Review Article

Clinical Associations of Cholesterol Levels in Non-Cardiovascular Diseases

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Abstract

Background: **Cholesterol is an essential biomolecule that plays multiple structural and metabolic roles in the human body. Although the risks associated with cholesterol imbalance are well established in relation to cardiovascular disease, its impact on other physiological systems has gained increasing attention in recent years.**

Objective: **To analyze the clinical implications of cholesterol metabolism in non-cardiovascular conditions as described in the scientific literature.**

Methods: **This systematic review was conducted according to PRISMA guidelines using a structured search strategy. A total of 1,041 records were identified, and after screening and eligibility assessment, 7 studies met the inclusion criteria and were included in the final qualitative synthesis.**

Results: **The analyzed studies demonstrated that cholesterol dysregulation is associated with multiple pathological processes beyond cardiovascular disease. Altered cholesterol metabolism was linked to metabolic disorders, hepatic dysfunction, insulin resistance, gut microbiota imbalance, inflammatory responses, and neurological impairment. The findings suggest that alterations in cholesterol metabolism are associated with metabolic dysfunction, hepatic abnormalities, gut microbiota modulation, insulin resistance, and neurological outcomes in selected non-cardiovascular conditions. Improvements in cholesterol-related biomarkers were frequently accompanied by favorable metabolic and clinical outcomes.**

Conclusions: **The available evidence indicates that cholesterol metabolism extends far beyond its traditional role in cardiovascular health and represents an important regulator of systemic homeostasis. Maintaining balanced cholesterol levels may contribute to the prevention and management of diverse metabolic, neurological, inflammatory, and other non-cardiovascular disorders, highlighting the broad clinical relevance of cholesterol regulation in human health.**

Keywords: **Dyslipidemias; Insulin Resistance; Non-Alcoholic Fatty Liver Disease; Gastrointestinal Microbiome; Systematic Review.**

Introduction

Cholesterol is a fundamental lipid biomolecule that plays indispensable roles in human physiology, being essential for cellular structure, metabolic regulation, and signaling pathways.[1-3] Present in all mammalian cell membranes, cholesterol contributes directly to membrane stability, permeability, and fluidity, thereby ensuring proper cellular function and integrity.[2] In addition to its structural role, cholesterol acts as a precursor for steroid hormones, vitamin D, and bile acids, highlighting its importance in endocrine regulation, digestion, and metabolic homeostasis.[1,2] Within the nervous system, cholesterol is highly concentrated in myelin sheaths and neuronal membranes, where it participates in synapse formation, neurotransmission, and maintenance of neuronal plasticity.[3]

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Despite its physiological importance, disturbances in cholesterol metabolism have been extensively associated with the development of numerous pathological conditions. Traditionally, dyslipidemia and elevated serum cholesterol levels have been recognized as major risk factors for cardiovascular diseases, particularly atherosclerosis, coronary artery disease, myocardial infarction, and ischemic stroke.[4-6] Excess circulating low-density lipoprotein cholesterol (LDL-C) promotes endothelial dysfunction, oxidative stress, vascular inflammation, and plaque formation, contributing significantly to morbidity and mortality worldwide.[4,5] Consequently, cholesterol metabolism has become one of the central targets of preventive and therapeutic strategies in modern medicine.

However, recent scientific evidence has demonstrated that the clinical implications of cholesterol imbalance extend far beyond the cardiovascular system. Increasing attention has been directed toward understanding the role of cholesterol metabolism in neurodegenerative, psychiatric, inflammatory, metabolic, endocrine, and neoplastic diseases.[7-18] Experimental and clinical investigations suggest that altered cholesterol homeostasis may induce neuroinflammation, mitochondrial dysfunction, oxidative damage, apoptosis, and neuronal degeneration, mechanisms frequently associated with psychiatric disorders and neurodegenerative diseases such as

Central Illustration: Clinical Associations of Cholesterol Levels in Non-Cardiovascular Diseases

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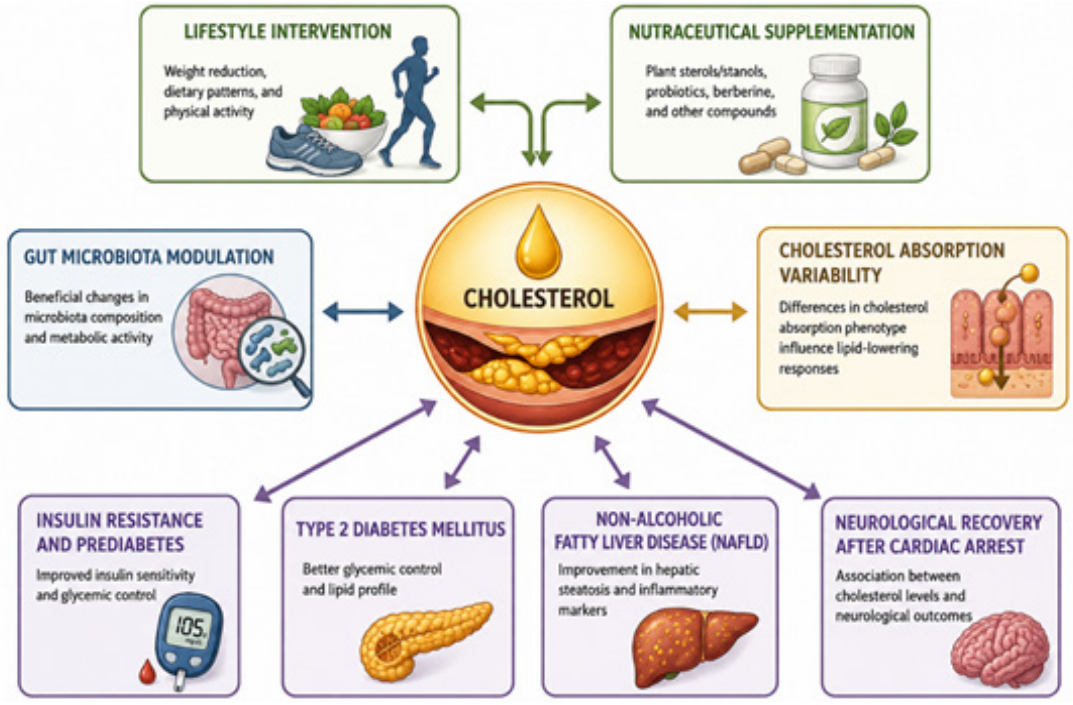

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Main non-cardiovascular conditions, interventions, and biological pathways associated with cholesterol metabolism identified in the studies included in this systematic review

Alzheimer's disease.[7,13] Furthermore, cholesterol metabolism has been implicated in tumor progression and cellular proliferation, especially in hepatocellular carcinoma and other malignancies, where dysregulated lipid metabolism may favor tumor growth and survival.[8-10]

In addition to neurological and oncological disorders, several studies have identified significant associations between hypercholesterolemia and chronic metabolic diseases, including diabetic dyslipidemia, insulin resistance, obesity-related complications, and chronic kidney disease.[11,12] Other investigations have linked cholesterol imbalance to osteoporosis, osteoarthritis, pituitary dysfunctions, immune-mediated diseases, and infectious conditions such as COVID-19, suggesting that lipid metabolism may influence inflammatory responses, immune regulation, and systemic disease progression.[14-18] These findings reinforce the concept that cholesterol metabolism is closely interconnected with multiple biological pathways and organ systems.

Under physiological conditions, cholesterol homeostasis is maintained through a tightly regulated balance involving endogenous synthesis, intestinal absorption, lipoprotein-mediated transport, cellular uptake, storage, and hepatic catabolism.[19] The liver is responsible for synthesizing more than 50% of total body cholesterol, primarily from acetyl-CoA through a complex enzymatic pathway involving multiple regulatory mechanisms.[19] Cholesterol transport occurs mainly through lipoproteins such as LDL and high-density lipoprotein cholesterol (HDL-C), which mediate cholesterol delivery and reverse cholesterol transport, respectively. Disruptions in these metabolic pathways, whether caused by dietary habits, genetic predisposition, sedentary lifestyle, or metabolic diseases, may result in excessive cholesterol accumulation and systemic metabolic dysfunction.[20]

Considering the increasing prevalence of dyslipidemia worldwide and the growing body of evidence associating cholesterol imbalance with numerous systemic disorders, it has become increasingly important to understand the broader clinical implications of altered serum cholesterol levels. Although several studies have individually investigated the relationship between cholesterol metabolism and specific diseases, the available evidence remains dispersed across different medical fields. Therefore, a systematic review is necessary to comprehensively synthesize and critically evaluate the current literature regarding the clinical implications of serum cholesterol dysregulation in different organ systems and pathological conditions, contributing to a broader understanding of its impact on human health and disease.

Although several reviews have previously examined specific aspects of cholesterol metabolism in individual disease contexts, the available evidence remains dispersed across different medical specialties and clinical conditions. Therefore, an updated synthesis of recent studies is warranted to better understand the broader clinical implications of cholesterol metabolism in non-cardiovascular diseases and to identify common mechanisms linking lipid dysregulation to systemic health outcomes. While cholesterol metabolism has been implicated in numerous disease categories, the present review specifically focuses on the recent clinical evidence identified through predefined eligibility criteria, providing a synthesis of the non-cardiovascular conditions represented in the included studies.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, aiming to identify, evaluate, and synthesize the available scientific evidence regarding the clinical implications of cholesterol dysregulation in non-cardiovascular diseases.

Search strategy

A systematic literature search was conducted in accordance with the PRISMA 2020 guidelines to identify studies investigating the relationship between cholesterol metabolism and non-cardiovascular diseases. The search was performed on January 15, 2026, using the PubMed, Web of Science, and SciELO databases. Studies published between January 1, 2022, and December 31, 2025, were considered eligible. This timeframe was selected to prioritize the most recent evidence and contemporary advances regarding the role of cholesterol in metabolic, neurological, inflammatory, hepatic, and other non-cardiovascular conditions, reflecting the rapidly evolving nature of research in lipid metabolism.

The search strategy was developed using Medical Subject Headings (MeSH) and corresponding Health Sciences Descriptors (DeCS), combined with free-text terms. The principal descriptors included "cholesterol," "hypercholesterolemia," "dyslipidemia," "metabolic diseases," "liver diseases," "neurological disorders," "inflammation," "insulin resistance," "microbiota," and "non-cardiovascular diseases." Boolean operators ("AND," "OR," and "NOT") were applied to optimize search sensitivity and specificity. In PubMed, the search strategy combined terms related to cholesterol metabolism with descriptors associated with non-cardiovascular conditions while excluding studies primarily focused on cardiovascular diseases. Equivalent search strategies were adapted for Web of Science and SciELO according to the indexing systems and search requirements of each database.

Whenever available, filters were applied to restrict results to studies involving human participants, published in English, Portuguese, or Spanish, and available in full text. Additional manual searches were conducted by screening the reference lists of all eligible articles and relevant review papers identified during the search process. Studies identified through manual searching were subjected to the same eligibility criteria and screening procedures applied to records retrieved from the electronic databases.

Following duplicate removal, titles and abstracts were screened according to predefined inclusion and exclusion criteria. Potentially eligible articles underwent full-text assessment. During this stage, studies were excluded when they did not evaluate non-cardiovascular outcomes, lacked sufficient methodological information, presented an ineligible study design, or represented duplicate publications or overlapping datasets. Specifically, 28 studies were excluded because they did not investigate non-cardiovascular outcomes, 17 due to insufficient methodological information, 15 because of ineligible study designs, and 9 owing to duplicate publications or overlapping populations.

Eligibility criteria

The inclusion criteria comprised original studies involving human participants that evaluated the association between serum cholesterol levels, cholesterol metabolism, or dyslipidemia and non-cardiovascular diseases. Observational studies, cross-sectional studies, cohort studies, case-control studies, and clinical investigations published in peer-reviewed journals were considered eligible for inclusion. Only studies available in full text and written in English, Portuguese, or Spanish were included in the review.

The exclusion criteria included review articles, editorials, letters to the editor, conference abstracts, case reports, duplicate publications, computational studies, in silico analyses, experimental studies involving animal models, and studies lacking sufficient methodological or clinical information. Articles whose primary focus was exclusively related to cardiovascular diseases or that did not directly investigate cholesterol-related clinical implications were also excluded.

Study selection

The study selection process was conducted in multiple stages. Initially, all records identified through database searching were exported and screened for duplicate removal. Subsequently, titles and abstracts were independently analyzed to identify potentially relevant studies according to the predefined eligibility criteria. Articles considered potentially eligible underwent full-text evaluation to determine final inclusion in the systematic review.

The study selection process was conducted independently by two reviewers. Initially, titles and abstracts were screened according to the predefined eligibility criteria, followed by a full-text assessment of potentially relevant articles. Disagreements regarding study eligibility were resolved through discussion and consensus after detailed evaluation of the articles. Inter-reviewer agreement was assessed using Cohen's kappa coefficient, which demonstrated substantial agreement between reviewers ($\kappa = 0.82$).

Data extraction and synthesis

Data extraction was performed systematically using standardized criteria to ensure consistency among the included

studies. The following information was extracted from each article: author names, year of publication, country of study, study design, sample characteristics, evaluated diseases, cholesterol-related parameters, methodological approaches, and principal clinical findings.

The selected studies were qualitatively synthesized and organized into tables to facilitate comparison and interpretation of the evidence. The analysis focused on identifying the main pathological conditions associated with cholesterol dysregulation, as well as the proposed biological mechanisms involved in disease development and progression.

Risk of bias assessment

A risk-of-bias assessment was performed according to the methodological design of each included study. Randomized controlled trials and randomized crossover studies were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool. Non-randomized intervention studies and post hoc analyses were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Prognostic observational studies were evaluated using the Quality in Prognosis Studies (QUIPS) tool. Risk-of-bias assessments considered domains related to participant selection, confounding, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting, as appropriate for each study design. The overall risk-of-bias judgment for each study was categorized according to the recommendations of the corresponding assessment tool.

Methodological considerations

Considering the heterogeneity of the included studies regarding design, population characteristics, and evaluated outcomes, a qualitative synthesis approach was adopted. The present systematic review aimed to provide a broad and updated overview of the current evidence concerning the systemic clinical implications of altered cholesterol metabolism beyond cardiovascular diseases.

Results

The study selection process is summarized in the PRISMA flow diagram (Figure 1). A total of 1,041 records were initially identified through searches conducted in PubMed (n = 612), Web of Science (n = 321), and SciELO (n = 108). After the removal of 184 duplicate records, 857 unique studies remained for title and abstract screening.

During the screening stage, 781 records were excluded because they were not directly related to cholesterol metabolism (n = 356), focused exclusively on cardiovascular diseases (n = 214), consisted of review articles, editorials, or letters (n = 127), or involved animal and in vitro studies (n = 84). Consequently, 76 articles were selected for full-text assessment.

Following eligibility evaluation, 69 studies were excluded due to the absence of non-cardiovascular outcomes (n = 28), insufficient methodological information (n = 17), ineligible study design (n = 15), or duplicate publications and overlapping datasets (n = 9). Ultimately, 7 studies met all eligibility criteria and were included in the final qualitative synthesis. These studies investigated the relationship between cholesterol metabolism and non-cardiovascular conditions, including obesity-related dyslipidemia, gut microbiota modulation, non-alcoholic fatty liver disease (NAFLD), insulin resistance, cholesterol absorption variability, and neurological outcomes following cardiac arrest.

Overall, the PRISMA selection process ensured a rigorous and systematic identification of the most relevant evidence available, allowing the inclusion of studies that directly addressed the clinical implications of cholesterol metabolism beyond cardiovascular disease. The analyzed studies primarily investigated obesity-related metabolic disorders, insulin resistance, gut microbiota modulation, NAFLD, cholesterol absorption variability, and neurological outcomes following cardiac arrest. Overall, the findings demonstrated that cholesterol dysregulation may contribute to multiple pathological mechanisms, including oxidative stress, chronic inflammation, mitochondrial dysfunction, immune imbalance, and cellular proliferation abnormalities, reinforcing the systemic impact of altered lipid metabolism beyond cardiovascular disorders. A synthesis of the characteristics, main findings, and key concepts of the studies is presented in Table 1.

Risk of bias

The risk-of-bias assessment indicated generally acceptable methodological quality among the included studies. The randomized controlled trials were classified as presenting low risk of bias or some concerns, mainly related to reporting details and crossover-specific methodological considerations. The non-randomized intervention study and the post hoc analysis were considered to have a moderate risk of bias due to the potential influence of confounding factors and limitations inherent to non-randomized designs. The prognostic observational studies were also classified as having a moderate risk of bias, primarily because of potential residual confounding and limitations related to outcome prediction models. Overall, no study was judged to present a critical risk of bias, although the heterogeneity of study designs should be considered when interpreting the findings.

The studies summarized in the Central Illustration collectively demonstrate that cholesterol is strongly associated with a broad spectrum of non-cardiovascular diseases, with complex and sometimes paradoxical relationships depending on its levels and fractions.

The studies included in this systematic review demonstrated that alterations in cholesterol metabolism are associated with several non-cardiovascular pathological conditions, including obesity, insulin resistance, metabolic dysfunction, neurological impairment, chronic inflammation, gut microbiota dysregulation, and NAFLD. Overall, the findings reinforce the systemic role of cholesterol beyond its traditional association with cardiovascular diseases.

Koeder et al. (2022)[21] demonstrated that a one-year lifestyle intervention based primarily on a plant-based diet, physical activity, stress management, and community support promoted significant reductions in body weight, body mass index, waist circumference, total cholesterol, calculated

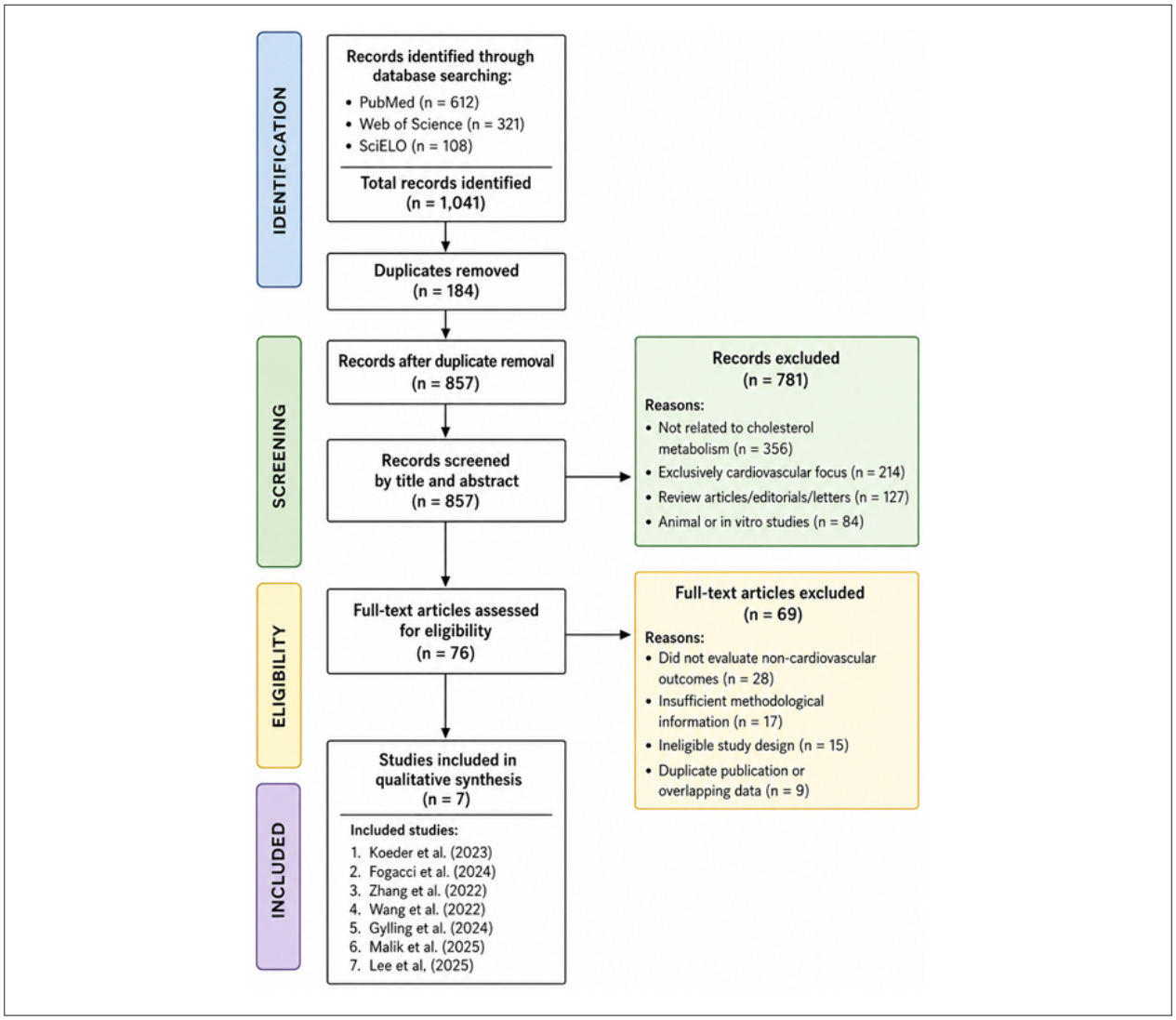

Figure 1 – *PRISMA flow diagram of the study selection process*

LDL-C, non-HDL-C, remnant cholesterol, glucose, glycated hemoglobin, and resting heart rate. These findings suggest that lifestyle modification may positively influence cholesterol metabolism while simultaneously improving multiple obesity-related metabolic risk factors.

The relationship between cholesterol metabolism and liver dysfunction was highlighted in the ANEMONE study conducted by Fogacci et al. (2024).[22] In this randomized placebo-controlled trial, supplementation with a nutraceutical compound containing bergamot polyphenols, artichoke extracts, coenzyme Q10, and zinc improved serum lipid concentrations, systemic inflammation markers, and indices of NAFLD in subjects with polygenic hypercholesterolemia. These results suggest that cholesterol dysregulation may contribute to hepatic metabolic impairment and systemic inflammatory processes.

Several studies also demonstrated important interactions between cholesterol metabolism and gut microbiota composition. One metabolic intervention study reported that increases in beneficial bacterial populations, particularly *Bifidobacterium* spp. and *Eubacterium eligens*, were associated with lower cholesterol concentrations and improvements in metabolic parameters in adults with prediabetes and insulin resistance. Conversely, *Ruminococcus gnavus*, which was positively correlated with hepatic insulin resistance, decreased after the intervention. These findings reinforce the concept that intestinal microbiota may directly influence cholesterol metabolism and metabolic homeostasis.

Another study involving berberine combined with *Bifidobacterium breve* demonstrated synergistic hypolipidemic effects in individuals with type 2 diabetes. The authors proposed that modulation of intestinal lipid metabolism by probiotics and berberine may reduce intraluminal lipid absorption, thereby improving plasma lipid regulation and metabolic control. These findings further support the importance of the gut–liver axis in cholesterol homeostasis and metabolic diseases.

Table 1 – Synthesis of the characteristics, main findings, and key concepts of the studies included in the review

Study	Country	Study design	Sample size	Cholesterol parameters	Primary outcome	Main quantitative findings	Statistical significance	Risk of bias
Koeder et al. (2022)[21]	Germany	Non-randomized lifestyle intervention	n = 115	Total cholesterol, LDL-C, non-HDL-C, REM-C	Obesity-related metabolic outcomes	Significant reductions in body weight, LDL-C, non-HDL-C, remnant cholesterol, glucose, and HbA1c following lifestyle intervention	$p < 0.001$	Moderate (ROBINS-I)
Fogacci et al. (2024)[22]	Italy	Randomized placebo-controlled trial	n = 113	Serum cholesterol and lipid profile	NAFLD and inflammatory markers	Significant improvements in lipid profile, systemic inflammation, and NAFLD indices following nutraceutical supplementation	$p < 0.05$	Low (RoB 2)
Zhang et al. (2022)[23]	USA	Randomized crossover clinical trial	n = 26	Cholesterol concentrations	Insulin resistance and gut microbiota	Increased *Bifidobacterium* spp., reduced *Ruminococcus gnavus*, lower cholesterol concentrations, and improved insulin resistance	$p < 0.005$	Some concerns (RoB 2)
Wang et al. (2022)[24]	China	Double-blind randomized placebo-controlled study	n = 365	Total cholesterol and LDL-C	Postprandial lipid metabolism in T2DM	Combined probiotic and berberine therapy significantly reduced total cholesterol and LDL-C levels	$p < 0.05$	Low (RoB 2)
Gylling et al. (2024)[25]	Finland	Post hoc analysis of randomized trials	n = 41	Cholesterol absorption markers	Cholesterol-lowering response	Phytostanol esters reduced cholesterol levels regardless of baseline absorption phenotype	$p < 0.05$	Moderate (ROBINS-I)
Malik et al. (2025)[26]	Czech Republic	Prognostic observational cohort study	n = 123	HDL-C and non-HDL-C	Neurological recovery after cardiac arrest	Higher HDL-C and non-HDL-C associated with better neurological outcomes and survival	$p < 0.05$	Moderate (QUIPS)
Lee et al. (2025)[27]	South Korea	Clinical observational study	n = 666	Total cholesterol	Neurological prognosis after cardiac arrest	Lower cholesterol levels associated with poorer neurological outcomes	$p < 0.05$	Moderate (QUIPS)

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: non-alcoholic fatty liver disease; non-HDL-C: non-high-density lipoprotein cholesterol; REM-C: remnant cholesterol; T2DM: type 2 diabetes mellitus.

Neurological outcomes associated with cholesterol levels were also identified in the analyzed literature. A clinical observational study evaluating patients with refractory cardiac arrest demonstrated that lower total cholesterol and non-HDL-C levels at admission were associated with worse neurological outcomes and poorer cerebral performance categories within 180 days. Patients with better neurological recovery presented significantly higher total cholesterol, HDL-C, and non-HDL-C concentrations compared with those with unfavorable neurological prognosis. These findings suggest that cholesterol levels may be associated with neurological resilience and recovery after severe cerebral ischemic injury.

The influence of cholesterol absorption efficiency on lipid metabolism was evaluated by Gylling et al. (2024)[25] in a post hoc analysis of randomized double-blind controlled trials. The study investigated the effects of phytostanol esters on serum lipids and cholesterol metabolism in individuals classified as low or high cholesterol absorbers. The results demonstrated that phytostanol esters reduced cholesterol levels independently of baseline cholesterol absorption efficiency, suggesting that cholesterol-lowering dietary interventions may exert beneficial effects regardless of individual metabolic phenotype.

Collectively, the findings of the included studies demonstrate that cholesterol dysregulation is closely associated with multiple systemic disorders beyond cardiovascular disease. Altered cholesterol metabolism appears to be associated with inflammatory pathways, hepatic function, insulin resistance, obesity-related metabolic alterations, gut microbiota composition, and neurological outcomes. These observations reinforce the concept that cholesterol plays a central role in systemic metabolic homeostasis and may contribute to the pathophysiology of several non-cardiovascular diseases.

Figure 2 summarizes the major mechanisms linking cholesterol metabolism to metabolic and clinical outcomes. Lifestyle interventions, nutraceutical supplementation, and gut microbiota modulation contribute to favorable changes in lipid metabolism, including reductions in total cholesterol, LDL-C, non-HDL-C, and remnant cholesterol. These effects influence key biological pathways related to obesity, hepatic metabolism, and gut microbiota function, ultimately affecting obesity-related dyslipidemia, NAFLD, prediabetes, and type 2 diabetes mellitus. Collectively, these pathways contribute to cardiometabolic risk and may also affect neurological outcomes following cardiac arrest. Recent evidence suggests that HDL-C, non-HDL-C, and total cholesterol levels are associated with neurological recovery and prognosis after cardiac arrest.

The lifestyle intervention pathway is supported by Koeder et al. (2022),[21] who demonstrated the beneficial effects of weight loss and plant-based dietary interventions on lipid markers associated with chronic disease risk. Evidence regarding nutraceutical supplementation and hepatic-inflammatory modulation is based on Fogacci et al. (2024),[22] who reported improvements in serum lipid profile, systemic inflammation, and NAFLD-related indices. The gut microbiota pathway is supported by Zhang et al. (2022)[23] and Wang et al. (2022),[24] who highlighted the role of microbiota composition, insulin sensitivity, and gut–liver interactions in cholesterol metabolism. Interindividual variability in cholesterol absorption and responsiveness to phytostanol esters is based on Gylling et al. (2024).[25] The association between cholesterol-related biomarkers and neurological outcomes after cardiac arrest is supported by Malik et al. (2025).[26]

Discussion

The findings should be interpreted in light of the limited number of eligible studies identified during the review process. The present systematic review demonstrated that cholesterol metabolism extends far beyond its classical role in cardiovascular diseases and is strongly associated with several non-cardiovascular pathological processes, including obesity, insulin resistance, metabolic syndrome, liver dysfunction, neurological impairment, systemic inflammation, and gut microbiota dysregulation. The analyzed studies reinforce the concept that cholesterol appears to be involved in multiple physiological and pathological pathways.

One of the most consistent findings observed among the included studies was the close relationship between cholesterol metabolism and metabolic disorders. The lifestyle intervention study conducted by Koeder et al.[21] demonstrated that reductions in total cholesterol, LDL-C, non-HDL-C, and remnant cholesterol occurred simultaneously with improvements in body weight, waist circumference, glucose metabolism, and glycated hemoglobin levels. These findings suggest that dyslipidemia is deeply integrated into the metabolic disturbances observed in obesity and insulin resistance. Importantly, the reduction in remnant cholesterol observed in this study deserves particular attention, since increasing evidence indicates that remnant lipoproteins may contribute not only to cardiovascular disease but also to systemic inflammation and metabolic dysfunction.

The relationship between cholesterol metabolism and insulin resistance was further supported by studies involving gut microbiota modulation.[23,24] The analyzed evidence demonstrated that increased abundance of beneficial bacterial populations, such as *Bifidobacterium* spp. and *Eubacterium eligens*, was associated with lower cholesterol concentrations and improved metabolic parameters in individuals with prediabetes and insulin resistance. Conversely, *Ruminococcus gnavus*, a bacterial species associated with inflammatory and metabolic dysfunction, showed positive correlations with hepatic insulin resistance. These findings reinforce the emerging concept of the gut–liver–metabolic axis, in which intestinal microbiota directly influences lipid absorption, bile acid metabolism, inflammatory signaling, and cholesterol homeostasis.

Similarly, the study involving berberine combined with *Bifidobacterium* demonstrated synergistic hypolipidemic effects in individuals with type 2 diabetes mellitus.[24] The proposed "gut lipid sink" mechanism suggests that microbiota-targeted interventions may reduce intestinal lipid availability and absorption, consequently improving plasma lipid regulation and metabolic control. These findings are particularly relevant because they indicate that cholesterol metabolism may be modulated not only through pharmacological lipid-lowering therapies but also through microbiota-directed metabolic interventions. Such evidence opens new perspectives for personalized therapies targeting

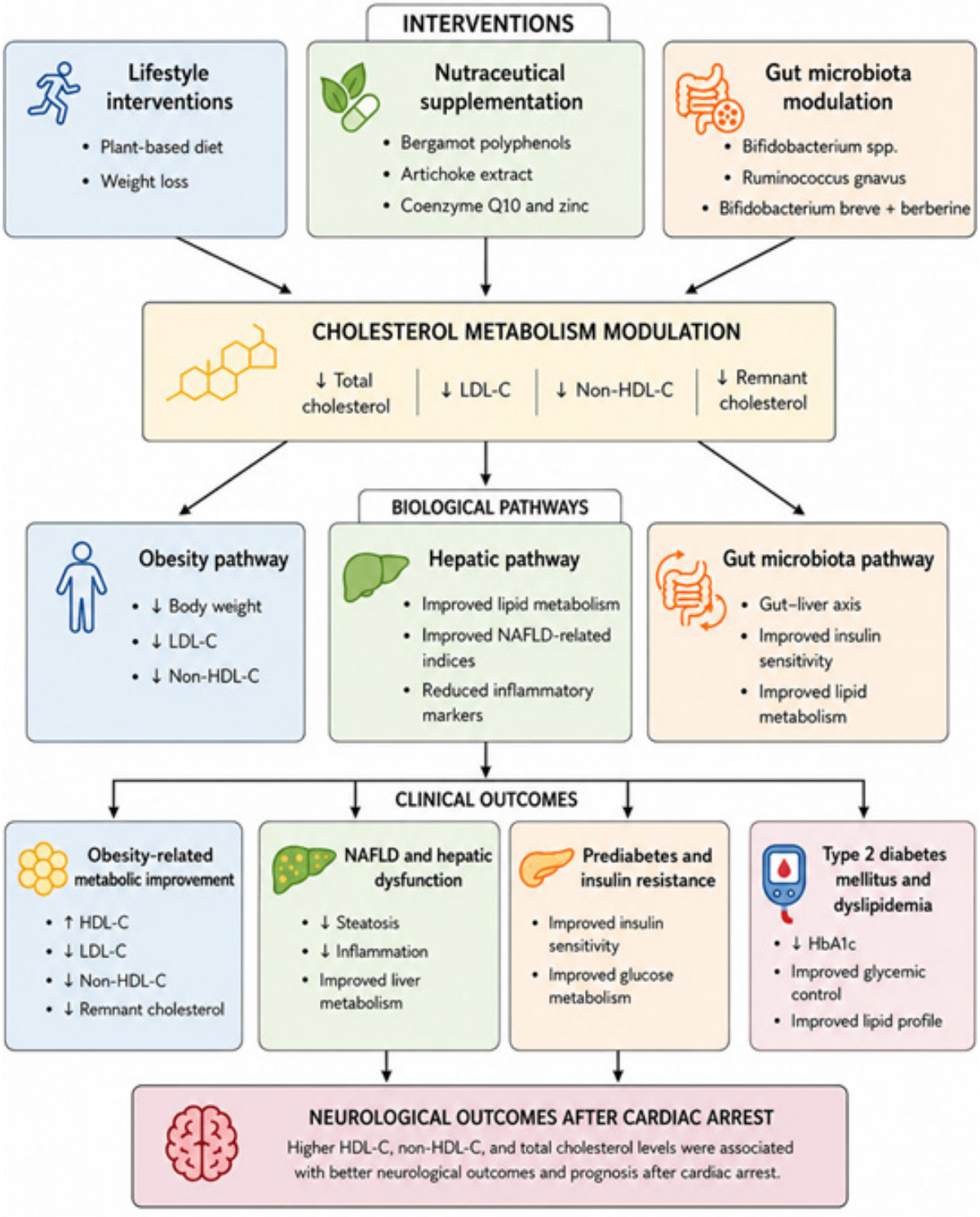

Figure 2 – *Integrated overview of cholesterol metabolism modulation, biological pathways, and non-cardiovascular clinical outcomes identified in the included studies. HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: non-alcoholic fatty liver disease; non-HDL-C: non-high-density lipoprotein cholesterol.*

intestinal microbiome composition in dyslipidemic and metabolically compromised patients.

Another important aspect identified in this review was the association between cholesterol metabolism and hepatic dysfunction, particularly NAFLD. Fogacci et al.[22] demonstrated that nutraceutical supplementation improved serum lipid concentrations, systemic inflammation, and NAFLD-related indices in individuals with polygenic hypercholesterolemia. NAFLD is increasingly recognized as a multisystem metabolic disease strongly associated with insulin resistance, chronic inflammation, obesity, and dyslipidemia. Excess hepatic cholesterol accumulation may promote lipotoxicity, oxidative stress, mitochondrial dysfunction, and inflammatory activation, contributing to disease progression toward steatohepatitis and fibrosis. Thus, the observed improvements in liver-related biomarkers following cholesterol reduction reinforce the role of lipid metabolism in hepatic pathological processes.

The neurological findings observed in this review also deserve careful consideration. Studies evaluating patients after cardiac arrest demonstrated that lower total cholesterol, HDL-C, and non-HDL-C levels were associated with worse neurological outcomes and poorer cerebral performance after severe ischemic injury.[26,27] Although hypercholesterolemia is traditionally considered harmful, these findings suggest that extremely low cholesterol levels in acute critical conditions may negatively affect neuronal recovery and membrane stability. Cholesterol plays a crucial role in neuronal membrane composition, synapse formation, myelin integrity, and neuroplasticity. Therefore, insufficient cholesterol availability during acute neurological injury may impair cellular repair mechanisms and neuronal resilience. These findings highlight the complex and sometimes paradoxical role of cholesterol in human physiology, particularly in neurological contexts.

The studies included in this review also reinforce the growing understanding that inflammation and cholesterol metabolism are closely interconnected. Chronic low-grade inflammation frequently accompanies dyslipidemia, obesity, insulin resistance, and metabolic syndrome. Altered cholesterol metabolism may stimulate inflammatory signaling pathways, oxidative stress, and immune dysfunction, while inflammatory cytokines may simultaneously alter hepatic lipid synthesis and lipoprotein metabolism. This bidirectional relationship likely contributes to the progression of multiple chronic diseases beyond the cardiovascular system.

Importantly, the analyzed studies indicate that cholesterol metabolism should not be interpreted exclusively through isolated LDL-C concentrations. Several studies highlighted the importance of additional lipid-related biomarkers, including non-HDL-C, remnant cholesterol, cholesterol absorption efficiency, and lipoprotein-related metabolic pathways.[21,25,26] These observations suggest that cholesterol metabolism is highly heterogeneous and influenced by dietary patterns, genetic background, microbiota composition, inflammatory status, and metabolic phenotype.

The present review has several limitations that should be acknowledged. First, the included studies demonstrated substantial methodological and clinical heterogeneity regarding study design, population characteristics, intervention strategies, evaluated outcomes, and follow-up periods. This heterogeneity limited direct comparisons among studies and precluded the performance of a formal meta-analysis.

Second, the final synthesis included only 7 studies, which may limit the comprehensiveness of the evidence and reduce the robustness of the conclusions. In addition, most of the included studies were observational in nature or involved non-randomized designs, which limits the ability to establish causal relationships and increases the potential influence of residual confounding. Third, many studies assessed surrogate metabolic markers rather than long-term clinical endpoints. Additionally, most studies focused on specific populations, which may limit the generalizability of the findings to broader populations.

Another limitation is the absence of prospective protocol registration in databases such as PROSPERO or the Open Science Framework. Although the review was conducted in accordance with PRISMA 2020 recommendations and predefined eligibility criteria were consistently applied throughout the study selection process, protocol registration would have enhanced methodological transparency and reduced the potential risk of post hoc modifications.

Furthermore, the search strategy was restricted to studies published between 2022 and 2025. While this approach was intentionally adopted to provide an updated synthesis of contemporary evidence, it may have excluded relevant studies published in earlier years. In addition, only studies published in English, Portuguese, and Spanish were considered eligible, introducing the possibility of language bias. Potential publication bias should also be considered, as studies reporting statistically significant or positive findings are generally more likely to be published than studies with null or negative results.

A further limitation is the absence of a formal certainty-of-evidence assessment using the GRADE approach. Although GRADE is widely recommended for evaluating the overall certainty of evidence in systematic reviews, the substantial heterogeneity of study designs, populations, interventions, and outcomes among the included studies limited the feasibility of applying a unified certainty-of-evidence framework. Nevertheless, formal risk-of-bias assessments were conducted using validated study design-specific tools (RoB 2, ROBINS-I, and QUIPS), providing a structured evaluation of the methodological quality of the included studies.

Despite these limitations, the available evidence suggests that cholesterol metabolism is associated with several non-cardiovascular conditions, particularly metabolic disorders, insulin resistance, gut microbiota regulation, NAFLD, and neurological outcomes following cardiac arrest. However, given the limited number of included studies, the predominance of observational evidence, and the methodological heterogeneity among studies, the conclusions should be interpreted with appropriate caution.

Overall, the findings of this systematic review reinforce the concept that cholesterol metabolism is deeply integrated into multiple physiological systems and disease mechanisms. Beyond its well-established cardiovascular implications, altered cholesterol homeostasis appears to be associated

with metabolic disorders, hepatic dysfunction, inflammatory imbalance, microbiota alterations, insulin resistance, and neurological outcomes. Future studies are necessary to better elucidate the molecular mechanisms linking cholesterol dysregulation to systemic diseases and to identify novel therapeutic strategies capable of modulating cholesterol metabolism in a more personalized and multisystemic manner.

Conclusion

The evidence included in this systematic review suggests that cholesterol metabolism may play an important role in several non-cardiovascular conditions, particularly obesity-related metabolic disorders, insulin resistance, gut microbiota regulation, NAFLD, and neurological outcomes following cardiac arrest. The findings indicate that alterations in cholesterol homeostasis are associated with multiple metabolic and physiological pathways beyond cardiovascular disease. However, the available evidence remains limited, and the small number of included studies, together with their methodological heterogeneity, warrants cautious interpretation. While LDL-C reduction remains a cornerstone of cardiovascular disease prevention, emerging evidence suggests that additional aspects of cholesterol metabolism, including cholesterol absorption, gut microbiota interactions, and broader metabolic pathways, may also contribute to selected non-cardiovascular conditions. These mechanisms should be viewed as complementary to, rather than replacements for, the established role of LDL-C in cardiovascular risk management.

Further high-quality studies are needed to clarify the clinical relevance of these pathways, explore their potential implications in other non-cardiovascular diseases, and strengthen the evidence base for personalized approaches to cholesterol management.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the preparation of this work. All analyses, interpretations, and conclusions were made independently, without influence from institutions, companies, or groups with financial or academic interests in the topic addressed.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Souza Junior MJV, Souza VV, Souza MJV, Silva OB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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