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Association between remnant cholesterol and chronic kidney disease: Systematic review and meta-analysis

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Abstract

Background and Aims: Adequate lipid control has emerged as a key factor in the prevention and management of chronic kidney disease (CKD). Remnant cholesterol (RC), a lipoprotein with an established association with cardiovascular risk, has been investigated in the context of CKD. Given the conflicting results from recent studies, we performed this meta-analysis to summarize the existing evidence on the association between RC and CKD.

Methods: Medline, Cochrane Library and Scopus were searched until 16 September 2024. Double-independent study selection, data extraction and quality assessment were performed. Evidence was pooled using random-effects meta-analyses. We set as primary end-point of interest the association between RC and CKD.

Results: Twelve studies (4 139 674 participants) were included. Participants with RC values in the highest quantile had significantly greater odds of CKD compared to those in the lowest quantile (Odds Ratio [OR] = 1.46, 95% confidence interval [CI] = 1.26–1.68). In a sensitivity analysis confined to subjects with type 2 diabetes (T2D), those in the higher RC quantile also exhibited significantly increased odds of CKD compared to those in the lowest quantile (OR = 1.46, 95% CI = 1.20–1.78). A significant inverse association was observed between RC and estimated glomerular filtration rate (Mean Difference [MD] = −1.43 mL/min/1.73 m^2 for each 1 mmol/L increase in RC, 95% CI = [−2.67, −0.19]). Additionally, individuals with T2D-related CKD had a 24% increased risk of progression to end-stage renal disease for each 1 standard deviation increase in RC (Hazard Ratio [HR] = 1.24, 95% CI = 1.04–1.47).

Conclusions: RC is directly associated with higher risk for CKD. Beyond traditional lipid markers, greater emphasis should be placed on RC levels in individuals with or at risk for CKD.

KEYWORDS

chronic kidney disease, end-stage renal disease, estimated glomerular filtration rate, remnant cholesterol

1 | INTRODUCTION

Chronic kidney disease (CKD), encompassing a range of pathophysiological alterations linked to kidney damage and impaired renal function, has emerged as a significant global health issue due to its high prevalence, mortality rates and economic burden.[1–3] It is estimated that approximately 850 million individuals globally suffer from CKD, with the majority residing in low-income and lower-middle-income countries.[4] Of note, a significant proportion of these individuals lack access to diagnostic, preventive and therapeutic measures. In contrast to deaths from cardiovascular, stroke and respiratory diseases, mortality from CKD has been rising, and it is projected to become the fifth leading cause of years of life lost globally by 2040.[5]

While type 2 diabetes (T2D) and hypertension continue to be the primary drivers of incident CKD,[6] numerous studies have demonstrated that dyslipidemia—closely associated with these entities—plays a crucial pathogenic role in the development and progression of CKD.[7–9] Although research to date has predominantly focused on traditional lipid parameters, there is a growing interest in alternative markers such as remnant cholesterol (RC). RC, a novel lipoprotein marker linked to elevated triglyceride levels, represents the cholesterol content of triglyceride-rich lipoproteins (TRLs), which include very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C) in the fasting state, as well as chylomicron cholesterol in the non-fasting state.[10]

RC has been identified as a significant risk factor for all-cause mortality, T2D and cardiovascular disease, offering prognostic value beyond that of conventional lipid parameters and potentially serving as a complementary tool for risk stratification and appropriate therapeutic management of these populations.[11–16] Building on this evidence, this systematic review and meta-analysis aimed to evaluate the association between RC and CKD, providing a comprehensive synthesis of the available data.

2 | MATERIALS AND METHODS

The present study adhered to the principles outlined in the Cochrane Handbook for Systematic Reviews,[17] with reporting conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Supplemental Table 1).[18] The study protocol was registered a priori on the Open Science Network (DOI 10.17605/OSF.IO/6W7P2), with no subsequent amendments made to the original protocol.

2.1 | Search strategy

The search strategy was developed by two researchers (P.K. and D.P.), and a systematic literature search was independently conducted by the two researchers across MEDLINE (via PubMed), Scopus and the Cochrane Database of Systematic Reviews, covering the period from inception to 16 September 2024. No restrictions were applied based on date, language, publication status or year. The basic terms included in search strings were remnant cholesterol and chronic kidney disease in both free text and Medical Subject Headings format. Searches were extended through manual investigation of clinicaltrials.gov, Epistemonikos database and Google Scholar search engine. Additionally, backward and forward citation chasing was conducted using the {citationchaser} R package.[19] The full search strategy is outlined in Supplemental Tables 2–4.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

Eligible studies included randomized controlled trials (RCTs) or observational studies that examined the relationship between RC levels and CKD in adult populations (aged 18 years or older).

2.2.2 | Exclusion criteria

Studies with the subsequent characteristics were excluded: (i) case reports, case series, narrative reviews; (ii) editorials, letters, commentaries, expert opinions; (iii) clinical practice guidelines, conference abstracts, protocols, dissertations; (iv) case-control studies, cross-over trials; and (v) not retrievable full text.

2.3 | Outcomes

The primary end-point for meta-analysis was the association between RC levels and the risk of CKD, defined by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2.[20] Secondary outcomes of interest included the associations between RC and eGFR, as well as the risk of progression to end-stage renal disease (ESRD), defined as an eGFR of less than 15 mL/min/1.73 m^2 over 3 months or the need for haemodialysis, peritoneal dialysis or kidney transplantation.[20]

2.4 | Study selection

In the initial phase, two authors independently screened each title and abstract from the records identified through the specified search strategy. To increase the sensitivity of the study selection process, discrepancies at this stage did not lead to exclusions. Following this, three investigators independently assessed the full texts. Any disagreements were resolved through consensus or by consulting a senior author. The Abstrackr tool was employed for screening during the initial phase,[21] and Mendeley was used for managing references.

2.5 | Data extraction

A data extraction form was developed and subjected to a pilot extraction process using a subset of four studies. After a series of training and calibration exercises, a standardized form for data extraction was finalized. Utilizing an independent, duplicated approach, any discrepancies were resolved through consensus or, when required, by consulting a senior author. For each study, we extracted data related to sample size, key clinical and demographic attributes, as well as adjusted effect estimates for the outcomes of interest, where such adjustments were provided. Data on RC values, calculated as total cholesterol minus low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), were included in the analyses as estimated in each primary study. Additionally, researchers from the included studies were contacted to request supplementary information if subgroup-level data were either missing or not explicitly reported in the published material. The methods used for RC measurements in each primary study are detailed in Supplemental Table 5.

2.6 | Quality assessment

Two authors independently assessed the quality of the identified studies using the Newcastle–Ottawa Scale (NOS).[22] The evaluation encompassed three main domains: Selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the absence of the outcome of interest at the study's inception), Comparability (cohort comparability based on study design or analysis) and Outcome (outcome assessment, duration of follow-up and adequacy of follow-up). Any discrepancies during the assessment were resolved through discussion or, if necessary, by consulting a third author.

2.7 | Data analysis

All analyses were conducted using R Statistical Software (version 4.2). Baseline characteristics of participants were reported as frequencies with percentages for categorical variables, and as means with standard deviations for continuous variables that followed a normal distribution; otherwise, medians with interquartile ranges were used. Adjusted odds ratios and hazard ratios for the predefined dichotomous outcomes were reported for comparisons between higher and lower quantile of remnant cholesterol, as stratified in each study. For pooled estimates of eGFR, the mean difference was applied. Effect estimates, along with 95% confidence intervals, were combined using random-effects models, employing the restricted maximum likelihood estimator for between-study variance, based on a frequentist approach. A two-tailed *p*-value of less than 0.05 was considered statistically significant for summary effect estimates. The I^2 statistic was used to quantify the proportion of total variability attributable to between-study heterogeneity, while Cochran's Q test was applied to formally assess heterogeneity. I^2 values ranged from 0% to 100%, with values between 0% and 30% suggesting insignificant heterogeneity, 30% to 50% indicating moderate heterogeneity, 50% to 75% reflecting substantial heterogeneity and values exceeding 75% representing considerable heterogeneity.[23] Small-study effects and potential publication bias were visually assessed using contour-enhanced funnel plots of effect size versus standard error. Egger's test was performed to formally evaluate the presence of publication bias.

2.7.1 | Sensitivity analysis

Multiple leave-one-out meta-analyses were conducted, systematically excluding one study at a time in each analysis. This approach was utilized to assess the impact of individual studies on the overall effect size estimate and to identify influential studies. Additionally, a sensitivity analysis was performed, incorporating only studies reporting outcomes for individuals with T2D, to further evaluate the robustness of the results obtained from the primary analysis within this specific patient population.

2.7.2 | Subgroup analysis

A subgroup analysis was conducted to investigate potential effect modification based on the study design (longitudinal vs. cross-sectional) of the included studies.

2.7.3 | Meta-regression analysis

Univariate meta-regression analyses were performed to investigate potential sources of heterogeneity and identify effect modifiers across the included studies, provided there were a sufficient number of studies available.[17] The meta-regression models incorporated the following independent variables: age, male sex, BMI, LDL-C and triglyceride levels, the percentage of participants with baseline T2D, hypertension and prescription of lipid-lowering agents.

3 | RESULTS

3.1 | Study selection and characteristics

The PRISMA diagram illustrating the database search and study selection process is presented in Supplemental Figure 1. Following the removal of duplicates, the initial set of 381 identified records was screened based on titles and abstracts. Of these, 360 records were excluded. The remaining 21 records underwent a detailed full-text assessment, leading to the inclusion of 12 studies that met the eligibility criteria.[24–35] The list of excluded studies, along with the reasons for their exclusion, is detailed in Supplemental Table 6.

The key characteristics of the studies included are summarized in Table 1. A total of 12 studies were analysed, encompassing 4 139 674 individuals. The percentage of male participants was 55%, with mean ages spanning from 43.2 to 63.8 years. The median follow-up period

TABLE 1 Characteristcs of included studies.

First Author, year	Study type	Median follow-up	Participants, n	Age in years, mean (SD)	Gender (male, %)	Baseline eGFR (mL/min/1.73 m^2)	Remnant cholesterol (mmol/L)	LDL cholesterol (mmol/L)	Triglyceride (mmol/L)	T2D (%)	BMI (kg/m^2)	Hypertension (%)
Yan P, 2021[24]	Cross-sectional	NA	7356	58.2 (9.8)	32.2	94.1	0.79	2.67	1.65	24	24	32.1
Wu Z, 2022[25]	Prospective cohort	5 years	4237	55.8 (12.8)	76.8	N/R	0.64[a]	2.9[a]	1.6[a]	47.3	26.4[a]	62.1
Hu Q, 2022[26]	Propensity score matched cross-sectional	NA	8226	49 (10)	60.4	93.2	0.54	3	N/R	8.7	24.1	23.5
Yuan T, 2023[27]	Cross-sectional	NA	13 024	63.8 (9.4)	46.8	88.3	0.63	3	1.8	18	23.6	63.7
Yuan Y, 2023[28]	Cross-sectional	NA	3383	54.2 (13.6)	61.4	N/R	0.67	2.8	1.6	100	26.3	36.5
He X, 2024[29]	Retrospective cohort	N/R	14 210	43.2 (25)	48.9	98.9	0.61	N/R	N/R	15.4	N/R	35.1
Zhu W, 2024[30]	Cross-sectional	NA	2709	60 (47–69)[b]	53.8	N/R	0.59[a]	2.82[a]	1.3[a]	100	30.1 (26.2–35)[b]	61.9
Jang SY, 2024[31]	Retrospective cohort	5.2 years	212 836	49.4 (11.8)	73	92.7	0.65	3	1.8	100	24.8	33.9
Jung HN, 2024[32]	Prospective cohort	10.3 years	3 856 985	46.3 (14.2)	54	87.7	0.59	3	N/R	8.5	23.6	25.4
Yuan Y, 2024[33]	Cross-sectional	NA	7696	51 (15)	47.8	79.1	0.37	2.93	1.76	10.6	23.5	13.4
Li Q, 2024[34]	Cross-sectional	NA	8678	59.6 (10)	57.3	97.5	0.55	3.34	1.62	100	26.9	0
Zhao Y, 2024[35]	Prospective cohort	27 months	334	51.1 (9.3)	70	60.7	0.68	1.2	1.8	100	25.6	86

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NA, not applicable; N/R, not reported; SD, standard deviation; T2D, type 2 diabetes.

[a]Reported as median.

[b]Reported as median (Q1-Q2).

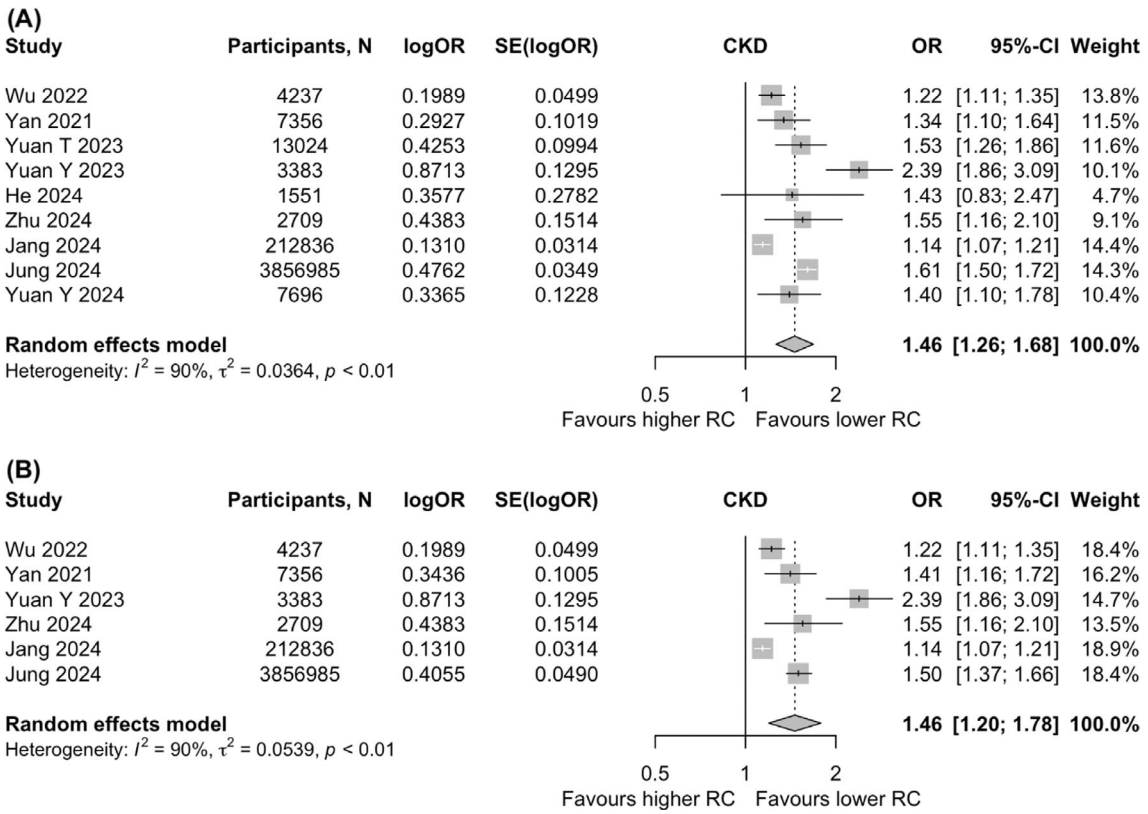

FIGURE 1 Forest plots of the association between remnant cholesterol (RC, higher vs. lower RC quantile) and chronic kidney disease (A) and sensitivity analysis including exclusively participants with baseline type 2 diabetes (B). CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; RC, remnant cholesterol; SE, standard error.

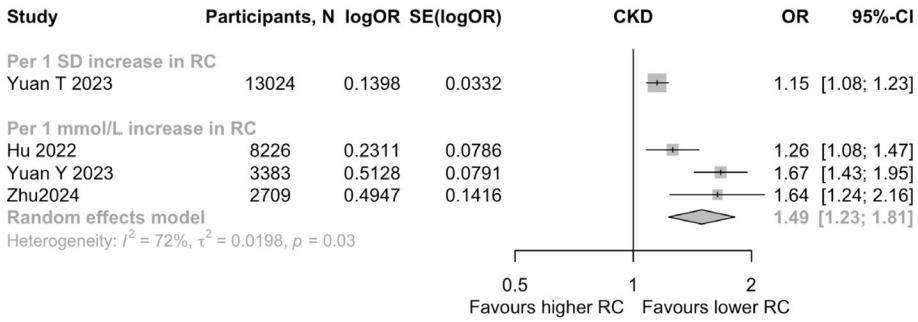

FIGURE 2 Forest plot illustrating the association between remnant cholesterol (RC) and chronic kidney disease, analysed per 1 standard deviation and 1 mmol/L increase in RC. CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; RC, remnant cholesterol; SE, standard error.

was 5.1 years (IQR = 4.3–7.8). The mean RC levels ranged from 0.37 to 0.79 mmol/L. The prevalence of T2D at baseline varied between 8.5% and 100% across the included studies. Among the included participants, 26% had concurrent hypertension.

All studies were deemed to have a low risk of bias, as evaluated using the Newcastle–Ottawa Scale (Supplemental Table 7).

3.1.1 | Remnant cholesterol and risk of chronic kidney disease

A total of nine studies, including 4 109 777 individuals, assessed the association between RC tertiles and CKD.[24,25,27–33] Participants with RC values in the highest quantile had significantly greater odds of CKD compared to those in the lowest quantile (Odds Ratio [OR] = 1.46, 95% confidence interval [CI] = [1.26, 1.68], p < 0.001; I^2 = 90%, heterogeneity p < 0.01; Figure 1A). Likewise, individuals with T2D and RC in the higher quantile exhibited significantly increased odds of CKD compared to those with RC in the lowest quantile (OR = 1.46, 95% CI = [1.20, 1.78], p < 0.0001; I^2 = 90%, heterogeneity p < 0.01; Figure 1B). No evidence of small-study effects or publication bias was identified based on the symmetrical, contour-enhanced funnel plots comparing effect size to standard error and Egger's tests (Supplemental Figure 2).

The association between RC and CKD remained robust when RC was analysed as a continuous variable, with a 49% increase in the odds of CKD for each 1 mmol/L increase in RC (OR = 1.49, 95% CI = [1.23, 1.82], p < 0.001; I^2 = 72%, heterogeneity p = 0.03; Figure 2).

3.1.2 | Remnant cholesterol and estimated glomerular filtration rate

A significant inverse association was observed between RC and eGFR. Specifically, each 1 standard deviation (SD) increase in RC was associated with a decrease of 1.99 mL/min/1.73 m^2 in eGFR (Mean Difference [MD] = −1.99, 95% CI = [−2.31, −1.68], $p < 0.001$; $I^2 = 0\%$, heterogeneity $p = 0.48$; Figure 3). Additionally, eGFR declined by 1.43 mL/min/1.73 m^2 for each 1 mmol/L increase in RC (MD = −1.43, 95% CI = [−2.67, −0.19], $p < 0.001$; $I^2 = 82\%$, heterogeneity $p = 0.02$; Figure 3).

3.1.3 | Remnant cholesterol and progression to end-stage renal disease

Individuals with T2D-related CKD had a 24% significantly increased risk of progression to ESRD for each 1 SD increase in RC (Hazard Ratio [HR] = 1.24, 95% CI = [1.04, 1.47], $p = 0.015$; $I^2 = 34\%$, heterogeneity $p = 0.22$; Figure 4).

3.1.4 | Sensitivity analysis

The sensitivity analysis, employing the leave-one-out approach, did not reveal any outlier or influential studies affecting the pooled effect estimates (Supplemental Figure 3).

3.1.5 | Subgroup analysis

Non-significant subgroup differences were observed regarding the association between RC and CKD, considering the study design (longitudinal vs. cross-sectional) of the analysed studies (Supplemental Figure 4).

3.1.6 | Meta-regression analysis

The results of the meta-regression analyses are presented in Supplemental Table 8. Based on these analyses for the primary outcome, the observed associations were not significantly modified by baseline participants' characteristics, including levels of other traditional lipid markers.

4 | DISCUSSION

This meta-analysis is the first to examine the association between RC and CKD, an area of considerable scientific interest. Participants with RC values in the highest quantile have a 46% higher likelihood of having CKD compared to those in the lowest quantile. This relationship was consistent when RC was considered as a continuous variable and was confirmed in a sensitivity analysis focusing solely on the T2D population. Additionally, RC levels were found to be inversely correlated with eGFR values. Notably, in patients with T2D-related CKD, elevated RC values significantly increased the risk of progression to ESRD by 24%.

Growing evidence has strongly implicated dyslipidemia as a causal factor in both atherosclerosis and nephropathy.[36] Hyperlipidemia can induce direct structural and functional alterations in podocytes, mesangial cells and proximal tubular cells, ultimately resulting in renal fibrosis and the progression of CKD.[37] The proposed mechanisms include not only the aggravation of renovascular atherosclerosis but also the development of glomerulosclerosis, intra-glomerular

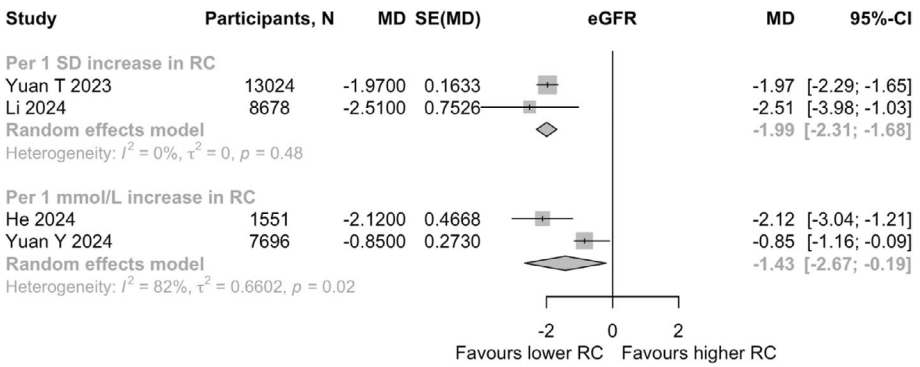

FIGURE 3 Forest plot illustrating the association between remnant cholesterol (RC) and estimated glomerular filtration rate (eGFR), analysed per 1 standard deviation and 1 mmol/L increase in RC. CI, confidence interval; eGFR, estimated glomerular filtration rate; MD, mean difference; RC, remnant cholesterol; SE, standard error.

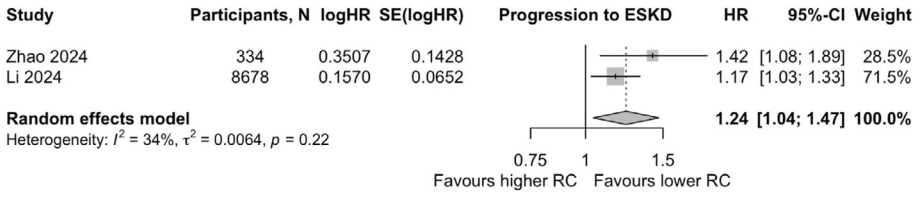

FIGURE 4 Forest plot illustrating the association between remnant cholesterol (RC) and the risk for progression to end-stage kidney disease, per 1 standard deviation increase in RC. ESDK, end-stage kidney disease; CI, confidence interval; HR, hazard ratio; RC, remnant cholesterol; SE, standard error.

hypertension and tubulointerstitial fibrosis, driven by factors such as oxidative stress, inflammation, reduced levels of vasodilators and growth-inhibitory cytokines and glomerular lipid accumulation.[38,39] Despite this theoretical framework, clinical studies have produced variable results concerning the predictive value of cholesterol and triglycerides (TGs) for CKD, leading to ambiguity about which specific lipid profile component most significantly affects CKD progression.[40–42] Emerging evidence indicates that RC may influence vascular disease beyond its traditional role in lipid metabolism.[12] RC has been recognized as a major factor contributing to residual cardiovascular risk, even when LDL-C levels are adequately controlled.[13] However, no specific recommendations exist to date regarding its routine measurement. Given the shared pathophysiology of microvascular and macrovascular diseases, there is a need for further research to elucidate the relationship between RC and microvascular dysfunction in the context of CKD.

The precise mechanism by which RC contributes to the pathophysiology of CKD remains poorly defined. In cases of atherogenic dyslipidemia, often observed in individuals with renal impairment, there is an overproduction and insufficient breakdown of TRLs, resulting in increased levels of remnant TRLs and RC.[13] Unlike LDL-C, these remnant TRLs can directly penetrate the arterial endothelium via active transcytosis. As a result, RC within these particles accumulates in subendothelial lesions, which initiates and worsens vascular disease.[43] At the endothelial surface, the triglyceride component of remnant TRLs undergoes lipolysis mediated by lipoprotein lipase, releasing large amounts of toxic fatty acids.[44] RC can enhance the expression of adhesion molecules, coagulation factors and inflammatory proteins in endothelial cells, thereby promoting monocyte recruitment, attachment and foam cell formation.[45,46] Additionally, preclinical studies have reported a relationship between atherogenic lipid profiles and endothelial dysfunction, partly due to the inactivation of nitric oxide synthase, as well as glomerulosclerosis.[47] This process fosters the production of proinflammatory cytokines and atherogenic adhesion molecules.[44] Of note, mediation analysis has shown that the proinflammatory state, marked by elevated high-sensitivity C-reactive protein (hs-CRP) or white blood cells (WBCs), partially mediates the relationship between RC and CKD, accounting for 10% ($p = 0.002$) and 12% ($p = 0.012$) of the association, respectively.[33] Whether RC acts as a primary pathogenetic factor in renal dysfunction or is simply a bystander in nephropathy requires further mechanistic studies. However, the observation that elevated RC is independently associated with the onset of ESRD, combined with substantial evidence linking RC to atherosclerosis, endothelial damage and inflammation, suggests that RC may adversely affect renal function. Importantly, RC-related nephropathy could emerge prematurely in individuals with apparently normal renal function, as high RC levels have been associated with an increased risk of ESRD even in those without dyslipidemia or CKD.

A significant proportion of included individuals had concomitant T2D. Prior research indicated that RC serves as a standalone risk factor of new-onset diabetes in both the general population and individuals undergoing kidney transplantation.[12,48–50] One such study identified that the link between RC and new-onset diabetes may be mediated by insulin resistance and a pro-inflammatory state.[12] Relevant research has further demonstrated a correlation between RC and insulin resistance.[51,52] The relationship between insulin resistance and the advancement of diabetic nephropathy (DN) has been extensively documented across numerous clinical studies.[53,54] Both in vivo and in vitro investigations have elucidated that insulin resistance plays a significant role in renal injury.[55] Insulin resistance accelerates glomerular hypertension and hyperfiltration by elevating levels of vascular nitric oxide (NO) and transforming growth factor β1 (TGF-β1), and by increasing sodium chloride sensitivity through the upregulation of sodium-glucose cotransporters.[56–58] Additionally, it contributes to endothelial dysfunction and proteinuria by enhancing adipokine levels, activating the TGF-β1/TGF-β receptor pathway and exacerbating profibrotic and pro-oxidant effects in glomerular cells through decreased adiponectin levels and possibly elevated leptin levels.[59–62]

Furthermore, previous research has identified a robust association between elevated RC and low-grade systemic inflammation, as indicated by increased levels of CRP and WBCs.[12,63] This suggests that high RC is frequently accompanied by a proinflammatory state. In the Chronic Renal Insufficiency Cohort (CRIC) study, pro-inflammatory markers—including interleukin (IL) 1β, IL-1 receptor antagonists, IL-6, tumour necrosis factor (TNF) α or circulating TNF Receptors I and II, CRP and fibrinogen—were found to be inversely associated with renal function and positively correlated with proteinuria.[64] Recent research has also demonstrated that low-grade chronic inflammation contributes to the progression of diabetic kidney disease, with several inflammatory biomarkers being reported as prognostic indicators for risk stratification of patients regarding disease progression and all-cause mortality.[65] However, it remains to be further investigated whether RC contributes to the progression of diabetic nephropathy through mechanisms involving insulin resistance and low-grade systemic inflammation.

Currently, statins are employed to reduce plasma LDL cholesterol concentrations,[66] while peroxisome proliferator-activated receptor (PPAR) agonists are used to decrease plasma TGs levels.[67] Nevertheless, the prescription of first-generation PPARα agonists, such as fibrates, has been constrained by adverse effects, notably increases in serum creatinine and homocysteine levels. In a randomized, placebo-controlled, double-blind, parallel-group phase II trial involving patients with hypertriglyceridemia receiving statin treatment, the novel second-generation PPARα agonist pemafibrate demonstrated efficacy, safety and tolerability. This agent effectively reduced triglycerides, apolipoprotein B-48, apolipoprotein CIII and RC concentrations.[68,69] This finding introduces a new potential option for lowering plasma TGs and RC concentrations. However, there are currently no studies investigating the effects of pemafibrate on kidney outcomes. Similarly, promising results have also been reported for another class of lipid-lowering agents—the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Evidence from the multicentre LIPID-REAL Registry indicates that evolocumab significantly reduced cholesterol remnants ($p = 0.017$) and provided a reduction in residual lipid risk beyond LDL-C reductions.[70] Therefore, further research is required to

validate the potential cardiovascular and renal benefits in real-world settings.

It has to be determined in future studies the true impact of reno-protective drug classes, such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and finerenone, on RC levels, and how the observed effect can—at some extent—mediate the observed renal benefits.[71–73]

Hypertension is a well-established risk factor for CKD, yet our meta-analysis found no significant evidence that hypertension modifies the association between RC and CKD. This suggests that, within the studies included in our analysis, the relationship between RC and kidney function appears to be independent of hypertension status. Despite this, the complex interplay between hypertension and CKD warrants further investigation. Future studies with larger sample sizes or stratified analyses may offer additional insights into how hypertension interacts with RC in different patient populations or stages of CKD.

4.1 | Strengths and limitations

Despite the rigorous execution of the current study, it is important to acknowledge several potential limitations. Firstly, this study was a trial-level meta-analysis without access to individual-level data. Secondly, since no relevant RCTs were available, all studies included in the analysis were observational in nature, introducing inherent differences in baseline patient characteristics, potential selection bias and relatively high heterogeneity. Nevertheless, it is worth noting that most effect estimates extracted from each study were adjusted for potential effect modifiers. Additionally, all studies except for He et al.[29] consistently demonstrated a significant association between higher RC levels and increased odds of CKD. Thirdly, most of the studies included predominantly Asian populations, which may limit the generalizability of the findings and the replicability of the association between RC and CKD in populations of different ethnic backgrounds. Fourthly, all but one study calculated the associations based on baseline RC levels, resulting in analyses conducted on baseline rather than cumulative RC measurements. Lastly, considering that the majority of the included populations had baseline T2D, no adjustments were made for the newer glucose-lowering medications with well-established cardiorenal benefits due to the lack of relevant data in the primary analysed studies. For the same reason, we were unable to perform subgroup analyses based on prior cardiovascular disease history, nor examine the association between RC and albuminuria levels.

5 | CONCLUSIONS

The present meta-analysis suggests that RC is directly associated with a higher risk of CKD and progression to ESRD in patients with T2D-related kidney disease. Additionally, RC levels may be inversely correlated with eGFR. Considering the relatively limited treatment options currently available for preventing and effectively managing CKD, RC potentially emerges as a novel therapeutic target for this patient population. However, the debate on the optimal RC levels and the potential additive benefit for patients who have already achieved the recommended LDL-C goals remains to be definitively addressed in future large-scale, rigorously designed RCTs.

AUTHOR CONTRIBUTIONS

Paschalis Karakasis: Conceptualization, Methodology, Investigation, Visualization, Project administration, Writing—original draft, Writing—review and editing. **Dimitrios Patoulias**: Conceptualization, Methodology, Investigation, Writing—original draft, Writing—review and editing. **Manfredi Rizzo:** Conceptualization, Writing—original draft, Writing—review and editing. **Nikolaos Fragakis**: Writing—review and editing. **Christos S Mantzoros:** Conceptualization, Writing—review and editing, Supervision. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16258.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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