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REVIEW ARTICLE

High Remnant Cholesterol Increased the Risk of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) or Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review and Meta-Analysis

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Abstract

Background. MAFLD is currently acknowledged as the most common chronic liver disease and is strongly associated with obesity, metabolic dysregulation and diabetes. MAFLD is defined by the accumulation of lipids within the liver due to impaired lipid metabolism.

Objective. The objective of this study is to assess the association between increased remnant cholesterol levels and the likelihood of developing MAFLD or NAFLD.

Methodology. A systematic review and meta-analysis were performed in accordance with PRISMA recommendations. Databases such as the Cochrane Library and PubMed were queried for relevant material through March 21, 2025, using specific keywords related to remnant cholesterol and fatty liver disorders. The inclusion criteria concentrated on research investigating the influence of remnant cholesterol on the incidence of NAFLD/MAFLD. Data extraction and quality evaluation were conducted utilizing the JBI Critical Appraisal Checklist for Cohort Studies and ROBINS-I instruments.

Results. Six studies were eventually included in our systematic review, including cross-sectional studies with a total of 45,821participants. The meta-analysis, conducted with Review Manager version 5.4, demonstrated a significant association between elevated remnant cholesterol levels and an increased risk of NAFLD/MAFLD, yielding a relative risk (RR) of 3.18 (95% CI 1.89-5.37; p <0.00001; I^2 = 99%). This indicates a robust link between remnant cholesterol and the prevalence of various hepatic disorders.

Conclusion. Remnant cholesterol is associated with MAFLD or NAFLD. Increased remnant cholesterol is a risk factor for MAFLD or NAFLD.

Key words: remnant cholesterol, insulin resistance, MAFLD, NAFLD

INTRODUCTION

Since the introduction of non-alcoholic fatty liver disease (NAFLD) in 1980, several trials have been conducted by various scientists and organizations to propose alternative nomenclature for the condition for diverse reasons.[1] In 2019, Eslam et al., recommended reclassifying classic NAFLD as metabolic dysfunction-associated liver disease (MAFLD).[2] The alteration of a single letter holds significant implications for researchers, physicians and patients. The authors articulated their perspective on a novel nomenclature by associating fatty liver with metabolic syndrome, the predominant and most severe cause of fatty liver illnesses, which is often inadequately assessed under the previous nomenclature. Furthermore, the revised nomenclature provides the healthcare community with an opportunity to mitigate the stigma associated with alcohol consumption, circumvent the negative connotations of NAFLD terminology and address trivialization.[3] The streamlined diagnostic criteria for MAFLD were established by consensus among an international panel of hepatologists in 2020.[4] These criteria facilitate the straightforward detection of fatty liver disorders due to their practical usefulness. The agreement defined MAFLD as the presence of steatosis, identified by imaging or histology, alongside either diabetes mellitus, obesity/overweight, or the presence of two of seven metabolic dysfunction criteria. The revised terminology and methodology elucidate the significance

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of metabolic dysfunctions in fatty liver disease, aligning the condition more closely with its etiology.

The novel nomenclature and its practical application invigorated researchers globally, leading to a significant increase in publications over the past two years. Recent studies have provided substantial evidence demonstrating the superiority of MAFLD criteria over NAFLD criteria. Numerous studies throughout various global regions, involving substantial patient populations in the United States, Europe, and Asia,, have shown that the efficacy of MAFLD criteria exceeds that of NAFLD criteria in multiple facets of fatty liver disease.

Among the significant findings, MAFLD criteria demonstrated superior efficacy in identifying individuals at risk of liver fibrosis compared with NAFLD criteria within the American population.[5] The fatty liver index showed a high diagnostic capability in identifying steatosis in individuals with MAFLD.[6] The Fibrosis-4 index and NAFLD fibrosis score can reliably exclude advanced fibrosis in individuals with MAFLD who are overweight, obese, or extremely obese.[7] MAFLD correlates with an increased incidence of hepatocellular carcinoma.[8] MAFLD, as opposed to NAFLD, is a predictor of extrahepatic malignancy.[8] MAFLD outperformed NAFLD in identifying individuals at elevated risk of renal disease.[9] A recent meta-analysis indicated that MAFLD correlates with heightened severity of COVID-19.[10] Renaming to MAFLD enhances awareness of the condition among primary care providers and clinicians in other specialties.[11] Alterations to MAFLD positively influence clinical trials. MAFLD assesses the severity of the coexistence of fatty liver disease with other hepatic disorders.[12–15]

As of the publication of this paper, the two prominent hepatology associations, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, have not yet adopted the new name. The discourse among these communities mostly concentrated on the untimeliness of transformation.[16] A primary discussion centers on non-metabolic or lean NAFLD. Evidence indicates that the non-metabolic NAFLD group appears equivalent to individuals without fatty liver for cardiovascular-related mortality and overall mortality. Furthermore, the non-metabolic NAFLD cohort appears to possess a low risk of fibrosis (0.8%).[17] Another issue pertained to pediatric non-alcoholic fatty liver disease (NAFLD). A recent study of 1,446 adolescents in the US aged 12 to 18 years from the National Health and Nutrition Examination Survey III found that the majority fit the criteria for MAFLD, supported by elastographic evidence of steatosis.[18] Further discussion pertained to clinical studies. A newly published report by a group of academics asserts that the new nomenclature and methodology with affirmative inclusion criteria facilitate patient recruitment and are more likely to yield favorable outcomes.[19] In the era of evidence-based medicine, we assert that an evidence-based discussion is essential. The MAFLD conceptual framework eliminates the notion of alcohol absence, connects liver disease frequently associated with metabolic dysregulation to its systemic effects, and enhances patient identification, risk stratification, disease awareness and collaboration with metabolic disease specialists.[20,21]

Metabolic dysfunction-associated fatty liver disease (MAFLD), the most prevalent chronic liver disease previously classified as nonalcoholic fatty liver disease (NAFLD), has been shown to impact roughly 33% of the global population, according to a recent meta-analysis involving approximately 9,808,677 individuals.[22,23] The rising incidence of MAFLD and its associated consequences coincides with the epidemics of obesity, systemic metabolic dysfunction and diabetes.[24] A diverse array of histological alterations contributes to the advancement of MAFLD, encompassing hepatic steatosis, fibrosis, cirrhosis and liver failure.[25] Moreover, it significantly contributes to the worldwide incidence of hepatocellular carcinoma.[26] MAFLD is a significant contributor to liver transplantation.[27] Examining risk factors for MAFLD can help identify high-risk groups and enhance management strategies by addressing the lack of targeted pharmaceutical treatments.[28]

MAFLD is defined by the accumulation of lipids within the liver due to impaired lipid metabolism.[29] The lipid profile associated with dyslipidemia in MAFLD is characterized by hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol levels and elevated low-density lipoprotein (LDL) cholesterol concentrations.[30] Recent analyses from a longitudinal study reveal that remnant cholesterol, defined as the cholesterol level in triglyceride-rich lipoproteins, is independently associated with NAFLD, particularly in males.[31,32] Remnant cholesterol has been recognized as an independent predictor of the occurrence of atherosclerotic cardiovascular disease.[33] A cohort research revealed that elevated remnant cholesterol levels are significantly linked to the incidence of ischemic stroke in the general population.[34] A recent investigation indicated that elevated remnant cholesterol correlates with the incidence and long-term mortality of patients with MAFLD; however, the potential linear or non-linear association remains unexamined.[35]

METHODOLOGY

Search strategy

This systematic review was registered in the Prospective Register of systematic Reviews (PROSPERO) under registration number: **CRD420251029326**. It is important to note that adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was ensured throughout the process of conducting and recording this meta-analysis. Cochrane Library and PubMed databases were utilized in order to carry out an exhaustive search of the available literature up until March 21st, 2025. When doing the literature

search, the keywords that were specified for use were "((("remnant"[All Fields] OR "remnants"[All Fields]) AND ("cholesterol"[Supplementary Concept] OR "cholesterol"[All Fields] OR "cholesterol"[MeSH Terms] OR "cholesterols"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields])) OR (("remnant"[All Fields] OR "remnant s"[All Fields] OR "remnants"[All Fields]) AND ("lipoprotein s"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[Supplementary Concept] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields] OR "lipoproteins"[MeSH Terms]))) AND ("Non-alcoholic fatty liver disease"[All Fields] OR ("naflds"[All Fields] OR "Non-alcoholic fatty liver disease"[MeSH Terms] OR ("non alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "Non-alcoholic fatty liver disease"[All Fields] OR "nafld"[All Fields]) OR "Metabolic dysfunction-associated fatty liver disease"[All Fields] OR "MAFLD"[All Fields])". Articles that have titles and abstracts that are pertinent to the topic at hand will be included to facilitate a comprehensive review and subsequent qualitative and quantitative analysis.

Inclusion and exclusion criteria

The inclusion criteria were structured according to the PICO framework. The population of interest were healthy individuals without known liver disease. The exposure was defined as high levels of remnant cholesterol, while the comparator group consisted of individuals with low levels of remnant cholesterol. The primary outcome was the prevalence of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MAFLD). Studies were excluded if full-text articles were unavailable or if the study design, exposure, or outcomes did not match the inclusion criteria. Detailed information on the search methods used in the study is presented in Figure 1. The definition of "high" versus "low" remnant cholesterol levels varied slightly across the included studies, depending on their respective population norms and analytical thresholds. In general, most studies dichotomized participants based on either quartiles, population medians, or predefined cut-off values derived from local clinical guidelines.

Data extraction and risk of bias assessment

After that, all authors began to retrieve data from the publications that we had selected. All authors independently screened the titles and abstracts for eligibility, followed by full-text assessment. Data extraction and quality appraisal were also conducted independently by two reviewers using a standardized form. Any disagreements during study selection or data extraction were resolved through discussion and consensus, with a third reviewer consulted when necessary. The JBI Critical Appraisal Checklist for Cohort Studies was used by all authors to assess the quality of the articles in accordance with the research methodology of the publications that were included in the review. The evaluation of quality was carried out in a collaborative

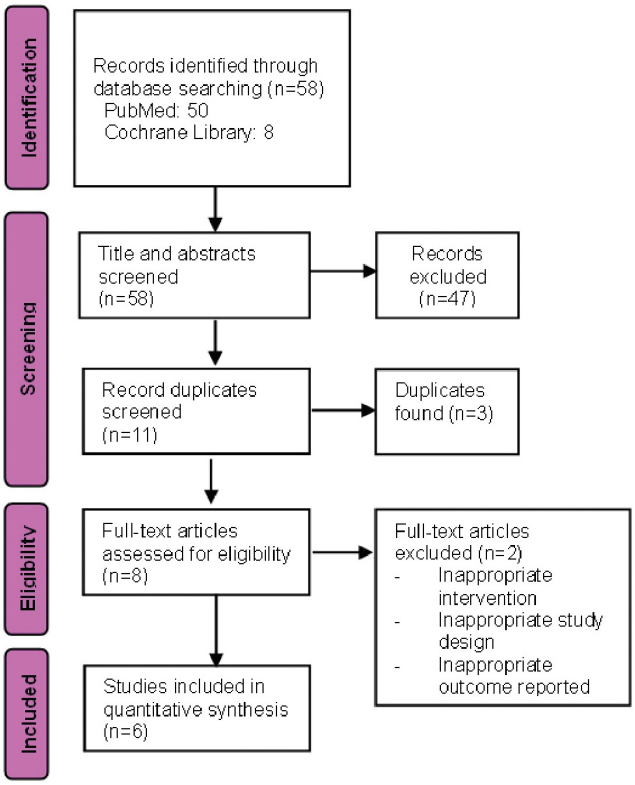

Figure 1. Diagram flow of literature search strategy for this meta-analysis.

manner by all of the reviewers until an agreement was reached. The ROBINS-I, which was provided by Cochrane for the type of study that was being evaluated, was utilized in order to carry out the assessment of the potential for bias.

Statistical analysis

A meta-analysis was carried out with the assistance of Review Manager version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). The relative risk (RR) and its confidence interval (CI) with a 95% level of certainty were chosen as the standard metrics to evaluate the effect that the exposure had on the primary outcome. The use of random-effects models allowed for the consolidation of effect estimates, which was necessary due to the predicted clinical heterogeneity. If the p-value is less than 0.05, the results of the analysis are regarded as being statistically significant. The Higgins I-squared (I2) statistical model was utilized in order to evaluate the heterogeneity of the data. Heterogeneity was evaluated and categorized as: Minimal (0-25%) Low (25-50%), Moderate (50-75%), or High o(greater than 75%).

The overall certainty of evidence for the primary outcome was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Factors such as risk of bias, inconsistency, indirectness, imprecision and potential publication bias were considered to qualitatively assess the strength of the findings.

Table 1. Characteristics and results of the included studies

Author	Year	Exposure	Control	Exposure (n)	Control (n)	Outcome measure	Prevalence of NAFLD/MAFLD	
							Exposure	Control
Hao, et al.	2025	High remnant cholesterol	Low remnant cholesterol	863	1018	Prevalence of MAFLD	495	153
Miao, et al.	2023	High remnant cholesterol	Low remnant cholesterol	5445	5346	Prevalence of NAFLD	1195	438
Zou, et al.	2021	High remnant cholesterol	Low remnant cholesterol	2851	2850	Prevalence of NAFLD	1271	77
Huang, et al.	2023	High remnant cholesterol	Low remnant cholesterol	1498	1536	Prevalence of NAFLD	986	357
Jia, et al.	2023	High remnant cholesterol	Low remnant cholesterol	2455	2458	Prevalence of NAFLD	1454	825
Pastori, et al.	2018	High remnant cholesterol	Low remnant cholesterol	399	399	Prevalence of NAFLD	356	276

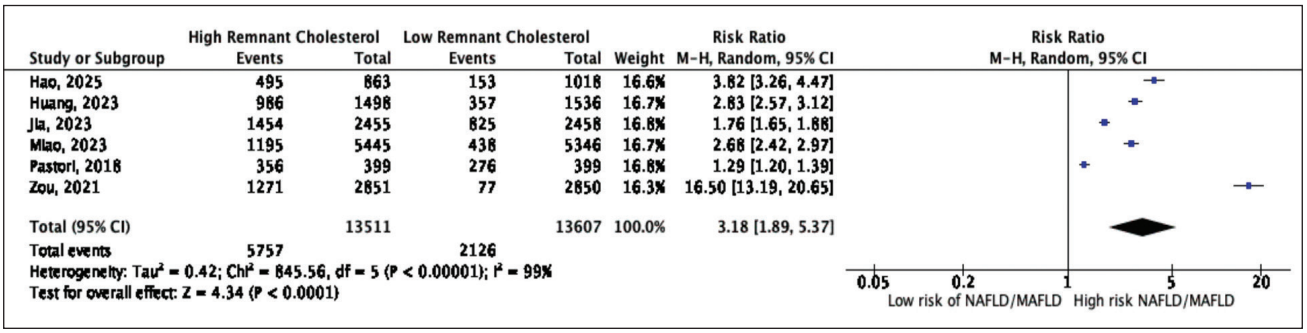

Figure 2. Pooled results for the risk of NAFLD/MAFLD in high remnant cholesterol level.

RESULTS

Six cross-sectional studies were eventually included in our systematic review (Table 1), and total participants included was 45,821. Our meta-analysis showed that high level of remnant cholesterol is associated with a significantly higher risk of NAFLD/MAFLD with an RR of 3.18 (95%CI 1.89-5.37; p <0,00001; I^2 = 99%) (Figure 2).

A sensitivity analysis was conducted by excluding the study of Zou et al. (2021), which visually appeared as an outlier in the funnel plot. However, the pooled analysis still demonstrated high heterogeneity (I^2 = 99%), indicating that no single study accounted for the observed variability. Subgroup analyses were not feasible due to the lack of consistently reported stratified data across studies. Therefore, a random-effects model was applied to account for this heterogeneity resulting to a more conservative estimate of the pooled association.

A funnel plot was generated to assess potential publication bias among the included studies (Figure 3). The plot demonstrated a degree of asymmetry, suggesting the possibility of publication bias. However, given the small number of studies included (<10), formal statistical tests such as Egger's regression test were not conducted, in accordance with current methodological guidance.

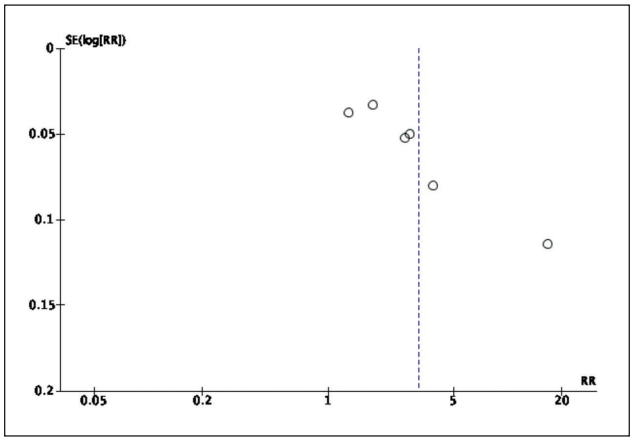

Figure 3. Funnel plot for the results of the included studies, indicating that the high heterogeneity was mainly caused by one outlier reported by the included study.

DISCUSSION

The correlation between MAFLD and residual cholesterol has been previously documented. The results of a longitudinal cohort research with 5,156 patients indicated that remnant cholesterol had an independent correlation with the incidence of MAFLD.[35] A notable association was identified between increased remnant cholesterol levels and the occurrence of MAFLD in a study by Wang et al.[36] MAFLD is defined by the abnormal accumulation of lipids in hepatocytes.[37] Recently, elevated remnant cholesterol has been hypothesized to have a role in the residual risk following effective LDL cholesterol primary prevention.[33,38] The remnant cholesterol, seen in triglyceride-rich lipoproteins, includes chylomicron remnants during the non-fasting state and intermediate- and very low-density lipoproteins during the fasting state.[39] Participants with MAFLD had elevated levels of remnant cholesterol. The pathophysiological processes behind remnant cholesterol-induced MAFLD are little elucidated. Insulin resistance, a prevalent underlying pathology, may elucidate the

association between remnant cholesterol and MAFLD. A recent study indicated that individuals with MAFLD had elevated HOMA-IR values, which are favorably correlated with remnant cholesterol levels.[36] These findings corroborated the hypothesis that insulin resistance may be crucial in the association between remnant cholesterol and MAFLD. Consistent with prior studies, the current study also shown a strong positive correlation between insulin resistance and MAFLD. The prevalent underlying pathophysiological anomaly in Type 2 Diabetes Mellitus (T2DM) and metabolic syndrome is insulin resistance, with Metabolic Associated Fatty Liver Disease (MAFLD) seen as a hepatic manifestation of systemic insulin resistance.[40] Hepatic steatosis is strongly correlated with insulin resistance in the liver and peripheral tissues, such as skeletal muscle and adipose tissue.[41] The insulin-resistant condition in the liver leads to inadequate inhibition of lipolysis in adipose tissue, resulting in increased free fatty acid influx to the liver, alongside heightened lipogenesis and enhanced ApoB production.[30] As a result, the synthesis of extremely low-density lipoproteins rises, shown by a rise in remnant cholesterol.[42]

Dyslipidemia is an established pathogenic component in NAFLD, as corroborated by several epidemiological and genetic research.[30,43] The elevation of intrahepatic triglycerides associated with insulin resistance is a significant trait.[44,45] Nevertheless, newer investigations have suggested alternative causes. In a research done by Yamaguchi et al., it was shown that TG does not appear to be lipotoxic and resembles an inert lipid.[46] The etiology of NAFLD may be intricately linked to the buildup of free cholesterol in the liver and the disruption of cholesterol homeostasis within the liver.[47–49] Nuño-Lámbarri et al., described that an imbalance in hepatic cholesterol exacerbates the buildup of free cholesterol in the liver.[50] Furthermore, Ducheix et al. indicated that excessive cholesterol buildup in cells activates the liver X receptor, which subsequently promotes or exacerbates hepatic steatosis.[51] Atherogenic dyslipidemia in peripheral blood may signify cholesterol buildup in hepatocytes and an increased risk of NAFLD.

Remnant cholesterol is a triglyceride-rich lipoprotein abundant in cholesterol, including chylomicron remnants, intermediate-density lipoprotein, and very-low-density lipoprotein.[52] It can incorporate many atherosclerotic consequences, such as monocyte activation, elevation of proinflammatory cytokines and heightened production of thrombogenic factors.[52,53] Recent findings have shown the association between RC and NAFLD. In 2018, Pastori et al., discovered for the first time that elevated levels of RC were independently and positively connected with NAFLD in patients with cardiac metabolic disorders, while Chin et al., identified a similar connection in teenagers.[54,55] This study confirmed the conclusion, and its findings endorse the function of RC as an independent risk factor for NAFLD in the general population. Consequently, another study revealed that the predictive capacity of RC for NAFLD was much superior to that of other lipid markers in males. Furthermore, a recent study by Campanella et al. examined 237 individuals with metabolic syndrome included in a randomized controlled trial and identified an association between RC and the severity of NAFLD.[56] This discovery indicates that RC may be of significant use in tracking the onset and progression of NAFLD.

A longitudinal cohort published by Cheng, et al. reported a data on the role of triglycerides (TG) in non-alcoholic fatty liver disease (NAFLD), indicating that elevated blood TG concentrations were linked to an increased risk of NAFLD over time.[57] The characterisation of the pathogenic pathways of NAFLD identifies the 'first strike' as initiated by lipid buildup in hepatocytes, whereby excessive fat consumption and insulin resistance are significant contributors.[58] While NAFLD correlates with elevated triglycerides in the liver, recent research indicates that free fatty acids (FFAs), rather than triglycerides, accumulate in lipid droplets, leading to inflammatory liver injury in nonalcoholic steatohepatitis. The hepatic metabolism of free fatty acids results in the generation of hazardous metabolites, primarily accountable for oxidative stress, inflammation, and damage to liver parenchyma.[59,60] The accumulation of triglycerides in the liver is presently regarded as a non-toxic and safer method of lipid storage, serving as an epiphenomenon that indicates alterations in the balance of free fatty acid flux and cellular stress; thus, steatosis can be identified as an initial adaptive response to hepatocyte stress due to heightened caloric intake.[61] During this process, potentially lipotoxic free fatty acids (FFAs) are converted into comparatively benign intracellular triglyceride (TG) molecules.[62] Numerous studies have identified insulin resistance as the predominant and prevalent possible factor contributing to the buildup of free fatty acids in the liver. The prevailing concept is that insulin resistance results in dyslipidemia.

Remnant-C is the by product of TRL metabolism, including chylomicron remnants during the non-fasting state and VLDL and intermediate-density lipoproteins during the fasting state. Prior research indicated that remnant-C was linked to an elevated risk of major adverse cardiovascular events (MACEs); however, the longitudinal association between serum remnant-C levels and the incidence of NAFLD has not been investigated.[63] A research conducted in Italian hospitals involving 798 individuals with cardio-metabolic disorders, showed that 79.2% exhibited NAFLD, indicated a link between circulating remnant-C levels and the severity of liver disease in NAFLD patients.[54] In accordance with this, adolescents exhibiting elevated remnant-C levels demonstrated more hepatic fat accumulation than those with reduced remnant-C levels in the Raine Study.[55]

A notable limitation of this meta-analysis is the presence of substantial heterogeneity among the included studies, as indicated by an I^2 value of 99%. This high degree of heterogeneity reflects considerable variability in study results and warrants cautious interpretation of the pooled effect estimate. In an attempt to explore and reduce this variability, we conducted a sensitivity analysis by excluding

the Zou et al., study, which initially appeared to be a visual outlier. However, the heterogeneity remained markedly high (I^2 = 99%), indicating that no single study was solely responsible for the overall inconsistency across effect sizes.

Subgroup analysis, which is a conventional method to explore sources of heterogeneity, was deemed infeasible due to limitations in the available data. Specifically, the included studies did not consistently report subgroup-specific outcomes based on key stratifying variables such as age, sex, ethnicity or study setting. Moreover, although some studies focused on MAFLD and others on NAFLD, the definitions and diagnostic criteria used were often overlapping or insufficiently detailed to permit meaningful categorization. As a result, formal subgroup stratification could not be implemented without risking misclassification bias or introducing further uncertainty into the analysis.

Despite these challenges, we addressed the observed heterogeneity through the application of a random-effects model, which is more appropriate than a fixed-effects model under conditions of high between-study variance. The random-effects model accounts for both within-study and between-study variability, thereby yielding a more conservative and generalizable estimate of the association between remnant cholesterol and fatty liver disease. The persistent heterogeneity may stem from differences in population characteristics (e.g., metabolic profiles, baseline cardiovascular risk), variations in the cut-off values used to define "high" remnant cholesterol, and inconsistencies in the diagnostic methods employed for NAFLD and MAFLD across studies. Furthermore, regional differences in lifestyle, diet and genetic predisposition may also have contributed to the observed effect size variability. While this limits the precision of the pooled estimate, the directionality of association remained consistent, reinforcing the overall conclusion of a significant link between elevated remnant cholesterol and fatty liver disease.

The possibility of publication bias was examined using a funnel plot, which appeared moderately asymmetric. This may suggest a tendency for smaller studies with negative or null findings to remain unpublished or excluded. However, with fewer than ten studies included in the meta-analysis, the power of such visual assessments is limited, and statistical tests such as Egger's or Begg's test are generally discouraged due to high false-positive and false-negative rates in small samples. Nonetheless, the observed asymmetry calls for cautious interpretation of the pooled effect estimate, as it may reflect selective publication of studies reporting stronger associations. Future systematic reviews incorporating a larger body of evidence would benefit from formal quantitative assessments of publication bias.

Based on the GRADE criteria, the certainty of the evidence was judged to be moderate. Although the analysis included observational studies, the large and consistent direction of the effect across different studies provided some confidence in the association. However, the very high heterogeneity (I^2 = 99%) and possible risk of publication bias limited the overall certainty. No major concerns were identified regarding indirectness or imprecision. Consequently, while the pooled result likely reflects a true association between remnant cholesterol and NAFLD/MAFLD, further well-designed studies are needed to confirm these findings and explore sources of heterogeneity.

CONCLUSION

This systematic review and meta-analysis highlight the substantial correlation between raised remnant cholesterol levels and the heightened risk of metabolic dysfunction-associated fatty liver disease (MAFLD) or non-alcoholic fatty liver disease (NAFLD). The results indicate that elevated remnant cholesterol is significantly associated with liver disorders, with a relative risk of 3.18, signifying a considerable effect on disease prevalence. The research emphasizes the significance of residual cholesterol as a pivotal factor in the pathogenesis of MAFLD or NAFLD, especially regarding its correlation with insulin resistance and dyslipidemia. These discoveries underscore the necessity for tailored therapies aimed at decreasing remnant cholesterol levels to reduce the incidence and development of fatty liver disorders. The findings further endorses the growing terminology and diagnostic criteria of MAFLD, which more accurately reflect the metabolic foundations of these liver illnesses, hence improving patient identification and therapy approaches.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
TB: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **HS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision; **AMA:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision.

Data Availability Statement
Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure
The authors declared no conflict of interest.

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