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Systematic Review

Association between Dyslipidaemia and Cognitive Impairment: A Meta-Analysis of Cohort and Case-Control Studies

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Abstract

Background: This study explored the specific relationship between different lipid indicators and cognitive impairment and aimed to provide a reference for implementing targeted lipid regulation measures to prevent and alleviate cognitive impairment. **Methods**: We searched three databases (PubMed, Embase, and Web of Science) for literature related to hyperlipidaemia, lipid levels, and cognitive impairment, and used the Newcastle-Ottawa Scale to evaluate the quality of the identified literature. A meta-analysis was performed using RevMan 5.4, and the combined effect size ratio using a random-effects model (odds ratio [OR] and 95% confidence interval [CI]) was used to evaluate the association between dyslipidaemia and cognitive impairment. **Results**: Among initially identified 2247 papers, we ultimately included 18 studies involving a total of 758,074 patients. The results of the meta-analysis revealed that patients with hyperlipidaemia had a 1.23-fold higher risk of cognitive impairment than those with normal lipid levels (OR = 1.23, 95% CI: 1.04–1.47, $p = 0.02$). Further subgroup analysis showed that elevated total cholesterol (TC) levels increased the risk of cognitive impairment by 1.59-fold (OR = 1.59, 95% CI: 1.27–2.01, $p < 0.0001$) and were more significant in older or male patients. Moreover, elevated triglyceride levels were inversely correlated with cognitive disorders, whereas elevated low-density lipoprotein cholesterol levels were unrelated to cognitive impairment risk. **Conclusions**: Dyslipidaemia was strongly associated with cognitive impairment, and elevated TC levels were a risk factor for cognitive impairment. Furthermore, the damaging effects of elevated TC levels on cognition were more pronounced in older and male populations.

Keywords: hyperlipidaemia; total cholesterol; triglyceride; low-density lipoprotein cholesterol; cognitive impairment; meta-analysis

1. Introduction

Cognitive impairment encompasses dysfunction in various areas, including memory, language, attention, and executive functioning. It is categorized into two different stages based on severity: mild cognitive impairment (MCI) and dementia, with Alzheimer's disease (AD) being the most prevalent form of dementia [1,2]. The US census reports an overall prevalence 11.3% for AD and 22.7% for MCI in individuals aged >65 years [3]. In China, dementia and MCI affect 6.0% and an estimated 15.5% of individuals aged >60 years [4]. Cognitive disorders significantly impact social functioning, reduce life satisfaction [5], increase the incidence of postoperative delirium and complications in surgical patients [6], and even contribute to mortality [7].

The primary risk factors for cognitive impairment include age, family background, cardiovascular disease, neurological disorders, and medications [1,4,8]. Dyslipidaemia is also closely associated with cognitive impairment [9]. Dyslipidaemia encompasses abnormalities in lipid levels, including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), commonly referred to as hyperlipidaemia [10,11]. Hyperlipidaemia can impair microvascular function, leading to memory deficits and reduced processing speed [12]. Hyperlipidaemia also increases the risk of cardiovascular diseases such as atherosclerosis [13], coronary heart disease [14], and cerebrovascular accidents [15] and leads to various degrees of cognitive impairment [16–18]. Dyslipidaemia is linked to cognitive impairment through the induction of an inflammatory response [19]. The interactions among dyslipidaemia, insulin resistance, and apolipoprotein E exacerbate the development of cognitive impairment [20]. Lipidomics can serve as a biomarker for early brain disease diagnosis, with various types of lipid dysregulation associated with neurodegenerative diseases [21]. Lipotoxicity is a metabolic disorder caused by lipid accumulation in non-adipose tissues, leading to cell dysfunction, lipid droplet formation, and cell death. Cerebral microvascular lipotoxicity can promote microglial activation and increased release

of inflammatory factors, leading to neurodegeneration and cognitive impairment [22]. However, existing research on the relationship between lipid levels and cognitive impairment varies significantly and lacks consistent results. For example, Han [23] found an inverse relationship between high levels of HDL-C and cognitive impairment, whereas TG, TC, and LDL-C showed no such connection. Conversely, in a case-control study, higher TC and LDL-C levels, as well as lower HDL-C levels, as risk factors for AD [24].

In light of these findings, we hypothesized a correlation between dyslipidaemia and cognitive impairment. To investigate this relationship, we conducted a meta-analysis of published literature exploring the link between hyperlipidaemia, blood lipid levels, and cognitive impairment, aiming to provide evidence for mitigating cognitive decline.

2. Materials and Methods

2.1 Protocol Guidance

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement Report and was registered on the PROSPERO platform (CRD42023395479). PRISMA checklist is shown in **Supplementary Table 1**.

2.2 Literature Search and Screening Strategy

Two researchers independently conducted searches in three databases: PubMed, Embase, and Web of Science, from the inception of databases to 1 March 2023. The search terms used were ('hyperlipidaemias' OR 'TG' OR 'triglyceride' OR 'cholesterol' OR 'TC' OR 'hyperlipemia' OR 'low density lipoprotein cholesterol' OR 'LDL-C') AND ('cognitive dysfunction' OR 'dementia' OR 'Alzheimer disease' OR 'cognitive impairment' OR 'cognitive decline') AND ('case-control studies' OR 'cohort studies') (**Supplementary Table 2**). A manual search was also conducted to identify relevant references in the literature.

Articles were selected for this study based on the following inclusion criteria: (1) patient age $\geq$18 years; (2) cohort studies or case-control studies; (3) studies including data on at least one of hyperlipidaemia, lipid levels (TC, TG, LDL-C) as exposure factors; and (4) English language. The exclusion criteria were as follows: (1) no reported cognitive impairment related to lipid levels; (2) studies that did not report effect sizes in terms of odds ratio (OR), relative risk, or relative hazard (HR), and did not provide 95% confidence intervals (CIs); (3) studies with elevated serum HDL-C levels; (4) Newcastle-Ottawa Scale (NOS) scores $<$6; and (5) repeated published literature.

2.3 Data Extraction and Literature Quality Evaluation

Studies were independently selected from the retrieved literature by the two researchers. In cases of disagreement, a third researcher determined study inclusion. Data were extracted and recorded using Microsoft Excel (Microsoft Office Excel 2016, Microsoft, Redmond, WA, USA). The key data extracted included the first author, publication year, study type, patient sex, sample size, lipid index, and lipid subgroup comparison. We also evaluated the literature quality according to the NOS, as recommended by the Cochrane Collaboration Network, and studies with scores $\geq$6 stars were included.

2.4 Outcome Indicators

The primary outcome indicator in this study was the relationship between cognitive impairment and dyslipidaemia. The secondary endpoint was the variation in cognitive function under the impact of specific lipid indicators. Cognitive impairment was assessed employing tools such as the Mini-Mental State Examination, Diagnostic and Statistical Manual of Mental Disorders, or International Classification of Diseases (ICD) codes as diagnostic criteria for dementia and AD.

2.5 Statistical Methods

Statistical analysis was performed using RevMan 5.4 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Considering the different groups of lipid levels between the studies, the OR (Relative Risk (RR), HR) values and 95% CI for the relationship between the highest vs. the lowest concentrations of lipid levels with cognitive impairment in each study were extracted for analysis, following reference to the relevant meta-analysis [25]. For instance, in the study by Rantanen *et al*. [26], which categorized the participants into four groups according to serum TC levels, and ORs and 95% CI subgroups of cognitive impairment risk in the fourth quarter (Q4) vs. the first quarter (Q1) were extracted for our meta-analysis. The magnitude of heterogeneity between studies was assessed using the Cochrane Q test and I^2 statistics. Heterogeneity was considered acceptable for $p > 0.1$ in the Q test and $I^2 < 50\%$. The analysis was performed using a fixed-effects model. Conversely, the analysis was performed using a random-effects model with the combined effect size ratio (OR) and the corresponding 95% CI, which was considered statistically significant when the p-value was < 0.05. When the heterogeneity between studies was high, subgroup and sensitivity analyses were performed to identify the possible sources of heterogeneity based on lipid levels, age, and sex. Funnel plots were used to assess publication bias.

3. Results

3.1 Literature Search and Research Basic Features

Fig. 1 illustrates the detailed literature screening process. In total, 2247 relevant papers were retrieved, including 714 in PubMed, 641 in Embase, and 892 in Web of Science. Endnote 20 software (Thomson Corporation Inc., Stanford, CT, USA) was used to eliminate 609 duplicates.

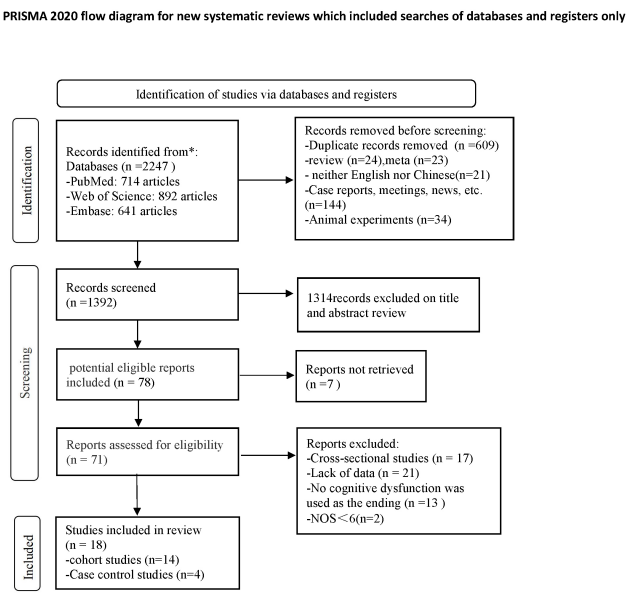

Fig. 1. Flowchart of study selection for the meta-analysis. NOS, Newcastle-Ottawa Scale. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

Subsequently, 78 papers were obtained by reviewing titles and abstracts. Ultimately, the meta-analysis included 18 studies after the final screening of the full text and references. These studies comprised four case-control studies [24,27–29] and 14 cohort studies [26,30–42]. Six papers were published before 2010, and 12 papers were published after 2010. Eight countries and 30 regions were included, with study sample sizes ranging from 117 to 469,466, totalling 758,074 individuals. A total of 25 data groups were included in the analysis of the correlation between hyperlipidaemia and the risk of cognitive impairment. Furthermore, five studies provided data on elevated TC levels and the risk of cognitive impairment in populations aged >60 years, and four studies provided data on elevated TC levels and the risk of cognitive impairment in a higher proportion of men. The basic characteristics of the included studies are presented in Table 1 (Ref. [24,26–42]).

3.2 Sensitivity Analysis and Publication Bias

The sensitivity analysis of elevated TC, TG, and LDL-C levels and their association with the risk of cognitive impairment revealed no substantial changes in the results after altering the model, indicating that the combined results from these studies remained stable and reliable (Table 2). Regarding the assessment of publication bias in the literature pertaining to hyperlipidaemia and the risk of cognitive impairment, the funnel plot displayed an asymmetric distribution of the included literature, with several articles falling outside the 95% CI (**Supplementary Fig. 1**).

3.3 Meta-Analysis of Hyperlipidaemia and the Risk of Cognitive Impairment

The meta-analysis, incorporating data from the 18 publications on hyperlipidaemia and the risk of cognitive impairment, revealed that individuals with hyperlipidaemia faced a 23% increased risk of developing cognitive impairment, which was a statistically significant difference. However, the heterogeneity test demonstrated a substantial degree of heterogeneity among the studies ($I^2 = 81\% > 50\%$, $p < 0.00001$) (OR = 1.23, 95% CI: 1.04–1.47, $p = 0.02$, Fig. 2).

3.4 TC Levels and Risk of Cognitive Impairment

Nine of the included studies (n = 86,890) provided specific data regarding the impact of TC levels on the risk of developing cognitive impairment. The results from the meta-analysis revealed that individuals with increased TC levels had a 1.59-fold increased risk of developing cognitive impairment after follow-up compared with normal TC levels (OR = 1.59, 95% CI: 1.27–2.01, $p < 0.0001$, Fig. 3). Notably, moderate heterogeneity was observed in the studies ($I^2 = 57\%$, $p = 0.010 < 0.1$), and this was analysed using a random-effects model.

3.4.1 Age Relationship between Elevated TC Levels and Cognitive Impairment

Among the studies, five and six studies provided ORs for elevated TC levels in relation to the risk of cognitive disability in individuals aged <60 and ≥60 years, respectively. The meta-analysis results demonstrated that elevated TC levels increased the risk of cognitive impairment. with individuals aged ≥60 years showing a 1.65-fold increased risk of cognitive impairment compared with those aged <60 years (OR = 1.65, 95% CI: 1.39–1.96, $p < 0.00001$, Fig. 4). Heterogeneity between the studies could not be considered based on the results of the heterogeneity test ($I^2 = 3\%$, $p = 0.40 > 0.1$).

3.4.2 Sex Relationship between Elevated TC Levels and Risk of Cognitive Impairment

In this analysis, four studies provided data on the association between elevated TC levels and cognitive impairment in patient populations comprising ≥50% men, whereas five studies provided data related to <50% men. The results of the meta-analysis revealed that individuals with cognitive impairment caused by elevated TC levels were more likely to be male. Specifically, a higher proportion of men with elevated blood cholesterol levels increased the risk of cognitive impairment by 2.13-fold (OR = 2.13, 95% CI: 1.53–2.98, $p < 0.00001$, as shown in Fig. 5). Importantly, no heterogeneity was observed among the studies ($I^2 = 0\%$, $p = 0.83 > 0.1$).

Table 1. Basic characteristics of the included literature.

Study	Publication year	Type of research	Percentage of males (%)	Sample size	Ending indicators	Risk factors	Subgroup comparison
Suryadevara, V [27]	2003	Case-control study	34%	100	Dementia	LDL-C	≥100 mg/dL
				100	Dementia	TC	≥200 mg/dL
Notkola, IL [30]	1998	Cohort study	100%	444	Dementia	TC	≥6.5; <6.5 mmol/L
Chen, H [24]	2019	Case-control study	57.26%	234	AD	TC	≥228.16 mg/dL
						TG	≥150.54 mg/dL
						LDL-C	≥128.3 9mg/dL
Zambón, D [31]	2010	Cohort study	45.30%	117	MCI	FH	Yes; No
Mundal, LJ [32]	2022	Cohort study	46.90%	73,233	Dementia	FH	Yes; No
Rantanen, K [26]	2014	Cohort study	100%	1049	AD	TC	Q1 vs. Q4
Nordestgaard, LT [33]	2021	Cohort study	36%	125,757	AD	TG	Q1 vs. Q4
Reitz, C [34]	2008	Cohort study	31.03%	854	MCI	LDL-C	Q1 vs. Q4
						TG	Q1 vs. Q4
Reitz, C [35]	2010	Cohort study	34.34%	1130	AD	LDL-C	Q1 vs. Q4
Solomon, A [36]	2007	Cohort study	61.69%	1321	Cognitive impairment	TC	Q1 vs. Q4
Solomon, A [37]	2009	Cohort study	45.86%	9744	Dementia	TC	Q1 vs. Q4
		Cohort study				TC	Q1 vs. Q3
Mielke, MM [38]	2010	Cohort study	0%	648	Dementia	TC	>6.5 mmol/L
					AD	TC	>6.5 mmol/L
He, Q [28]	2016	Case-control study	40.96%	227	MCI	LDL-C	Q1 vs. Q4
Li, G [39]	2005	Cohort study	40.45%	2141	AD	TG	Q1 vs. Q4
					Dementia	TG	Q1 vs. Q4
Gong, J [40]	2022	Cohort study	45.77%	469,466	Dementia	TG	Q1 vs. Q4
Ancelin, ML [41]	2013	Cohort study	38.91%	7053	AD	TG	≥1.45 mmol/L
Zhang, H [29]	2021	Case-control study	58.35%	497	MCI	LDL-C	>2.686 mmol/L
Yang, Z [42]	2022	Cohort study	50.81%	63,959	Dementia	TG	Q1 vs. Q5

AD, Alzheimer's disease; MCI, mild cognitive impairment; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolaemia; Q1, first (lowest) quarter; Q3, third quarter; Q4, fourth quarter; Q5, fifth quarter.

Table 2. Sensitivity analysis of high TC, TG, and LDL-C levels and the risk of cognitive impairment.

Study exposure indicators	Models	Consolidation model		Change model	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Elevated TC	R	1.59 (1.27–2.01)	<0.0001	1.45 (1.27–1.64)	<0.00001
Elevated TG	F	0.85 (0.79–0.92)	<0.0001	0.85 (0.79–0.92)	<0.0001
Elevated LDL-C	R	1.45 (0.74–2.83)	0.28	1.03 (0.84–1.28)	0.75

R, random-effects model; F, fixed-effects model; OR, odds ratio; CI, confidence interval.

Table 3. Subgroup analysis of elevated LDL-C levels and the risk of cognitive impairment.

Subgroup factors	No. of studies	OR (RE)	95% CI	Heterogeneity test			Overall effect		Interaction *p*-value
				Q	*p*	I^2	Z-value	*p*-value	
Summary	6	1.45	0.74–2.83	46.38	<0.00001	89%	1.08	0.28	
Year of publication									
≤2010	3	1.3	0.58–2.89	11.24	0.004	82%	0.64	0.52	0.77
>2010	3	1.63	0.45–5.98	35.13	<0.00001	94%	0.74	0.46	
Study Type									
Case-control study	4	1.21	0.92–1.60	43.26	<0.00001	93%	1.36	0.17	0.08
Cohort study	2	0.83	0.60–1.15	0.11	0.74	0%	1.12	0.26	
Male ratio									
≥50%	2	1.07	0.74–1.55	35.1	<0.00001	97%	0.36	0.72	0.83
<50%	4	1.02	0.79–1.32	11.24	0.01	73%	0.14	0.89	

RE, relative error.

3.5 TG Levels and the Risk of Cognitive Impairment

In this analysis, eight studies provided data on TG levels and the risk of developing cognitive impairment. The results of the meta-analysis showed a significantly negatively between elevated TG levels and cognitive impairment (OR = 0.85, 95% CI: 0.79–0.92, $p < 0.0001$) (Fig. 6). No inter-study heterogeneity was observed ($I^2 = 0\%$, $p = 0.43 > 0.1$).

3.6 LDL-C Levels and Risk of Cognitive Impairment

In this analysis, six datasets were included, with three studies [24,27,29] reporting an association between elevated LDL-C levels and cognitive impairment, and three other studies [28,34,35] reporting no such correlation. The results of the meta-analysis showed no significant correlation between elevated LDL-C level and the risk of cognitive impairment (OR = 1.45, 95% CI: 0.74–2.83, $p = 0.28$, as shown in **Supplementary Fig. 2**). However, significant inter-study heterogeneity was observed (I^2 = 89%, $p < 0.00001$). Subgroup analysis showed that s sources of heterogeneity based on study publication year (≤ 2010 or >2010), study type (case-control or cohort), and sex ratio (male ≥50% or <50%) were not the source of the observed heterogeneity (Table 3).

4. Discussion

The aggregate analysis in this study included a total of 18 studies related to lipid levels and cognitive disorders. The results demonstrated a 1.23-fold increased risk of developing cognitive impairment in individuals with hyperlipidaemia. Further subgroup analysis showed that elevated TC levels were associated with an increased risk of cognitive impairment, whereas increased LDL-C levels were not. Additionally, high TG levels were found to be protective against cognitive impairment. Furthermore, older or male patients with elevated TC levels had a high risk of developing cognitive impairment.

Elevated TC levels increased the risk of cognitive impairment by 1.59-fold in the present meta-analysis, consistent with the findings reported by An *et al*. [43] and Chen *et al*. [24]. Previous meta-analyses have also shown that increased TC concentrations lead to an increased incidence of AD [44]. Hypercholesterolaemia exacerbates the impairment of cognitive function by inducing neuroinflammation [45] and the levels of inflammatory factors, interleukin (IL)-6 and tumour necrosis factor (TNF)-α, are differentially increased in patients with hypercholesterolaemia [46]. Increased expression of pro-inflammatory factors disrupts the integrity of the blood-brain barrier, leading to the diffusion of peripheral inflammatory factors along the concentration gradient into the central nervous system. This induces central nervous system inflammation and cognitive deficits [47,48]. Hypercholesterolaemia is closely associated with endothelial dysfunction, resulting in a higher degree of vascular endothelial dysfunction and lower cognitive function scores [49]. Hypercholesterolaemia can inhibit inwardly rectifying potassium ion channels (Kir2.1) through cholesterol-protein interactions, contributing to the impaired nitric oxide (NO) biological activity secreted by endothelial cells [50]. NO is produced by vascular endothelial cells through endothelial NO synthase (eNOS), and hy-

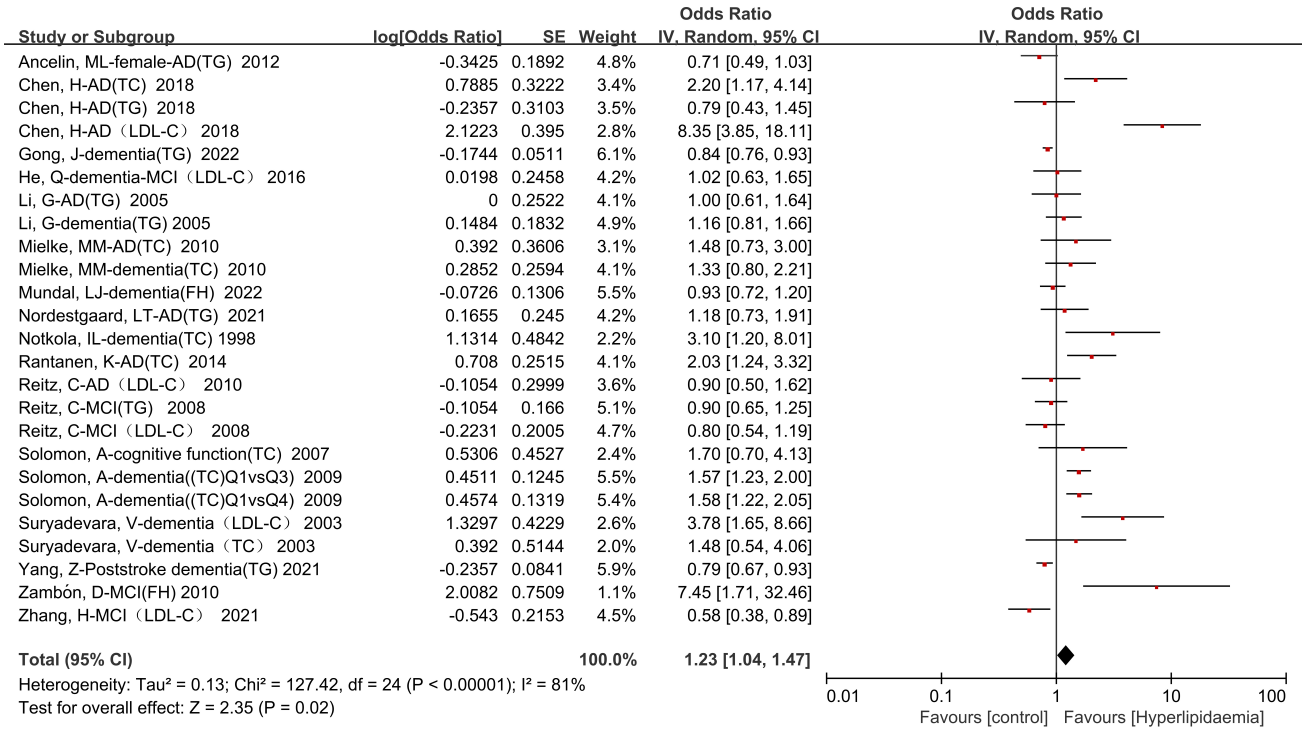

Fig. 2. Forest plot of meta-analysis results depicting the relationship between hyperlipidaemia and cognitive impairment. SE, standard error; Tau^2, tau-squared; Chi^2, chi-square test; df, degrees of freedom; I^2, I-squared: used to characterize the percentage of variation (heterogeneity) in the total variation due to non-sampling errors due to individual studies; IV, inverse variance.

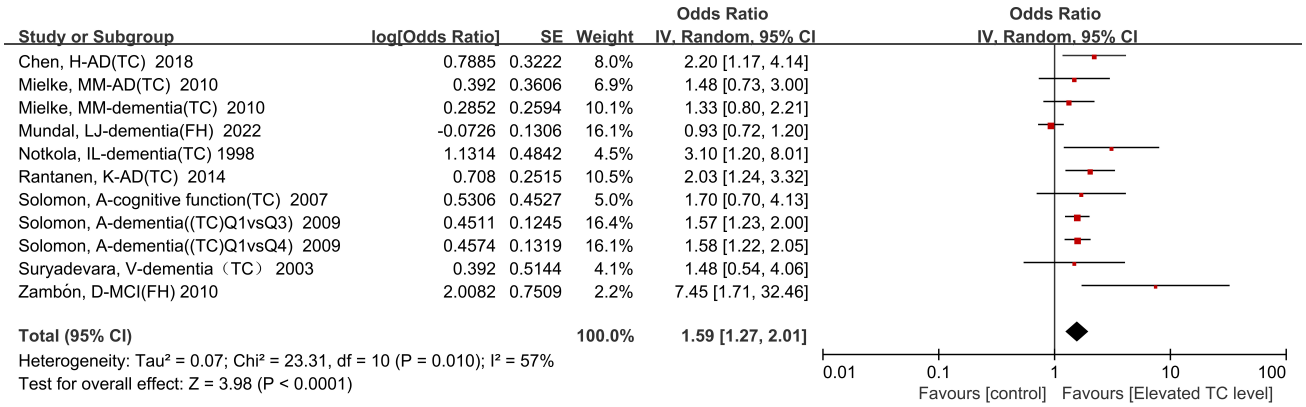

Fig. 3. Forest plot of meta-analysis results depicting the relationship between elevated TC level and the risk of cognitive impairment.

percholesterolaemia can lead to decreased eNOS expression or partial loss of function. Partial eNOS deficiency exacerbates behavioural disorders, amyloid-β (Aβ) brain deposition, and pathological changes of microglia in mice [51]. However, we observed moderate heterogeneity in our studies (I^2 = 57%). Thus, we conducted a sensitivity analysis using the one-by-one exclusion method to identify the potential sources of heterogeneity. Heterogeneity decreased significantly (I^2 = 0%) after excluding the study by Mundal *et al.* [32]. The resulting overall combined OR estimate was statistically significant (OR = 1.66; 95% CI: 1.44–1.92, $p < 0.00001$). Mundal *et al.* [32] used a 1:20 ratio for matching controls, creating an excessive sample size gap between patients with familial hypercholesterolaemia and normal controls. Furthermore, the diagnosis of dementia in the study relied primarily on International Classification of Diseases-10 (ICD-10) codes in physician medical records, which may lead to an incomplete diagnosis of dementia due to death misclassification or confusion regarding the cause of death, contributing to missing data and somewhat increasing the heterogeneity of the study results. After removing the study by Mundal *et al.* [32], we ob-

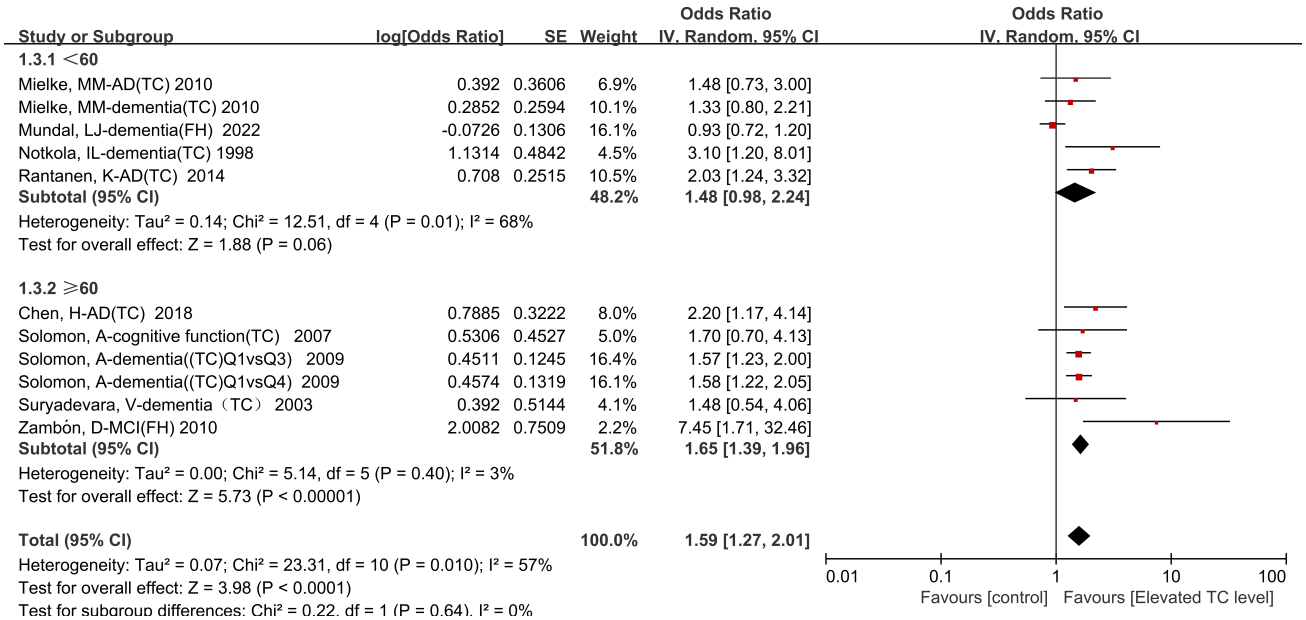

Fig. 4. Forest plot of elevated TC levels and cognitive impairment by age.

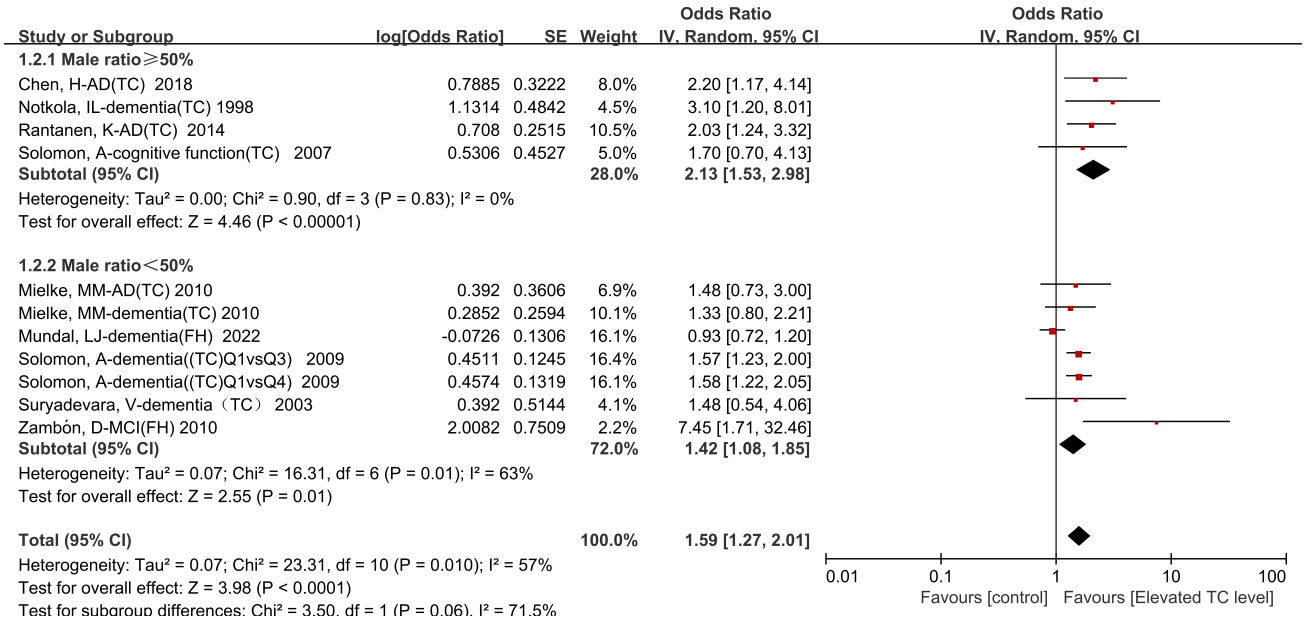

Fig. 5. Forest plot of elevated TC levels and cognitive impairment by sex ratio.

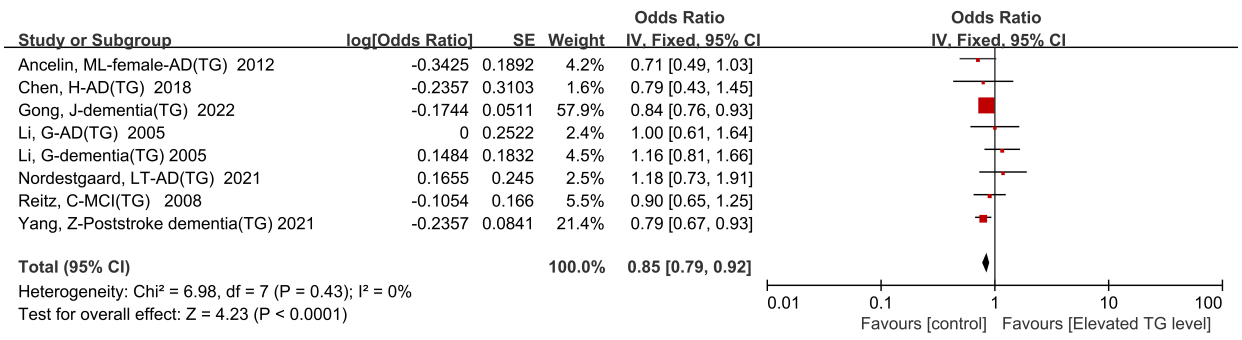

Fig. 6. Meta-analysis graph of elevated TG levels and risk of cognitive impairment.

served a more significant risk of elevated TC levels leading to cognitive disability across studies conducted after 2010 than before 2010. The prevalence of hypercholesterolaemia increased from 1.6% to 5.8% in a survey of adult blood lipid levels in China between 2002 and 2015 [52]. This may be attributable to the economic and societal developments, which may have resulted in a shift in the dietary patterns towards high-fat animal foods and a gradual increase in the prevalence of dyslipidaemia [53].

The results of our meta-analysis also revealed an age-sex disparity in the interaction between elevated TC levels and cognitive impairment risk. Zhao *et al*. [54] also reported a positive association between high TC levels and cognitive impairment in older men. In a study assessing the dietary intake of older Chinese individuals, daily cholesterol consumption was higher in men than in women caused by differences in dietary habits and preferences. Older individuals showed the highest percentage of excess cholesterol intake, which is directly correlated with TC levels. High dietary consumption of cholesterol increases the risk of borderline elevated cholesterol levels and hypercholesterolaemia in older men [55,56]. Ma *et al*. [57] demonstrated that hypercholesterolaemia is involved in the development of atherosclerosis and exacerbates cognitive deficits by impairing vascular function. The higher the serum cholesterol concentration in older people, the more significant the degree of cognitive decline.

The association between elevated TG levels and cognitive disorders remains controversial. A 20-year cohort study by Power *et al*. [58] showed reduced executive performance, attention duration, and processing speed in patients with increased TG levels. The cognitive-impairing effects of elevated TG levels are primarily caused by impaired vascular endothelial function. The more severe the impairment of microvascular endothelial function, the worse the executive and verbal memory abilities of the patient [59]. Takaeko *et al*. [60] observed that patients with low TG levels had higher vasodilation and better vascular endothelial function compared with patients with high TG levels. The results of our meta-analysis showed that increased TG concentrations were negatively associated with cognitive impairment, consistent with the findings reported by Zhao *et al*. [54], Lv *et al*. [61], and others. However, owing to the limited number of included studies, only two studies [40,42] showed a significant correlation between TG levels and cognitive impairment; the remaining studies showed no obvious statistical significance. Therefore, further clinical trials are required to verify the association between high TG levels and cognitive impairment.

Elevated serum LDL-C levels increase the risk of AD [62,63]. LDL promotes the release of inflammatory mediators TNF-α and IL-6 by activating microvascular endothelial cells. These mediators disrupt the function of the blood-brain barrier, ultimately leading to cognitive impairment [64]. However, our meta-analysis results revealed no significant relationship between elevated LDL-C levels and the risk of cognitive dysfunction. This discrepancy may be due to the substantial differences in the initial recruitment time of the participants included in the studies and the varying levels of statin use at baseline. Although we adjusted for possible confounding factors (such as age, lipid-lowering therapy, cardiovascular events), residual variables, which could not be adjusted for owing to variations in the confounding factors considered by each study, may be present. Statins can reduce the risk of dementia, AD, and MCI, but not vascular dementia. Short-term statin use helps delay the deterioration of the neuropsychiatric state and improve the activities of daily living in patients with AD [65,66]. Therefore, the impact of statin use on cognitive function cannot be ignored. Second, our results were based on studies with high heterogeneity, and our subgroup analyses of publication time, research type, and sex did not reveal the source of heterogeneity. Therefore, caution should be exercised when interpreting the association between LDL-C level and cognitive impairment. Lipid management guidelines generally prioritize lowering LDL-C levels, recommending lifestyle interventions with moderate-intensity statins as the initial medication and, if necessary, cholesterol uptake inhibitors (ezetimibe) and/or pre-protein convertase chymotrypsin 9 inhibitors [67,68]. Dietary choices have a significant impact on blood lipid levels, and different countries have varying dietary habits and recommended dietary guidelines. The United States recommends the Dietary Approaches to Stop Hypertension diet to regulate blood lipid levels, whereas European countries recommend the Mediterranean diet to reduce LDL-C levels [69]. China suggests limiting daily cholesterol intake to $<$300 mg for groups at high risk for atherosclerotic cardiovascular disease based on the healthy dietary pattern.

The study has several limitations. First, the results were highly heterogeneous and limited by the characteristics of the observational studies. Second, the criteria for categorizing blood lipid subgroups differed among studies, which inevitably influenced the research results when determining the OR (RR) value of the ratio of the highest and lowest blood lipid concentrations. Furthermore, some related studies have suggested that elevated HDL-C levels are positively correlated with cognitive function [70]. However, we did not conduct a meta-analysis of HDL-C because the included studies did not provide data on the correlation between HDL-C levels and cognitive impairment.

5. Conclusions

In conclusion, the results of our meta-analysis suggest that hyperlipidaemia increases the risk of cognitive impairment. Elevated serum TC levels exacerbate the development of cognitive disabilities and are more likely to be observed in older male patients. TG levels were negatively correlated with the risk of impaired cognition, whereas serum LDL-C levels were not significantly associated with

cognitive impairment. Understanding the interaction between blood lipid levels and cognition can provide valuable insights for tailoring specific blood lipid regulation strategies for high-risk individuals with lipid disorders, potentially reducing the incidence of cognitive impairment. To strengthen our understanding and support the prevention and treatment of conditions related to cognitive function, further comprehensive clinical studies investigating the interplay between lipids and cognition are necessary.

Abbreviations

AD, Alzheimer's disease; MCI, mild cognitive impairment; CI, confidence interval; HDL-C, High-density lipoprotein cholesterol; ICD, International Classification of Diseases; LDL-C, Low-density lipoprotein cholesterol; NO, nitric oxide; NOS, Newcastle-Ottawa Scale; OR, odds ratio; RE, relative error; HR, relative hazard; TC, total cholesterol; TG, triglyceride.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

XXD, DYZ, YZ and HXZ designed the research study. YZ and HXZ performed the research. YZ, HXZ, JC and YTZ completed data selection and extraction. YZ and HXZ analyzed the data. XXD, DYZ, YZ and HXZ contributed to the writing of the article. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2302040.

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