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Exploring the correlation of remnant-like particle cholesterol levels with CKD developing risk: a comprehensive systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a progressing illness worldwide and the relationship between remnant-C and CKD is still uncertain. Indeed, this study aims to evaluate the relationship between remnant-C and the risk of CKD development in a systematic review and meta-analysis study.

Materials and Methods: This study surveyed databases like Web of Science, Cochrane, ProQuest, PubMed, Embase, and Google Scholar up to December 17, 2024. Data analysis was performed by STATA 14 software, and the test confidential level was $P<0.05$.

Results: Remnant-C causes a higher risk of CKD (OR: 1.31, 95% CI: 1.22, 1.41). In addition, the remnant-C in second quartile (R:1.20, 95% CI: 1.13, 1.27), third quartile (OR:1.26, 95% CI: 1.13, 1.40), 4th quartile (OR:1.62, 95% CI: 1.42, 1.86), second tertile (OR:1.12, 95% CI: 1.06, 1.19) and 3rd tertile (OR:1.23, 95% CI: 1.16, 1.31) further increased CKD risk. According to the subgroup analysis, remnant-C in the group with the range of 40 to 49 years (OR:1.32, 95% CI: 1.18, 1.48), 50 to 59 years (OR:1.26, 95% CI: 1.14, 1.40), 60 to 69 years (OR:1.39, 95% CI: 1.14, 1.69), in men (OR:1.23, 95% CI: 1.13, 1.33) and women (OR:1.51, 95% CI: 1.25, 1.82) lead to higher risk of CKD. Additionally, remnant-C in diabetic patients (OR: 1.35, 95% CI: 1.22, 1.48), individuals with body mass index (BMI) <25 (OR: 1.28, 95% CI: 1.15, 1.43), and individuals with BMI>25 (OR:1.39, 95% CI: 1.20, 1.60) lead to a higher risk of CKD, either.

Conclusion: Our study reveals that remnant-C causes a higher risk of CKD, and a higher level of remnant-C leads to a higher risk of CKD. Notably, remnant-C causes CKD in women more than men and in individuals with BMI >25 kg/m^2 more than ones with BMI<25 kg/m^2, shedding new light on the gender and BMI-specific risks associated with remnant-C.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42025632075) and Research Registry (UIN: reviewregistry1936) websites.

Implication for health policy/practice/research/medical education:
This meta-analysis encompassed nine observational studies, comprising four cohorts and five cross-sectional studies. It revealed a significant association between remnant cholesterol levels and the risk of chronic kidney disease (CKD). The findings indicated that as remnant cholesterol levels rose, the likelihood of developing CKD correspondingly increased. Furthermore, the analysis highlighted a gender disparity, demonstrating that remnant cholesterol posed a greater risk for the development of CKD in women compared to men.

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Meta-analysis

Introduction

Chronic kidney disease (CKD) is a global health concern, affecting 10% of the population worldwide and posing a significant challenge to public health (1). By 2040, it is estimated that CKD will become the 5th leading cause of death globally (2). The progression of CKD toward end-stage renal disease (ESRD) imposes substantial human health and socioeconomic burdens (3). High blood pressure, diabetes, hyperuricemia, and obesity are known risk factors for CKD (4). The lipid profile of CKD patients is typically characterized by triglyceride-rich lipoprotein particles, increased levels of low-density lipoprotein (LDL), and decreased levels of high-density lipoprotein (HDL) (5,6).

The resting cholesterol (remnant-C) is part of triglyceride-rich lipoproteins which involve very-low-density lipoprotein and intermediate-density lipoprotein under fasting conditions and chylomicron residues in non-fasting situations (7). Remnant-C is a novel mortality risk factor particularly for diabetes and cardiovascular disease (8-10). Recent studies showed remnants-C is associated with the incidence of diabetic nephropathy development in patients with diabetes type II (11), and the progression of diabetic nephropathy and retinopathy in patients with diabetes type I (12). Furthermore, unlike other cholesterols, the higher remnant-C level is probably more strongly associated with inflammation and disease progression (13,14). A study conducted in China in 2022, revealed that remnant-C caused a higher risk of CKD (15). However, another study in 2024 in America showed that in the second and third quartiles, there is no significant relation between remnant-C and CKD (16). This study aims to evaluate the correlation between remnant-C and CKD risk by systematic review and meta-analysis.

Materials and Methods

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (17). The protocol of this study is registered on the PROSPERO (International Prospective Register of Systematic Reviews) website.

Searching strategy

In this study, various databases are investigated, such as Web of Science, Cochrane, ProQuest, PubMed, Embase, and Google Scholar. All searches were done without time or place limitation, and all related data up to December 17, 2024, are surveyed. Our search strategy involved Medical Subject Headings (Mesh) words and their analogs like "Renal Insufficiency, Chronic", Chronic Kidney Disease, Chronic Renal Disease, remnant-like particle cholesterol, RLP-C cholesterol, and Remnant Cholesterol. After that, keywords are combined with logical operators (AND, OR). Besides that, the references of each source are searched. The search strategy for the Web of Science database was as follows: "Renal Insufficiency, Chronic" OR Chronic Kidney Disease OR Chronic Renal Disease (All Fields) AND remnant-like particle cholesterol OR RLP-C cholesterol OR Remnant Cholesterol (All Fields).

PECO (population, exposure, comparison, outcomes)

In this study, we followed the PECO criteria to structure our research. This involved defining the population under study, the specific exposure being investigated, the comparison group, and the primary outcomes of interest**.**

Eligibility criteria

Inclusion criteria include observational studies assessing the relation between remnant-C and risk of CKD. Exclusion criteria include duplicate studies, review articles, low quality studies identified by quality control, the studies without full-text access, studies with insufficient data, the conference studies.

Quality control

Two reviewers used the Newcastle Ottawa Scale tool to evaluate the quality of the studies. Each question in this tool was assigned with one star (except the comparison question which allocated 2 stars). So, the sum of the scores was in the range of 0 (the worst quality) and 10 (the best quality) (18). The studies, scoring higher than 6, were included in the present study.

Data extraction

Two reviewers extracted the following data: author name, age, country, RC level, year, type of study, case number, the odd ratio between remnant-C and risk of CKD along with a 95% confidential interval (for all cases and men and women, separately), and the odd ration of the relation between remnant-C and risk of CKD in patients with hypertension, diabetes and overweight or obesity. The third reviewer examined the data to resolve discrepancies.

Statistical analysis

The logarithm of the criteria, such as odds ratio (OR) and hazard ratio (HR), was conducted for data analysis, and these data were combined, eventually. The I^2 index was carried out to evaluate the study's heterogeneity. In the present study, the random effect model was applied. Data analysis was performed by STATA 14 software, and the confidential test interval was considered $P<0.05$.

Results

A total of 266 articles were initially identified from the mentioned databases. The duplicated articles (141 articles) were removed. After that, the abstracts of 125 articles were assessed, and the 6 ones with imperfect information and incomplete text were excluded. Among the 119 complete articles, 49 studies were removed due to insufficient analysis. 70 articles progressed to the next level, of which 61 were excluded according to other exclusion criteria and 9 studies eventually remained (Figure 1).

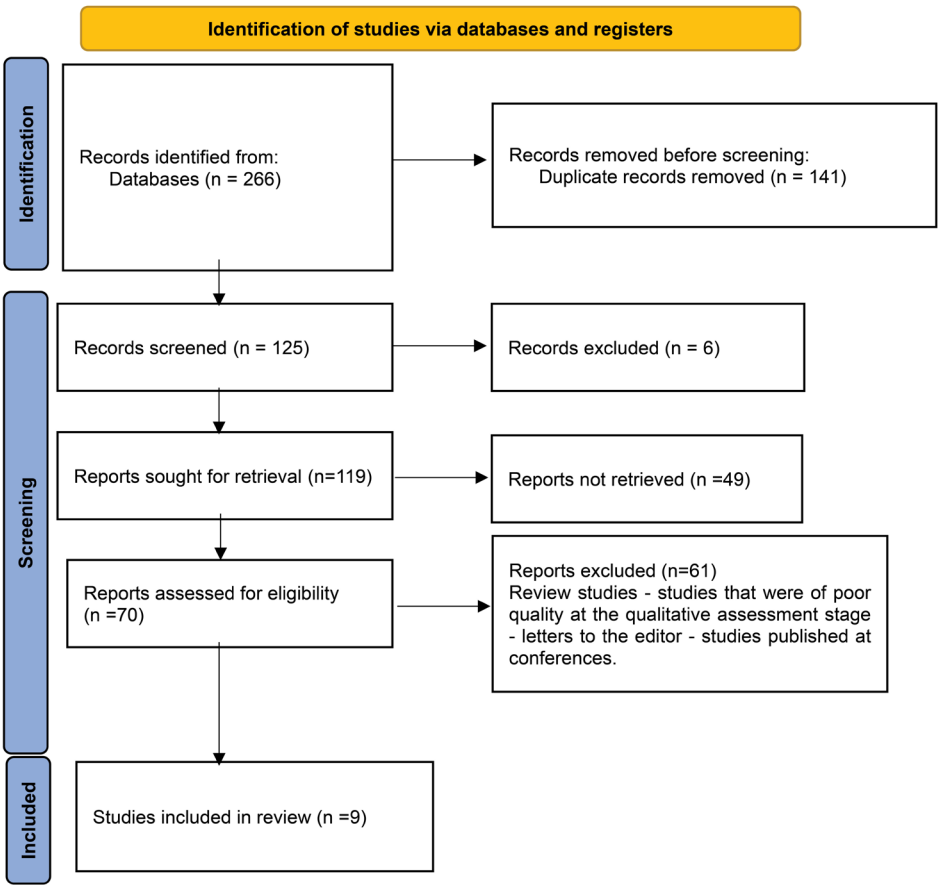

Figure 1. The PRISMA flowchart of study.

This meta-analysis involves 9 observational studies (four cohorts and five cross-sectional studies) (Table 1). Figure 2 illustrates that remnant-C is associated with an increased risk of CKD (OR:1.31, 95% CI: 1.22, 1.41).

Remnant-C leads to a higher risk of CKD in cohort (OR:1.32, 95% CI: 1.20, 1.46) and cross-sectional (OR:1.31, 95% CI: 1.16, 1.47) studies (Figure 3).

Based on subgroup analysis, remnant-C causes a higher risk of CKD in China (OR:1.35, 95% CI: 1.20, 1.50), South Korea (OR:1.29, 95% CI: 1.14, 1.45), and America (OR:1.28, 95% CI: 1.06, 1.55) (Figure 4).

At the ages 40-49 years (OR:1.32, 95% CI: 1.18, 1.48), 50-59 years (OR:1.26, 95% CI: 1.14, 1.40) and 60-69 years (OR:1.39, 95% CI: 1.14, 1.69), remnants lead to higher risk of CKD (Figure 5).

In the second quartile (OR:1.20, 95% CI: 1.13, 1.27), third quartile (OR:1.26, 95% CI: 1.13, 1.40), and 4th quartile (OR:1.62, 95% CI: 1.42, 1.86), remnant-C lead to higher risk of CKD. In addition, in the second tertile (OR:1.12, 95% CI: 1.06, 1.19) and third tertile (OR:1.23, 95% CI: 1.16, 1.31), a higher risk of CKD is a consequence of remnant-C (Figure 6).

Remnant-C leads to a higher risk of CKD in both men (OR:1.23, 95% CI: 1.13, 1.33) and women (OR:1.51, 95% CI: 1.25, 1.82) (Figures 7 and 8).

In patients with hypertension (OR:1.35, 95% CI: 1.22, 1.48), diabetes (OR:1.32, 95% CI: 1.10, 1.59), individuals with body mass index (BMI) <25 kg/m^2 (OR:1.28, 95% CI: 1.15, 1.43) and individuals with BMI>25 kg/m^2 (OR:1.39, 95% CI: 1.20, 1.60), remnant-C is associated with higher risk of CKD (Figures 9-12).

Meta-regression data shows no significant statistical relation between "remnant-C and CKD relation" and case number (P=0.778). The publication bias diagram confirmed an unbiased search process, either (P=0.380; Figures 13 and 14).

Discussion

Indeed, remnant-C increases CDK risk by 31%. This increase was 20% in the 2nd quartile, 26% in the 3rd quartile, 62% in the 4th quartile, 12% in the second tertile, and 23% in the 3rd tertile. Remnant-C increased in CKD in 32% of the 40-49 years group, 26% in the 50-59 years group, and 39% in the 60-69 years group. Remnant-C led to a higher risk of CKD at 23% in men and 51% in women. Besides that, remnant-C increases CKD risk in 35% of patients with hypertension, 32% of patients with diabetes, 28% of individuals with BMI<25 kg/m^2, and 39% of individuals with BMI>25 kg/m^2.

In a cross-sectional study by Yan et al in middle-aged and

Table 1. Summarized information of the studies that were included in the systematic review and meta-analysis

First author, year	Country	Type of Study	Sample size	Mean age (year)	Stage	RC level	The relationship between remnant cholesterol and CKD		
							OR	Low	Up
Jang SY, 2024 (19)	South Korea	Cohort	71561	50.1	Tertile 2	NR	1.121	1.056	1.19
			70674	48	Tertile 3	NR	1.234	1.159	1.314
Yuan Y, 2024 (20)	China	Cohort	1929	50	Quartile 2	0.20-0.36 mmol/L	1.3	1.04	1.64
			1955	51	Quartile 3	0.37-0.65 mmol/L	1.37	1.09	1.72
			1913	51	Quartile 4	>0.65 mmol/L	1.4	1.1	1.78
Zhu W, 2024 (16)	USA	Cross-sectional	NR	60	Quartile 2	>0.41,≤ 0.59 mmol/L	1.115	0.844	1.473
			NR	60	Quartile 3	>0.59, ≤0.85 mmol/L	1.238	0.936	1.637
			NR	60	Quartile 4	>0.85 mmol/L	1.551	1.157	2.079
Yuan T, 2023 (21)	China	Cross-sectional	3319	63.7	Quartile 2	0.41-0.63 mmol/L	1.12	0.93	1.35
			3205	64.1	Quartile 3	0.63-0.83 mmol/L	1.15	0.95	1.39
			3350	63.4	Quartile 4	≥0.83 mmol/L	1.53	1.26	1.86
Yuan Y, 2023-A (22)	China	Cross-sectional	520	56.6	Quartile 2	1.04–1.77 mg/dl	1.3	1.01	1.68
			189	57.5	Quartile 3	1.18–2.03 mg/dl	1.6	1.23	2.07
			87	62.1	Quartile 4	1.74, 2.95 mg/dl	2.39	1.86	3.09
Hu Q, 2022 (15)	China	Cross-sectional	5530	48.42	Total	0.65 mmol/L	1.259	1.076	1.474
Yan P, 2021 (23)	China	Cross-sectional	1807	57.09	Quartile 2	0.5–0.69 mmol/L	1.042	0.848	1.282
			1880	57.85	Quartile 3	0.70–0.95 mmol/L	0.989	0.802	1.218
			1843	58.69	Quartile 4	≥ 0.96 mmol/L	1.344	1.097	1.648
Zhao Y, 2024 (24)	China	Cohort	86	51.2	Quartile 2	0.53–0.65 mmol/L	1.375	0.562	3.367
			81	50.4	Quartile 3	0.76–0.92 mmol/L	1.531	0.627	3.742
			83	50.9	Quartile 4	1.17–1.89 mmol/L	3.351	1.452	7.735
Jung HN, 2024(25)	South Korea	Cohort	964638	47.3	Quartile 2	16.38–20.99 mg/dL	1.22	1.14	1.31
			963878	49.5	Quartile 3	21.00–27.43 mg/dL	1.3	1.21	1.39
			962656	49.5	Quartile 4	≥ 27.44 mg/dL	1.61	1.5	1.72

NR: Not reported, OR: Odds ratio, RC: Remnant Cholesterol.

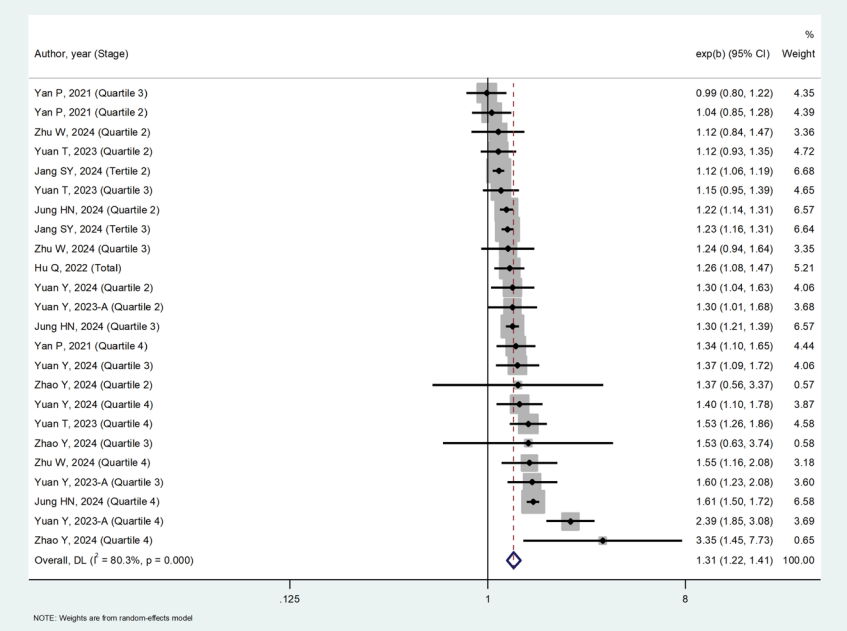

Figure 2. Forest plot showing the relationship between remnant cholesterol and risk of CKD.

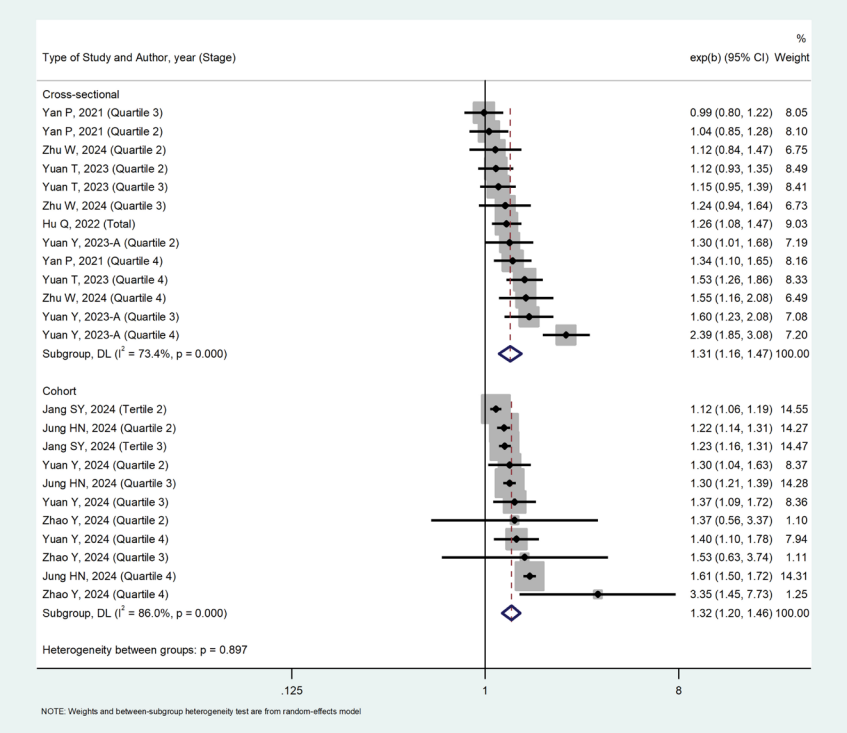

Figure 3. Forest plot showing the relationship between remnant cholesterol and risk of CKD by type of study.

old populations in China, participants of the first quartile of remnant-C were at higher risk of CKD compared to the last quartile (OR: 1.34, 95% CI: 1.09, 1.64) (23). In our study, the higher level of remnant-C was associated with an increased risk of CKD, either.

Jang et al in a cohort study of 212836 participants, showed the relation between higher remnant-C level with CKD incidence (HR: 1.23, 95 % CI: 1.15,1.31) (19). According to the study of Yuan et al in China, elevated levels of remnant-C caused a higher risk of CKD (per SD increment; OR: 1.15, 95% CI: 1.08, 1.23) (21). Zou et al (2011-2018) in a cross-sectional study, revealed that remnant-C (OR: 1.63, 95% CI: 1.24, 2.15) and triglyceride (OR:1.25, 95% CI: 1.10, 1.42) are related to a higher risk

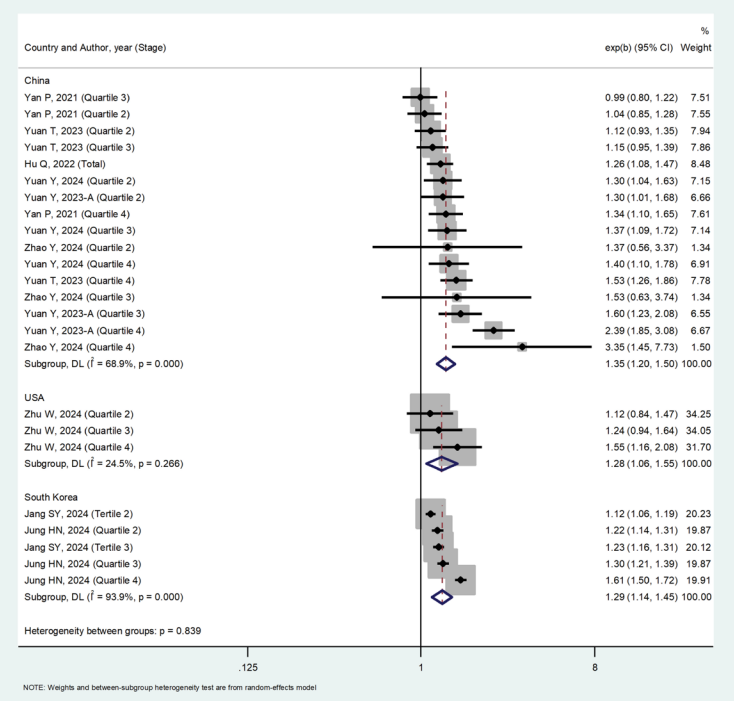

Figure 4. Forest plot showing the relationship between remnant cholesterol and risk of CKD by countries.

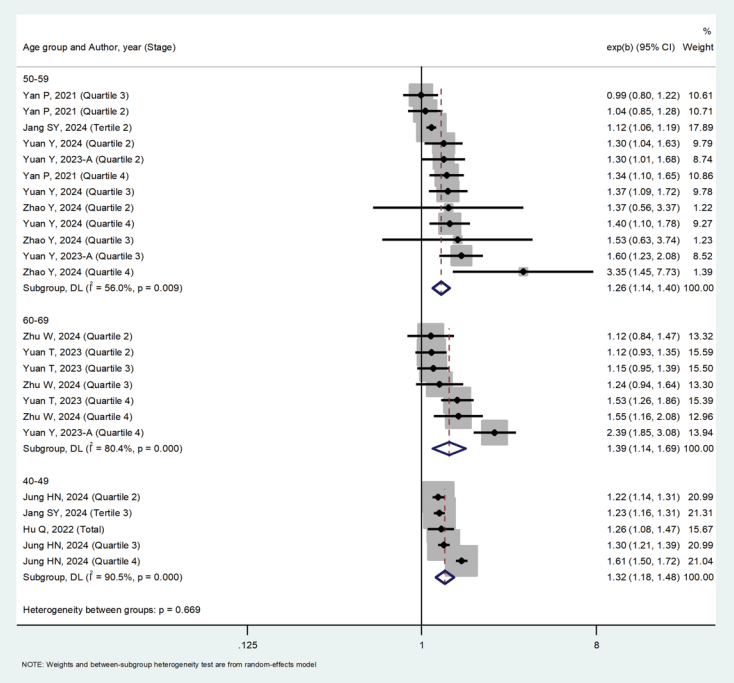

Figure 5. Forest plot showing the relationship between remnant cholesterol and risk of CKD by age group.

of CKD (16). In another cross-sectional study by Yuanel et al, they illustrated that increased remnant-C levels were associated with higher risk of CKD (OR: 1.67, 95% CI: 1.43,1.95) (22). In the present meta-analysis, both cohort and cross-sectional studies concluded that remnant-C is a risk factor for CKD development. These data are consistent with our findings.

Lamprea-Montealegre et al in a cohort study on CKD patients, approved the relation between atherosclerosis with apolipoprotein B (HR:1.19, 95% CI, 1.12, 1.27), triglyceride (HR: 1.06, 95% CI: 1.00, 1.13), triglyceride to HDL-cholesterol ratio (HR: 1.10, 95% CI: 1.03, 1.18) and triglyceride-rich cholesterol lipoproteins (HR: 1.14, 95% CI: 1.05, 1.25) (26). In a meta-analysis study by Ali

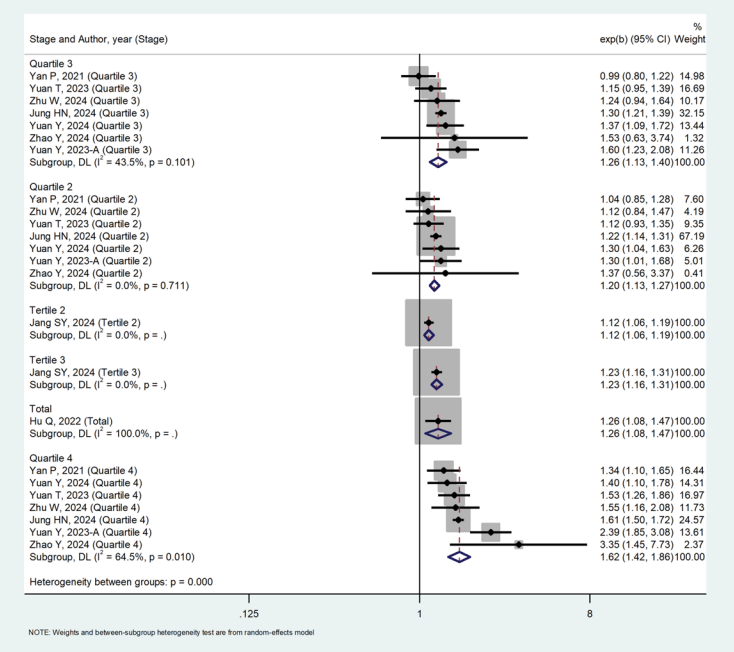

Figure 6. Forest plot showing the relationship between remnant cholesterol and risk of CKD by stage.

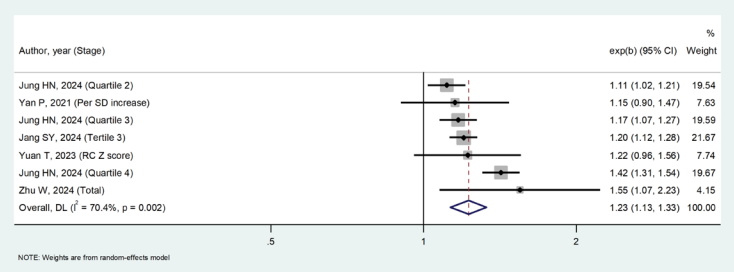

Figure 7. Forest plot showing the relationship between remnant cholesterol and risk of CKD in males.

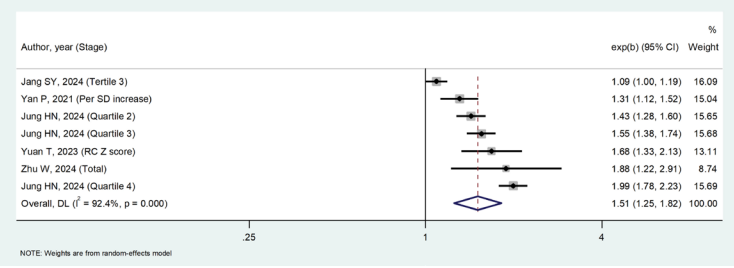

Figure 8. Forest plot showing the relationship between remnant cholesterol and risk of CKD in females.

et al, increased levels of triglyceride-glucose index (TyG) led to increasing the risk of CKD in the whole population (OR: 1.37, 95% CI: 1.25, 1.5), women (OR: 1.38, 95% CI: 1.19, 1.61) and men (OR: 1.31, 95% CI: 1.13, 1.50) (27). According to the study by Miao et al, total cholesterol (OR: 0.75, 95% CI: 0.57, 0.93) and HDL-C (high-density lipoprotein cholesterol) (OR: 0.85, 95% CI: 0.68, 1.01) are associated with CKD (28). These studies postulated that increasing the lipid profiles leads to a higher risk of CKD which is consistent to our findings.

Meanwhile, Delialis et al in a meta-analysis study concluded on a linear (HR: 1.27, 95% CI: 1.12, 1.43) and non-linear (HR: 1.59, 95% CI: 1.35, 1.85) relation between remnant-C level and risk of cardiovascular disease in arteriosclerosis (29). Data from the Yang et al meta-analysis study showed that a higher level of remnant-C is associated with increasing risk of cardiovascular disease (RR: 1.53, 95% CI: 1.41,1.66), brain stroke (RR: 1.43,

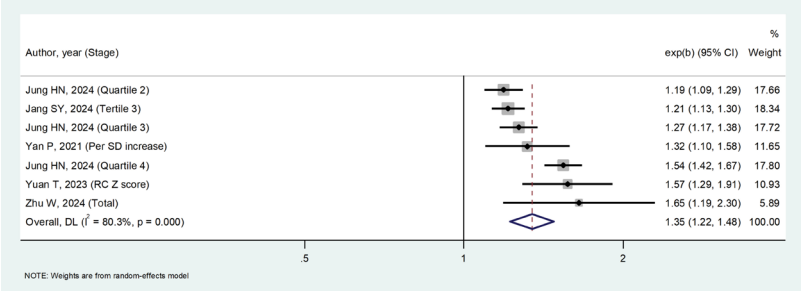

Figure 9. Forest plot showing the relationship between remnant cholesterol and risk of CKD in patients with hypertension.

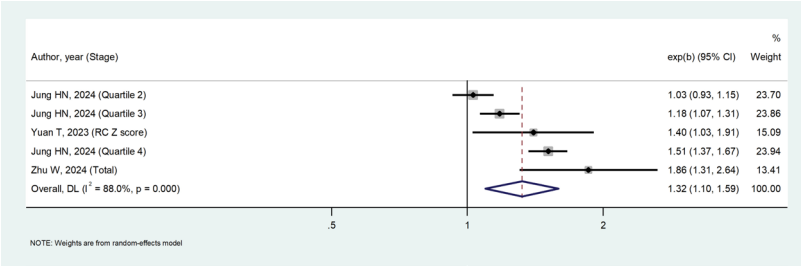

Figure 10. Forest plot showing the relationship between remnant cholesterol and risk of CKD in patients with diabetes.

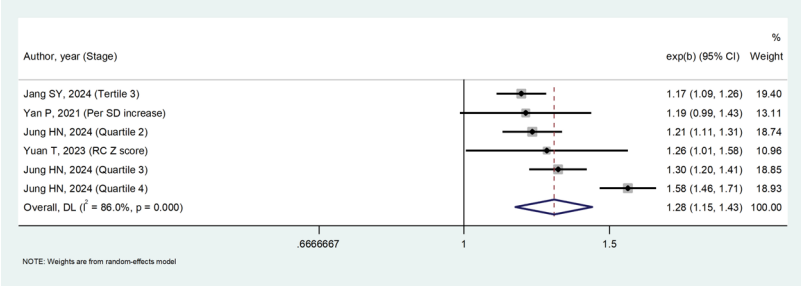

Figure 11. Forest plot showing the relationship between remnant cholesterol and risk of CKD in people with BMI<25 kg/m^2.

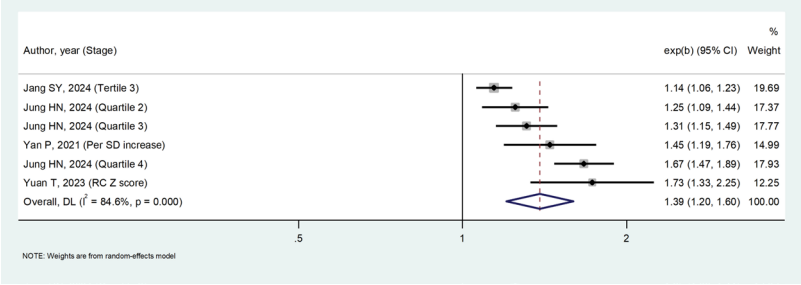

Figure 12. Forest plot showing the relationship between remnant cholesterol and risk of CKD in people with BMI>25 kg/m^2.

95% CI: 1.24,1.66) and overall mortality (RR: 1.39, 95% CI: 1.27,1.50) too (30). In another meta-analysis by Bia et al, at any unit increase of remnant-C level (HR: 1.13, 95% CI: 1.08, 1.17), the risk of cardiovascular events rises (31). These data revealed that remnant-C is a risk factor for cardiovascular disease, and brain stroke and may lead to death as well. These studies conformed to the present study since they affirmed remnant-C as a risk factor.

Conclusion

One-third of both individuals with high levels of remnant-C, develop CKD. The higher level of remnant-C increased the risk of CKD. Remnant-C causes CKD in women more than men and in overweight or obese

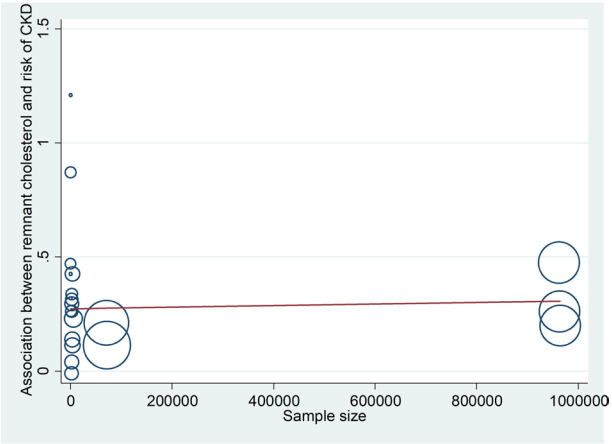

Figure 13. The meta-regression diagram showing the relationship between remnant cholesterol and risk of CKD by sample size.

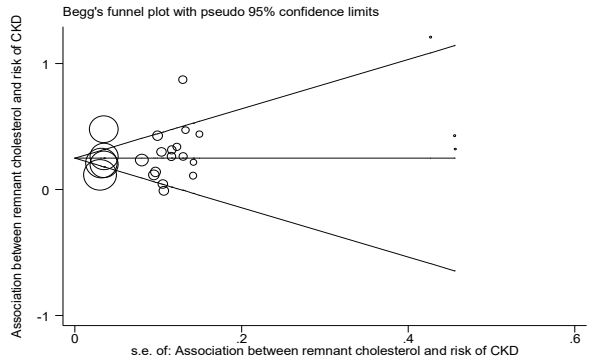

Figure 14. Chart of publication bias.

people more than once with a BMI<25 kg/m^2. Moreover, age does not appear to be a key parameter in elevating CKD risk in individuals with high levels of remnant-C. In addition, hypertension patients showed a higher risk for CKD compared to diabetic patients. As a result, women, obese people, and patients with the risk of hypertension and diabetes are advised to monitor their remnant-C, to mitigate CKD development.

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Authors' contribution

Conceptualization: Halime Aali and Sara Bazgiri.
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Formal analysis: Seyed Saied Rajaei Ramsheh.
Investigation: Dadkhoda Soofi and Zahra Jamalafrouz.
Methodology: Mahboobeh Askarizade, Seyed Saied Rajaei Ramsheh.
Project Management: Dadkhoda Soofi.
Supervision: Halime Aali.
Validation: Mahboobeh Askarizade and Erfan Shafiei.
Visualization: Zahra Bazargani and Fariba Asadi Noghabi
Writing-original draft: All authors.
Writing-reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42025632075) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1936) websites. Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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