sensitivity analyses were performed using a leave-one-out approach by sequentially excluding individual studies to assess the robustness of pooled estimates.

Country(ies) involved China.

Keywords Remnant cholesterol; hypertension; systematic review; meta-analysis.

Contributions of each author

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