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Original Article

Assessing the causal role of lipid metabolites in Alzheimer's disease: A mendelian randomization study

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ABSTRACT

Background: The causal relationship between lipid metabolites and Alzheimer's disease (AD) remains unclear and contradictory. This study aimed to systematically assess the causal relationship between lipid metabolites and AD.

Methods: A two-step bidirectional Mendelian Randomization (MR) study was employed. The principal analytical technique used to evaluate causation was inverse variance weighting (IVW). Furthermore, mediation analysis was conducted to evaluate the possible function of lipidomes as mediators in the lipid-AD pathway.

Results: Among the 213 lipid metabolites analyzed, significant causal associations with AD were identified Cholesterol esters in large LDL(L-LDL-CE) (OR = 1.236, 95 %CI = 1.052–1.453, $P = 0.010$), Total cholesterol in large LDL(L-LDL-TC) (OR = 1.506, 95 %CI = 1.235–1.835, $P < 0.001$), Total cholesterol in medium LDL(M-LDL-TC) (OR = 1.378, 95 %CI = 1.132–1.677, $P = 0.001$). Mediation analysis further revealed ceramide (d42:2) and phosphatidylinositol (PI) (18:1_18:1) as potential mediators in this relationship.

Conclusion: The identification of specific lipid metabolites with causal effects on AD provides new insights into AD pathogenesis and highlights potential targets for preventive strategies.

1. Introduction

Alzheimer's disease (AD) is widely regarded as the most prevalent progressive and irreversible neurological condition, affecting more than 50 million individuals worldwide, according to epidemiological studies [1,2]. Driven by the world's aging population and the growing burden of disease and healthcare costs, the affected population of AD is projected to exceed 150 million by mid-century [3]. In the 1980s, Glenner and Wong first identified the amyloid-β (Aβ) peptide, a discovery that significantly advanced research on AD [4]. Unfortunately, despite extensive research efforts spanning several decades involving both animal models and clinical trials, no effective preventive measures for AD have been successfully developed to date [5].Consequently, identifying factors associated with AD is crucial for enabling early detection and effective management.

Changes in serum lipoproteins, a key measurable indicator of lipid metabolites, directly reflect the fundamental status of lipid metabolites in the human body [6]. Despite prior genetic evidence suggesting that disruptions in lipid metabolism are associated with an increased risk of early AD, contradictory findings persist [7]. For instance, some studies have indicated that dysregulation in lipid metabolites, characterized by reduced HDL-C levels, is causally associated with various cognitive disorders [8,9]. Besides, AD has been correlated with elevated LDL-C levels, according to a meta-analysis involving 5286 people [10]. Similarly, research by Dias demonstrated that higher LDL-C levels during midlife increase the likelihood of developing AD in later years [11]. However, other studies indicate that late-life LDL-C levels might not be correlated with AD and could even provide some protective benefits [12,13]. Due to ethical constraints and the slow progression of the disease, conducting randomized controlled trials (RCT) or animal studies to examine the

Abbreviations: AD, Alzheimer's disease; GWAS, genome-wide association study; MR, Mendelian randomization; IVW, inverse variance weighting; WMN, weighted median; LOO, leave-one-out analyses; L-LDL-CE, Cholesterol esters in large LDL; L-LDL-TC, Total cholesterol in large LDL; M-LDL-TC, Total cholesterol in medium LDL; PI, Phosphatidylinositol; RCT, randomized controlled trials; LD, linkage disequilibrium; OR, odds ratios; CI, confidence intervals; BBB, blood-brain barrier.

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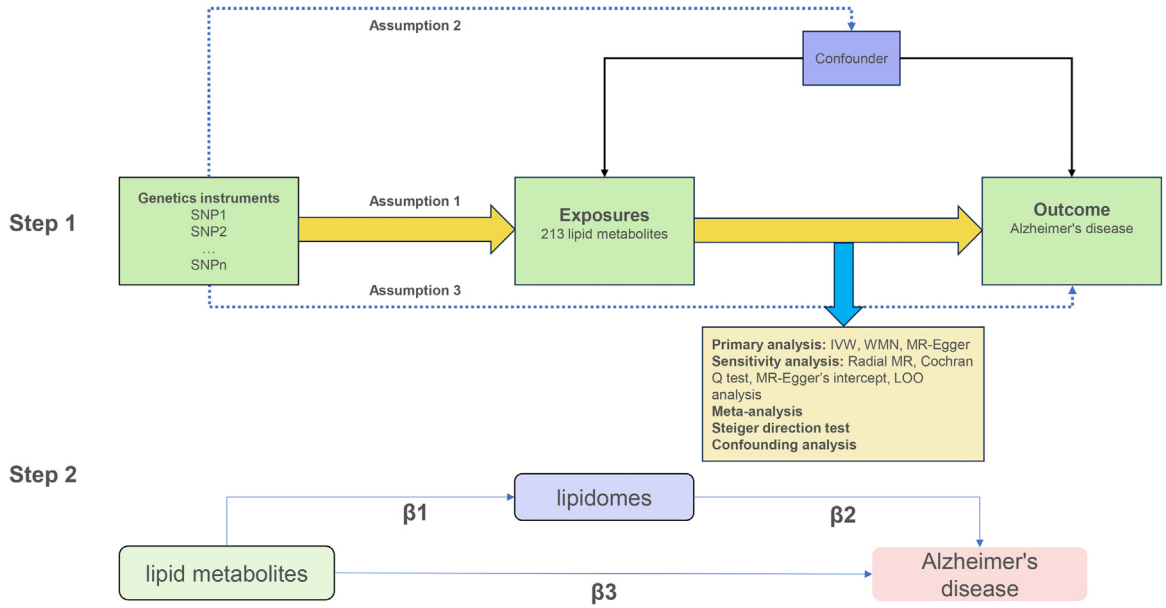

Fig. 1. Overview of the current Mendelian randomization study.
Footnotes: Step 1: Assumption 1, genetic variants are robustly associated with exposure; Assumption 2, genetic variants are not associated with confounders; Assumption 3, genetic variants affect the outcomes only through the exposure of interest.
Step 2: The lipidome-mediated indirect effect was calculated as $\beta_1 \times \beta_2$. and the mediation percentage as $\beta_1 \times \beta_2/\beta_3$. β_1 represents the MR effect of lipid metabolites on lipidomes, β_2 represents the MR effect of lipidomes on AD, and β_3 represents the total effect of lipid metabolites on AD. IVW, inverse variance weighted; WMN, weighted median; AD, Alzheimer's disease; LOO, leave-one-out.

connection between dyslipidemia and AD is both challenging and time-intensive.

Mendelian Randomization (MR) offers a useful alternative approach to ascertain the causation without RCT [14]. Since genotypes are established before disease onset and typically remain independent of disease progression, MR allows for more reliable causal inferences. Recent advancements in genomics and metabolomics have facilitated the discovery of lipid-related loci, lipoproteins, and small molecules, providing new insights into the biology of human metabolic biology and informing further analysis of MR [15]. Most prior MR studies on the relationship between lipid metabolites and AD are preliminary and superficial. Therefore, the objective of this study was to assess lipid metabolites in relation to AD further and to explore potential mechanisms.

2. Methods and materials

2.1. Study design

This MR study is divided into two steps. The first step involved a preliminary evaluation of the associations between 213 lipid metabolites and AD, which were then validated through replication cohort studies and meta-analyses. Various methods were applied to eliminate reverse causation and confounders. The second step involved mediator analysis of 179 lipidomes to identify potential mediators involved in the process (Fig. 1). In this study, the presented *P*-values were adjusted using the Bonferroni correction to account for multiple testing across four comparisons derived from two exposure datasets and two outcome datasets ($P < 0.0125$). The final results are reported as odds ratios (OR), 95 % confidence intervals (CI), and Bonferroni-adjusted *P*-values [16]. Statistical evaluations were performed with 'Two Sample MR package' (0.5.11) in R (4.3.2) and Reviewer Manager (5.4.1) software.

2.2. GWAS data for lipid metabolites

The characterization of lipid metabolites was derived from a study by Minna K [17]. Specifically, this study incorporated 213 circulating lipid metabolite profiles by MR analysis for up to 136,016 participants from 33 cohorts.

2.3. GWAS data for AD

The data on AD were sourced from a study by Brian W, which included the ADGC and other cohorts. This analysis involved 63,926 participants and included up to 10,528,610 SNPs [18].

The replication cohort and meta-analysis data were obtained from the IGAP consortium, encompassing 17,008 CE cases and 37,154 control subjects, analyzing 7,055,882 SNPs [19].

2.4. GWAS data for lipidome

Lipidome summary statistics acquired from Ottensmann L's study. Four categories and thirteen lipid classes worth 179 lipidomes each had their SNPs examined in the study, comprised of 7174 unrelated Finnish people from the Gene RISK cohort [20].

2.5. Instrument selection

A robust MR design must meet three fundamental criteria: (1) it is highly correlated with exposure; (2) it is unaffected by confounding variables; and (3) it solely affects the exposure of interest [21]. The independence of pleiotropy is the collective term for the second and third assumptions, which can be examined using various statistical methods [22]. Based on previous studies, thresholds were set at $P < 5 \times 10^{-8}$. SNPs below the thresholds were excluded in this study [23]. From the outcome data, SNPs connected to exposure were extracted, and those with F-statistics less than ten related to the result were removed. Finally, the SNPs were harmonized and aligned by alleles.

2.6. Primary analysis

Following the synchronization of effect alleles, several MR methods were employed. These methods included inverse variance weighted

(IVW), weighted median (WMN), MR-Egger, the weighted mode, and the simple model [24–27]. The Wald ratios for each SNP are merged in the IVW approach, the main technique used in MR investigations to get a composite estimate. This approach is thought to be the most successful in estimating causal effects in MR study [24]. Consequently, To establish preliminary causal connections between lipid metabolites and AD, The IVW approach was the primary methodology used in this study [28]. However, it is also vulnerable to pleiotropy bias. When data heterogeneity is present, other approaches complement IVW estimation.

2.7. Sensitivity analysis

The study included some sensitivity analyses [29]. Heterogeneity and MR-Egger methods ($P < 0.05$ based on the Cochran Q statistic) were used to detect potential horizontal pleiotropy [23]. Radial MR used heterogeneity tests (corrected Q statistic) to identify and exclude anomalous pleiotropic SNP [30]. MR-Egger's intercept was employed to identify pleiotropy [31]. Also, leave-one-out analyses (LOO) were carried out to evaluate whether SNP influenced the MR estimates [32].

2.8. Meta-analysis

A replication study of the IVW was carried out using AD data from the IGAP consortium. Subsequently, a meta-analysis was performed to validate the reliability [19].

2.9. Direction validation

Additionally, the Steiger test was employed in this investigation to ascertain whether reverse causality bias impacted the discovered causal linkages [33]. This test assessed whether the included SNPs explained more AD variability than the identified metabolites. If the SNP combinations contributed a greater percentage to the genetic susceptibility for AD compared to the metabolites ($P > 0.05$), it highlighted the potential for bias in causal inference.

2.10. Confounding analysis

To explore the pleiotropic pathways associated with AD and minimize the impact of confounding factors, three common risk factors were identified from the latest UKB prospective cohort study [34]. These factors included alcohol consumption, vitamin C deficiency, and CRP levels. The relationship between these confounders and lipid metabolites was analyzed using the IVW approach. Additionally, multivariable MR (MVMR) analysis was performed to adjust for multiple potential confounders simultaneously [35,36]. All relevant data were sourced from the IEU online database and are presented in **Supplementary Table S1**.

2.11. Mediation analysis

Furthermore, mediation analyses were conducted in three stages: first, to assess lipid metabolites on AD; second, to examine the indirect effect of the identified lipid metabolites on lipidomes; and finally, to assess the lipidomes and AD. The lipidome-mediated indirect effect was calculated as $\beta_1 \times \beta_2$. and the mediation percentage as $\beta_1 \times \beta_2/\beta_3$. β_1 illustrates the metabolic rate impact of lipid metabolites on lipidomes. β_2 represents the MR implications of lipidomes on AD, and β_3 indicates the total impact of lipid metabolites on AD (Fig. 1).

3. Results

3.1. Associations of genetic lipid metabolites with AD

Initially, 35 metabolites significantly associated with AD were identified using IVW methods (Fig. 2). Following this, outliers were removed through sensitivity analyses and radial MR methods to ensure consistent directionality across all MR methods. Ultimately, three candidate metabolites were identified as being strongly associated with AD: Cholesterol esters in large LDL(L-LDL-CE) (OR = 1.236, 95 %CI = 1.052–1.453, $P = 0.010$), Total cholesterol in large LDL(L-LDL-TC) (OR = 1.506, 95 %CI = 1.235–1.835, $P < 0.001$), Total cholesterol in medium LDL(M-LDL-TC) (OR = 1.378, 95 %CI = 1.132–1.677, $P = 0.001$) (Fig. 3). l-LDL-CE, l-LDL-TC, and M-LDL-TC were correlated with an elevated likelihood of AD. The MR estimates were directionally consistent across all methods, reinforcing the robustness (Fig. 4). No outliers were recognized in the Radial MR analysis (no yellow points in the figure) (**Supplementary Figure**). Moreover, Cochran Q-derived $P - values > 0.05$, which revealed no sign of horizontal pleiotropy and no discernible heterogeneity (Table 1). Finally, LOO analyses found no high-impact SNPs and funnel plots exhibited symmetry (**Supplementary Figure**).

Table 1
Sensitivity analysis for the causal association between lipid metabolites and AD.

MR methods	Cochran's *P value*	MR Egger's intercept	*P value*
L-LDL-CE		0.001	0.873
IVW	0.932		
MR-Egger	0.914		
L-LDL-TC		0.002	0.840
IVW	0.816		
MR-Egger	0.773		
M-LDL-TC		−0.003	0.721
IVW	0.741		
MR-Egger	0.696		

Abbreviation: IVW, inverse variance weighting; AD, Alzheimer's disease; MR, Mendelian randomization; l-LDL-CE: Cholesterol esters in large LDL; l-LDL-TC: Total cholesterol in large LDL; M-LDL-TC: Total cholesterol in medium LDL.

Table 2
Steiger direction test from lipid metabolites to AD.

Exposure	L-LDL-CE	L-LDL-TC	M-LDL-TC
Direction	TRUE	TRUE	TRUE
Steiger *P*	3.34E-88	7.45E-64	2.31E-61

L-LDL-CE: Cholesterol esters in large LDL; l-LDL-TC: Total cholesterol in large LDL;
M-LDL-TC: Total cholesterol in medium LDL.

3.2. Meta-analysis

The analyses were repeated using the IGPA consortium's AD data to validate the findings further. As anticipated, the metabolites exhibited a trend consistent with the previous results when analyzed with the IGPA Consortium data. The meta-analysis also showed consistent findings regarding the direction (Fig. 5).

3.3. Direction validation

The Steiger *P-values* indicated that the identified causal relationships were not influenced by reverse causality bias in the Steiger tests (Table 2).

3.4. Confounding analysis

Although sensitivity analyses failed to reveal any bias that would invalidate the MR estimates, pleiotropic pathways associated with AD were further examined to rule out the influence of confounders. The IVW approach examined the causal association between l-LDL-CE, l-LDL-TC,

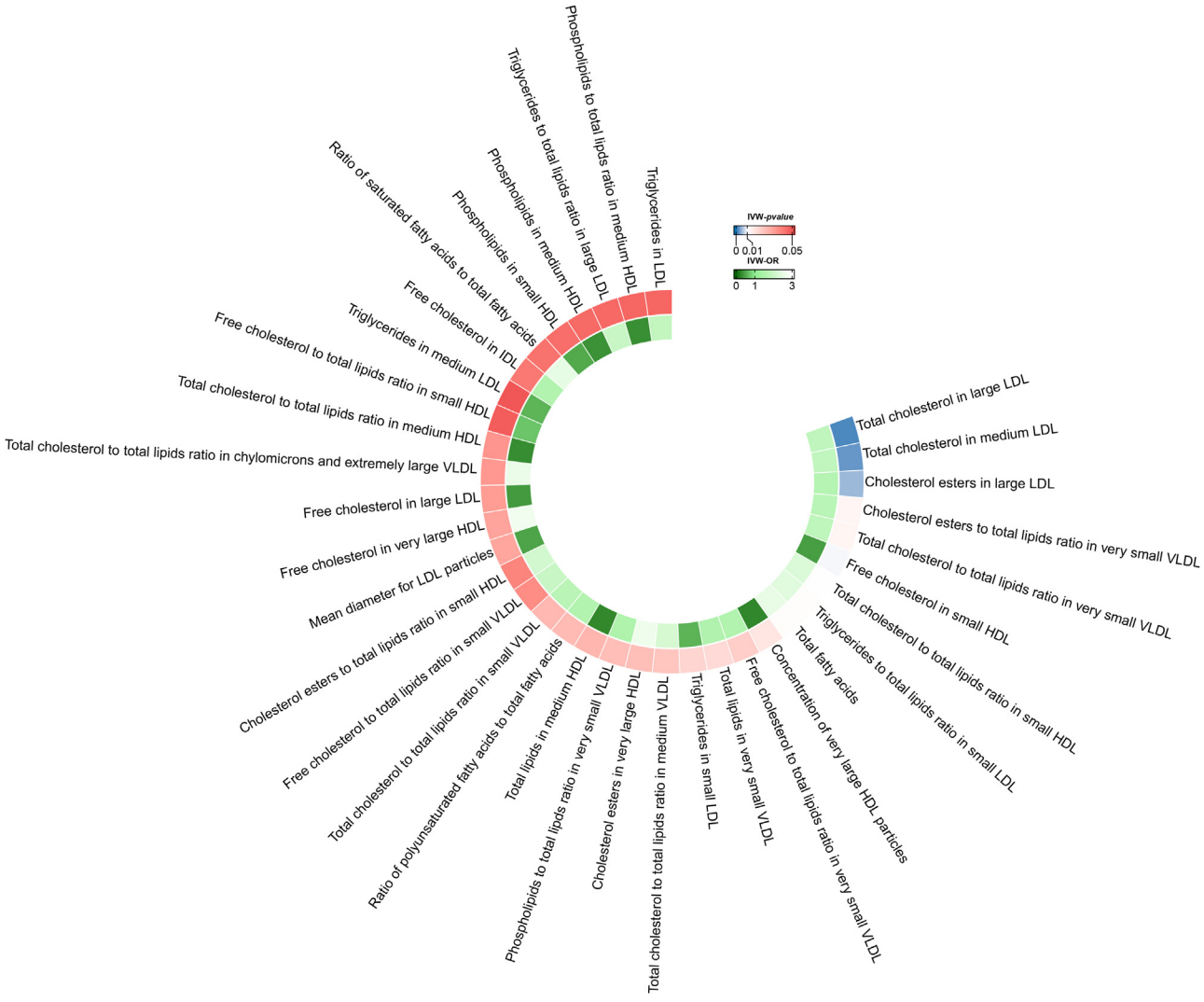

Fig. 2. Preliminary MR estimates for the associations between Lipid Metabolites and the risk of AD.
Footnotes: From the outer to inner circles, they represent the *P value* and the odds ratio of IVW methods, respectively. And the shades of color reflect the magnitude of the value. IVW, inverse variance weighted.

exposure	outcome	nsnp	method	pval	OR(95% CI)
Cholesterol esters in large LDL	Alzheimer's disease	36	MR Egger	0.381	1.200 (0.803 to 1.793)
		36	Weighted median	0.126	1.203 (0.950 to 1.523)
		36	Inverse variance weighted	**0.010**	1.236 (1.052 to 1.453)
		36	Simple mode	**0.027**	1.712 (1.085 to 2.702)
		36	Weighted mode	0.364	1.179 (0.830 to 1.673)
Total cholesterol in large LDL	Alzheimer's disease	24	MR Egger	0.165	1.436 (0.877 to 2.354)
		24	Weighted median	**0.003**	1.527 (1.160 to 2.011)
		24	Inverse variance weighted	**<0.001**	1.506 (1.235 to 1.835)
		24	Simple mode	0.087	1.539 (0.960 to 2.469)
		24	Weighted mode	0.090	1.433 (0.963 to 2.133)
Total cholesterol in medium LDL	Alzheimer's disease	24	MR Egger	0.104	1.488 (0.940 to 2.356)
		24	Weighted median	0.064	1.296 (0.985 to 1.705)
		24	Inverse variance weighted	**0.001**	1.378 (1.132 to 1.677)
		24	Simple mode	0.160	1.434 (0.882 to 2.331)
		24	Weighted mode	0.209	1.300 (0.873 to 1.935)

Fig. 3. Forest plot of the MR analyses for the association of lipid metabolites and the risk of Alzheimer's disease.
Footnotes: OR, odds ratio; CI, confidence interval.

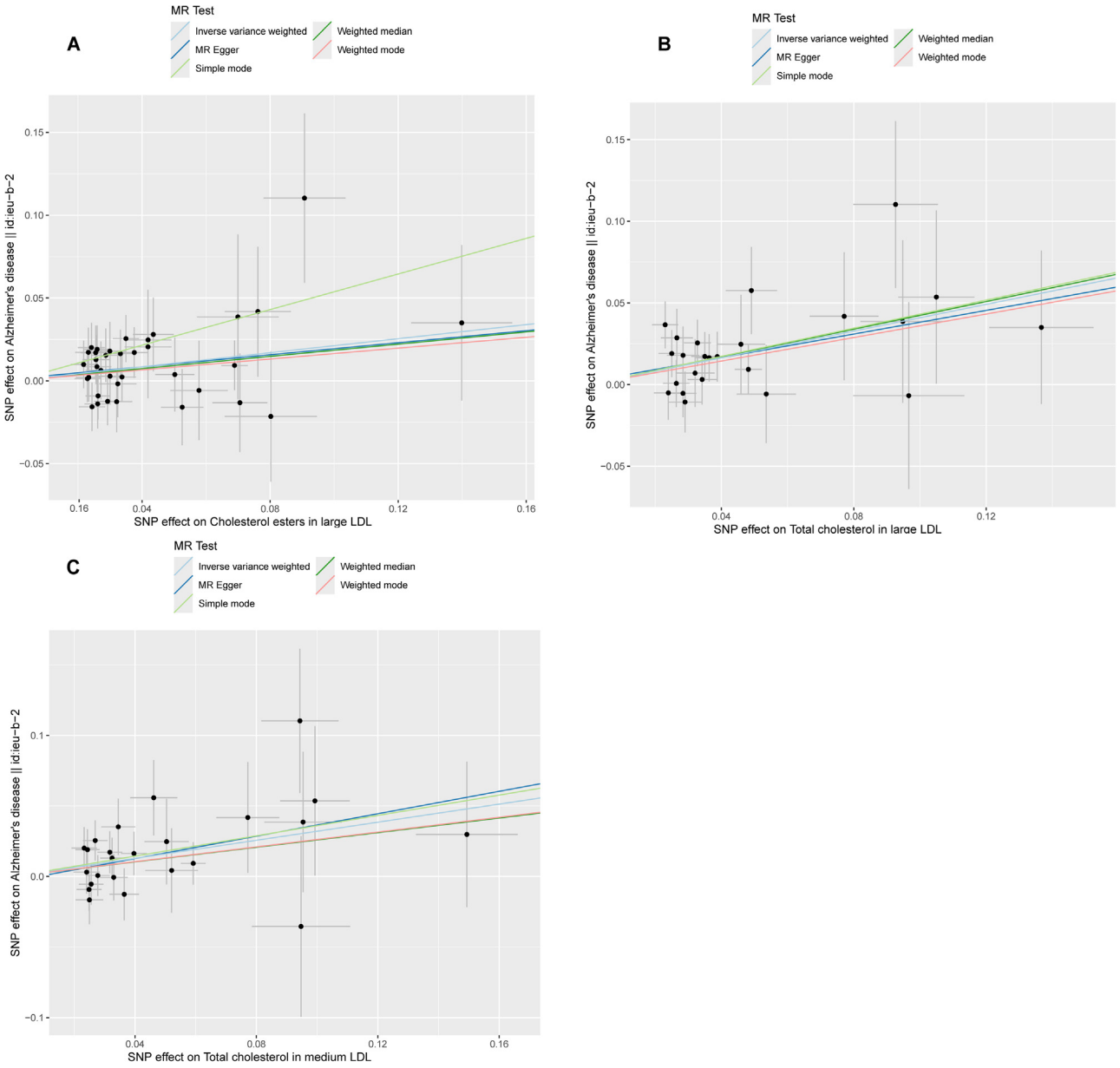

Fig. 4. Scatter plots of the MR analyses for the association of lipid metabolites and the risk of Alzheimer's disease.
Footnotes: (A) Causal effect of Cholesterol esters in large LDL on AD; (B) Causal effect of Total cholesterol in large LDL on AD; (C) Causal effect of Total cholesterol in medium LDL on AD; AD, Alzheimer's disease; AD, Alzheimer's disease.

and M-LDL-TC and AD confounders, such as alcohol consumption, vitamin C deficiency, and CRP levels. The findings showed that these exposures are not associated with these confounders (Table 3). To investigate the causal relationships between common confounding factors and AD, we included BMI, statin use, and SAH levels in MVMR analyses. The results demonstrated that l-LDL-CE was associated with an increased risk of AD (OR = 1.63, 95 % CI = 1.21–2.21, $P = 0.001$), as was l-LDL-TC (OR = 1.63, 95 % CI = 1.22–2.19, $P < 0.001$), and M-LDL-TC (OR = 1.73, 95 % CI = 1.30–2.30, $P < 0.001$). These findings are consistent with the causal associations identified in univariable MR analysis (**Supplementary Fig. 5**).

3.5. Mediation analysis

Finally, through mediation analysis, this study identified two mediators: ceramide (d42:2) and phosphatidylinositol (PI) (18:1_18:1). The effects of l-LDL-CE, l-LDL-TC, and M-LDL-TC on AD may be mediated

Table 3
Mendelian randomization estimates of the associations between lipid metabolites and risk factors.

Exposure	Outcome	Causal effect (95 % CI)	*P value*
L-LDL-CE	Alcohol consumption	1.08 (0.98–1.19)	0.104
	Vitamin deficiency	1.11 (0.94–1.31)	0.218
	CRP levels	1.07 (0.69–1.67)	0.762
L-LDL-TC	Alcohol consumption	1.07 (0.96–1.19)	0.240
	Vitamin deficiency	1.08 (0.91–1.30)	0.376
	CRP levels	1.05 (0.60–1.81)	0.875
M-LDL-TC	Alcohol consumption	1.05 (0.95–1.17)	0.349
	Vitamin deficiency	1.04 (0.88–1.25)	0.602
	CRP levels	1.16 (0.61–2.22)	0.657

L-LDL-CE: Cholesterol esters in large LDL; l-LDL-TC: Total cholesterol in large LDL;
M-LDL-TC: Total cholesterol in medium LDL; CRP, c-reactive protein; CI, confidence interval.

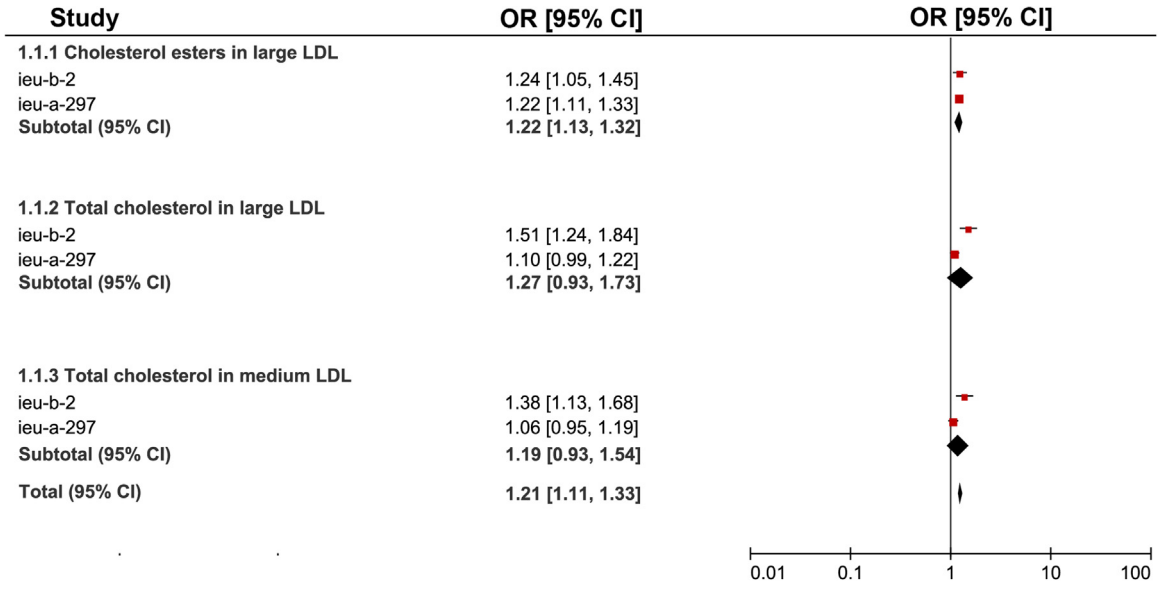

Fig. 5. Meta-analysis of the causal associations between lipid metabolites and Alzheimer's disease.
Footnotes: OR, odds ratio; CI, confidence interval.

Table 4
The result of the mediation analysis.

Exposure	Mediation	Outcome	Mediated proportion	*P value*
L-LDL-CE	Ceramide (d42:2) levels	AD	3.18 %	0.319
L-LDL-CE	Phosphatidylinositol (18:1_18:1) levels	AD	−2.92 %	0.282
L-LDL-TC	Ceramide (d42:2) levels	AD	6.86 %	0.337
L-LDL-TC	Phosphatidylinositol (18:1_18:1) levels	AD	−6.08 %	0.290
M-LDL-TC	Ceramide (d42:2) levels	AD	3.99 %	0.351
M-LDL-TC	Phosphatidylinositol (18:1_18:1) levels	AD	−3.50 %	0.256

L-LDL-CE: Cholesterol esters in large LDL; l-LDL-TC: Total cholesterol in large LDL; M-LDL-TC: Total cholesterol in medium LDL; AD, Alzheimer's disease; Phosphatidylinositol (18:1_18:1) is a phosphatidylinositol molecule containing two 18:1 fatty acid chains."18:1_18:1″ indicates that both fatty acid chains attached to the glycerol backbone of this phosphatidylinositol molecule are 18:1, In this case, each chain contains 18 carbons and one double bond; Ceramide (d42:2) levels, Ceramide (d42:2) is a ceramide consisting of dihydrosphingosine bound to a 42-carbon fatty acid and containing two double bonds. In this case, "d42:2″ indicates that the sphingomyelin molecule contains a 42-carbon backbone with two double bonds.

through the elevation of ceramide (d42:2) and the reduction of PI (18:1_18:1), with the mediating effects further calculated in Table 4.

4. Discussion

The most interesting finding was that higher l-LDL-CE, l-LDL-TC, and M-LDL-TC were associated with the likelihood of developing AD. The liver transports excess cholesterol to the bloodstream through VLDL, which is later converted to LDL [37]. LDL particles are categorized by size into l-LDL, M-LDL, and S-LDL, with l-LDL and M-LDL containing higher levels of CE and TC [38,39]. It has been suggested that increased LDL-CE may indirectly impact the central nervous system [40]. A previous serum metabolomics study by Varma VR found that dysregulation of cholesterol metabolites was strongly associated with dementia [41]. Studies on mice have demonstrated that a cholesterol-rich diet impairs the blood-brain barrier (BBB) [42]. A high-cholesterol diet will lead to higher TC levels in their plasma as well as more Aβ protein deposition in the brain, exacerbating the progression of AD [43]. Pathological studies also indicate that abnormal cholesterol metabolites may act as a mediator in the onset of AD [44]. A significant correlation was seen between elevated LDL-TC levels and heightened buildup of neuropathological markers of AD in the brain [45]. A study by Wiredu K further confirmed that elevated levels of TC and LDL were linked to increased density of neuroinflammatory plaques in AD patients [46]. Additionally, increased LDL-CE enhances intestinal cholesterol absorption, raising blood cholesterol levels and exacerbating AD progression [47]. These key mechanisms either directly contribute to or mediate the development of AD.

Thus, it can be inferred that l-LDL-CE, l-LDL-TC, and M-LDL-TC represent the cholesterol content within LDL particles. However, previous studies have reported that higher cholesterol levels may be protective in AD [12,48,49]. While the exact biological mechanisms remain unclear, larger LDL sizes have been observed in long-lived individuals and their offspring [50]. Certain studies corroborate the findings of this study, indicating that elevated circulating LDL-C increased the risk of AD, potentially attributed to its greater atherogenic potential and pro-inflammatory properties [51,52]. An extensive long-term study conducted by the UKB, involving almost 2 million participants, revealed an association between LDL-C and developing dementia [53]. Meta-analysis and systematic reviews have shown that for every incremental rise of 1 $mmol/L$ in LDL-C, the incidence of dementia rises by 8 % [54]. Compared with extensive prospective RCTs that require long-term observations and are relatively impractical, MR studies provide new insights in a more efficient way in terms of time and effort. In this MR study, we identified l-LDL-CE, l-LDL-TC, and M-LDL-TC as risk factors for AD development. Therefore, we recommend monitoring l-LDL-CE,

l-LDL-TC and M-LDL-TC in AD patients, which will be an effective measure to prevent AD.

Current clinical practice widely acknowledges the critical importance of early diagnosis and intervention in managing AD [55]. Pathological changes in AD typically commence at least a decade before clinical symptoms manifest. Advances in neuroimaging and mass spectrometry have facilitated the detection of lipidomic alterations during the earliest stages of AD [56,57]. Given the critical role of lipid metabolism in AD, integrating lipid risk assessments into elderly care programs is highly recommended. Regular monitoring of lipid profiles, combined with cognitive evaluations and neuroimaging, allows for a more comprehensive assessment and screening of individuals at high risk for AD [58–60]. Disruptions in lipid metabolism are significant contributors to cognitive decline [58,61,62].Furthermore, specific LDL subtypes exhibit varying associations with different stages of AD progression [63]. Monitoring changes in LDL subtypes may aid in early AD detection and guide the development of targeted therapeutic strategies [64,65]. Although the relationship between statin use and AD risk remains controversial, maintaining lipid balance through a combination of lifestyle modifications and pharmacological interventions is proposed for the prevention and early management of AD [58]. Additionally, individualized treatment plans tailored to personal lipid profiles and other risk factors may further enhance therapeutic outcomes [66–68]. In conclusion, for the elderly population, longitudinal lipid monitoring and timely interventions are essential strategies for mitigating AD risk.

Additional mediation analyses indicate that ceramide (d42:2) and PI (18:1_18:1) may mediate the relationship between lipid metabolites and AD development. Both ceramides and PI are crucial for lipid homeostasis, and their dysregulation is closely linked to AD development [69]. A longitudinal study found that higher ceramide levels elevate the risk of developing AD [70]. Recent animal studies confirm that ceramide levels are abnormally elevated in AD model [71]. Metabolome-wide association studies further highlight ceramide's critical role in AD development [72]. Additionally, LDL may facilitate ceramide transport, leading to an increase in ceramide levels [73]. PI serves as an intracellular messenger, supporting the plasticity of hippocampal synapses and cognition function in AD models mediated by the PI3K/Akt/Wnt/β-Catenin signalling cascade [74]. A decrease in PI levels may exacerbate AD development due to impeding signalling in microglia and the construction of actin cytoskeletal networks [75]. A mouse experiment suggests that PI may reduce cholesterol levels by activating lysosomes via the LDL receptor pathway [76]. Thus, the effects of l-LDL-CE, l-LDL-TC, and M-LDL-TC on AD may be mediated through increased ceramide and decreased PI. Nonetheless, the current understanding of ceramide (d42:2) and PI (18:1_18:1) remains limited, and additional investigation is required to fully elucidate the underlying molecular pathways.

The current study has several strengths. First, it utilizes the latest and most extensive range of lipid metabolites, with broad coverage and large sample size, focusing on lipid metabolites that may contribute to AD, which have been less explored at the particulate level in previous research. Second, various methods were employed in this study to test the reliability of the MR hypotheses, confirming the consistency of direction across MR models and the robustness of estimates. Furthermore, common confounders were also controlled to Mitigate the confounding factors and reduce the reverse causality. Additionally, replication studies and meta-analyses reinforced the findings, which confirmed the causal effects. Third, mediation analysis allowed the identification of mediating substances.

Despite these strengths, the study has certain limitations. First, the applicability of the MR results to other populations is constrained by the predominantly European descent of the participant pool. Future studies should seek to verify these findings in different populations as more GWAS data becomes available. In addition, the present study revealed an important role for l-LDL-CE, l-LDL-TC, and M-LDL-TC in the prediction of AD, which has previously received less attention, and that ceramide(d42:2) and PI (18:1_18:1) levels have been identified as mediators. Given that there are still relatively few studies, animal experiments or well-carried-out RCTs should be used to validate the result further. Finally, although two mediating chemicals were identified, their relatively minor quantities as mediators require careful consideration. In the future, this study underscores the significance of considering these metabolites when designing intervention trials and preventing AD.

5. Conclusion

The MR study identified the elevated risk of AD and l-LDL-CE, l-LDL-TC, and M-LDL-TC, exploring the role of ceramide(d42:2) and PI (18:1_18:1) mediators. This study presents fresh perspectives on AD mechanisms and suggests potential targets for preventive strategies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Haoxiang Hu: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. Jiesheng Mao: Validation, Writing – Original Draft, Writing – Review & Editing. Yunhan Zhao: Resources Data Curation. Yihan Zhang: Data Curation. Caixiang Zhuang: Writing – Review & Editing Visualization. Jianghai He: Methodology. Xiaokai Yang: Supervision, Project administration. All authors have reviewed and consented to the final manuscript version for publication.

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Data availability statement

The datasets supporting the conclusions of this article are available in the GWAS Catalog (https://www.ebi.ac.uk/gwas/home).

Declarations

Generative AI in scientific writing

No generative AI or AI-assisted technologies were used in the writing process.

Ethics statement and consent to participate

Not applicable.

Consent for publication

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100067.

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