A Causal Relationship Between the Lipidome and Central Nervous System Tumors

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BACKGROUND: **The incidence of central nervous system (CNS) tumors is increasing. However, despite advances in treatment, the etiological factors and mechanisms remain poorly understood. Recent studies have increasingly linked the lipidome to the development of CNS tumors. However, the actual association between liposomes and nervous system tumors remains speculative and lacks definitive conclusions.**

METHODS: **To address this gap, we used a Mendelian randomization approach to systematically evaluate the association between the lipidome and 5 common types of CNS tumors.**

RESULTS: **Our findings revealed a causal association between 16 lipids and glioblastoma, 6 lipids and benign meningiomas, 2 lipids and pituitary tumors and craniopharyngiomas, 3 lipids and benign cranial nerve tumors, and 2 lipids and benign spinal cord tumors.**

CONCLUSIONS: **This study represents the first comprehensive examination of the association between lipid groups and common CNS tumors, offering crucial insights for further fundamental research into the etiology and clinical management of these conditions.**

INTRODUCTION

Central nervous system (CNS) tumors comprise a spectrum of solid tumors that primarily affect the brain and spinal cord and include primary and systemic metastatic tumors. Common types include gliomas, meningiomas, pituitary tumors, and spinal cord tumors.[1] These tumors pose significant challenges owing to their high mortality and disability rates,[2] making treatment arduous. While the overall incidence of CNS tumors remains relatively low, it has been steadily rising in recent years owing to various contributing factors,[3] making them a focal point of neurosurgical research. Notably, CNS tumors not only profoundly impact adult patients but also severely affect the quality of life of pediatric patients after treatment,[4] underscoring the importance of early diagnosis and interventional treatment. Currently, surgical resection, chemotherapy, and radiotherapy are the primary treatment modalities for CNS tumors[5]; however, superior options are lacking. CNS tumors can also exert a significant social and economic burden on affected individuals.

Despite the tumors originating from the nervous system, the mechanisms driving their development and the factors influencing them remain unclear. However, previous studies have found that lipid peroxidation plays an essential role in the development of brain tumors.[6] Arachidonic acid, an abundant lipid in the brain, and its analogs can act as mediators of iron death in neurons,[7,8] which is closely linked to CNS tumor initiation and progression,[9] shedding light on the mechanisms of tumorigenesis in the

Key words
- Causal inference
- Central nervous system tumors
- Lipidome
- Mendelian randomization

Abbreviations and Acronyms
CI: Confidence interval
CNS: Central nervous system
GWAS: Genome-wide association studies
IV: Instrumental variable
IVW: Inverse-variance weighted
MR: Mendelian randomization
OR: Odds ratio
SNP: Single nucleotide polymorphism

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Citation: World Neurosurg. (2025) 204:124590. http://doi.org/10.1016/j.wneu.2025.124590

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

nervous system. Additionally, docosahexaenoic acid has shown promise in combating CNS tumors,[10,11] whereas O-acetylated gangliosides have been proposed as markers for identifying neural ectodermal tumors because of their re-expression in cancer.[12] Several recent studies have linked serine hydrolases in lipid metabolism to CNS disorders,[13] which reflects the specificity of the lipid composition in the CNS.

The lipidome has emerged as a critical player in specific CNS tumors, and research has indicated that brain-produced arachidonic acids, predominantly prostaglandins, and leukotrienes, drive the development and progression of glioblastomas and meningiomas through a cascade of reactions as well as increasing the drug resistance of glioblastomas.[14-16] Additionally, recent studies have shown that glioblastomas can accumulate fatty acids, potentially influencing growth and development by altering diacylglycerol acyltransferase-1 activity.[17] However, specific types of fatty acids remain underexplored.[18] Elevated phospholipid levels have been observed in eosinophilic cell tumors within nonfunctioning pituitary adenomas,[19] whereas lipid metabolism disorders have been implicated in craniopharyngioma development,[20] with observational studies confirming their association.[21] Previous studies have also found that Merlin, an NF2 oncoprotein associated with type 2 neurofibromatosis, is dependent on lipid rafts,[22] although the precise role of lipid rafts remains poorly understood.

While knowledge gaps persist regarding the association between the lipidome and CNS tumors, evidence suggests a close association, warranting further investigation. Addressing these gaps could significantly advance clinical treatment and basic research on CNS tumors. While randomized controlled experiments have inherent limitations, such as susceptibility to interference from objective factors, genome-wide association studies (GWAS) offer a promising avenue for exploring genetic traits,[23] providing the basis for a Mendelian randomization (MR) study to explore the association between the lipidome and CNS tumors. MR, a genetically inherited method for causal inference studies,[24-26] holds potential in this regard by leveraging single nucleotide polymorphisms (SNPs) for analysis.

METHODS

Study Design

In this study, we employed MR as the core methodology to investigate causal associations between 5 CNS tumors and 179 lipidomes. However, adherence to the following 3 conditions was necessary for the genetic variants in this study. First, genetic variants must act directly on exposure factors. Second, genetic variation must remain unaffected by other factors to ensure independence. Third, genetic variation can only affect the outcome by acting on exposure factors with no alternative pathways.[27,28] All research data in this study were obtained from publicly available human genome sequencing, and statistical analyses were conducted solely on publicly available data without information on specific individual patients, precluding the need for additional ethical approval.

Data Source

Lipidome data were obtained from a combined univariate and multivariate GWAS involving 7147 Finnish individuals (4579 females and 2595 males), encompassing 13 categories of 179 lipid species. The investigators correlated these data with the FinnGen database, which houses lipid-related genetic information from 377,277 participants. A colocalization analysis between GWAS and expression quantitative trait loci data was performed[29] to obtain more comprehensive and precise data on the lipidome. The data were cataloged in a publicly accessible GWAS database under the code GCST90277238-GCST90277416. Regarding CNS tumors, data for 5 common categories — glioblastoma, meningioma, pituitary and craniopharyngioma, cranial nerve tumors, and spinal cord tumors — were sourced from the FinnGen database (https://www.finngen.fi/en/access results), a database containing genetically inherited loci from a large number of individuals.[30] In particular, data for glioblastoma included 16,380,466 SNPs from 218,792 individuals (ncase = 91), data for meningioma included 16,380,466 SNPs from 218,792 individuals (ncase = 1280), and data for pituitary and craniopharyngiomas incorporated 16,380,466 SNPs from 218,792 individuals (ncase = 735). For cranial nerve tumors, the dataset comprised 16,380,466 SNPs from 218,792 individuals (ncase = 357), whereas spinal cord tumors included data from 16,380,466 SNPs obtained from 218,792 individuals (ncase = 196).

Selection of Instrumental Variables

This process was performed with the lipid group as the exposure factor, and 5 types of neural tumors as the outcomes, imposing rigorous parameter limits to ensure authenticity. We controlled the criteria for selecting SNPs associated with the lipid group to less than 5×10^{-8} and then used these selected SNPs as instrumental variables (IVs) for subsequent studies. To mitigate the SNP chain imbalance-induced result bias, parameters such as r2 were set to no more than 0.001 and kb to no less than 10,000 during the clumping process.[31] SNPs with palindromic sequences were excluded to maintain the consistency and credibility of the gene effect. Finally, we obtained the statistical parameter F based on the information of the extracted SNPs and required the F value to be >10. The remaining SNPs were deemed weak IVs,[32] which we excluded, considering that they would have a detrimental effect on our probing questions.

Statistical Analysis

MR analysis was conducted to investigate the association between the lipid groups and common CNS tumors using 4 methods: inverse-variance weighted (IVW), MR-Egger, weighted median, and weighted mode. The IVW method is considered more reliable in most cases[33] and serves as the primary evaluation criterion, whereas the other methods are used for supplementary analyses. The choice of these complementary methods allows for cross-validation of causal estimates and helps mitigate potential biases arising from invalid IVs or horizontal pleiotropy. The MR-Egger method provided results after excluding invalid IVs,[34] making our findings more robust. The weighted median method, encompassing most SNPs, was used to analyze causality holistically.[35] Heterogeneity in results was assessed using the Cochran Q statistic and the Rucker Q statistic methods, with a desired P value > 0.05 to ensure result reliability.[36] These statistics help determine whether variation in effect estimates is due to true differences or random chance.

We also explored the possibility of horizontal polytropy in our findings using these 2 methods. The primary method is the MR-PRESSO method, which can be validated even in the presence of horizontal pleiotropy using a small number of instruments. It identifies outliers and adjusts them,[37] thereby enhancing the precision of our validation. Additionally, we employed the MR-Egger intercept to complement the results with a P value > 0.05. These approaches collectively allow us to assess and correct for potential violations of MR assumptions, ensuring robust causal inference. Furthermore, we assessed the effect of each SNP on the results by individually removing them using a "leave one out" approach.[38] The effects of individual SNPs have also been estimated. Overall, these multiple layers of sensitivity analyses strengthen the credibility and reliability of our MR findings. All calculations were performed using R version 4.3.2.

RESULTS

To investigate the lipidome of the 5 common types of CNS tumors, we identified 7 protective factors and 9 risk factors specifically associated with glioblastoma, primarily based on results derived using the IVW method. We also identified 6 protective factors against meningiomas. Additionally, one risk factor and one protective factor were identified in pituitary tumors and craniopharyngiomas. Furthermore, 2 protective factors and one risk factor were identified for cranial neuromas, and one protective factor and one risk factor were identified for spinal cord tumors (Figure 1). Following the examination of the Q statistic values and the MR-PRESSO test, we found no evidence of horizontal pleiotropy or heterogeneity.

Causal Effect of Lipidome on Glioblastoma

In the MR study, several lipid species were identified as protective factors against glioblastoma. These included diacylglycerol (18:1_18:1) (odds ratio [OR], 0.305; 95% confidence interval [CI], 0.103–0.905; P = 3.2E-02) and diacylglycerol (18:1_18:2) (OR, 0.441; 95% CI, 0.210–0.928; P = 3.1E-02), sphingomyelin (d36:1) (OR, 0.508; 95% CI, 0.276–0.935; P = 3.0E-02), sphingomyelin (d38:2) (OR, 0.467; 95% CI, 0.243–0.897; P = 2.2E-02), triacylglycerol (51:3) (OR, 0.357; 95% CI, 0.128–0.998; P = 4.9E-02), triacylglycerol (52:6) (OR, 0.398; 95% CI, 0.175–0.907; P = 2.8E-02), and triacylglycerol (54:7) (OR, 0.358; 95% CI, 0.137–0.934; P = 3.6E-02). Several lipid species were identified as risk factors for glioblastoma. These included phosphatidylcholine (16:0_18:2) (OR, 1.694; 95% CI, 1.080–2.658; P = 2.2E-02), phosphatidylcholine (18:1_18:1)

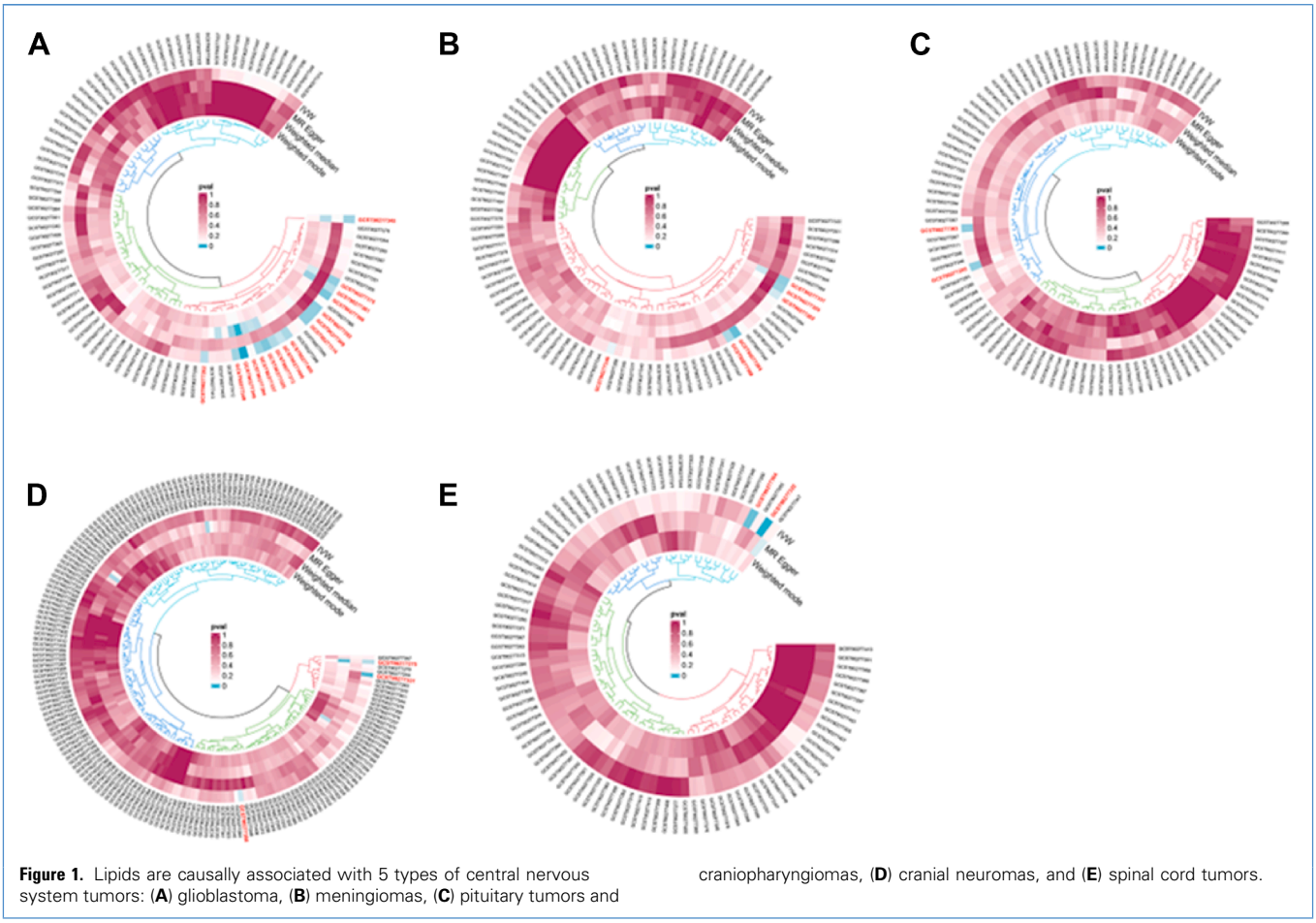

Figure 1. Lipids are causally associated with 5 types of central nervous system tumors: (**A**) glioblastoma, (**B**) meningiomas, (**C**) pituitary tumors and craniopharyngiomas, (**D**) cranial neuromas, and (**E**) spinal cord tumors.

(OR, 2.236; 95% CI, 1.146–4.363; P = 1.8E-02), phosphatidylcholine (18:1_18:2) (OR, 1.613; 95% CI, 1.069–2.434; P = 2.3E-02), phosphatidylcholine (18:2_18:2) (OR, 2.247; 95% CI, 1.122–4.501; P = 2.2E-02), phosphatidylcholine (O-16:0_18:1) (OR, 3.325; 95% CI, 1.223–9.036; P = 1.9E-02), phosphatidylcholine (O-18:1_16:0) (OR, 2.980; 95% CI, 1.144–7.762; P = 2.5E-02), phosphatidylethanolamine (16:0_18:2) (OR, 1.478; 95% CI, 1.048–2.084; P = 2.6E-02), phosphatidylethanolamine (16:0_20:4) (OR, 1.671; 95% CI, 1.199–2.328; P = 2.4E-03), and phosphatidylethanolamine (18:1_18:1) (OR, 1.751; 95% CI, 1.071–2.862; P = 2.6E-02) (Table 1).

Causal Effects of Lipid Groups on Meningiomas

In our study, using MR, we identified several lipid species as protective factors against meningiomas, without identifying any risk factors. These included phosphatidylcholine (16:0_18:2) (OR, 0.872; 95% CI, 0.766–0.993; P = 3.8E-02), phosphatidylcholine (16:0_20:2) (OR, 0.824; 95% CI, 0.706–0.962; P = 1.4E-02), phosphatidylcholine (O-16:0_18:1) (OR, 0.723; 95% CI, 0.544–0.961; P = 2.5E-02), phosphatidylcholine (O-18:1_16. 0) (OR, 0.723; 95% CI, 0.547–0.955; P = 2.2E-02), phosphatidylethanolamine (16:0_20:4) (OR, 0.906; 95% CI, 0.822–0.997; P = 4.4E-02), and sphingomyelin (d34:0) (OR, 0.841; 95% CI, 0.720–0.982; P = 2.9E-02) (Table 1).

Table 1. Mendelian Randomization Analysis Between the Lipidome and Central Nervous System Tumors

Exposure	Outcome	Method	nSNP	*P*	OR (95% CI)
Diacylglycerol (18:1_18:1)	Glioblastoma	IVW	4	3.20E-02	0.305 (0.103–0.905)
Diacylglycerol (18:1_18:2)	Glioblastoma	IVW	5	3.10E-02	0.441 (0.210–0.928)
Sphingomyelin (d36:1)	Glioblastoma	IVW	8	3.00E-02	0.508 (0.276–0.935)
Sphingomyelin (d38:2)	Glioblastoma	IVW	5	2.20E-02	0.467 (0.243–0.897)
Triacylglycerol (51:3)	Glioblastoma	IVW	5	4.90E-02	0.357 (0.128–0.998)
Triacylglycerol (52:6)	Glioblastoma	IVW	3	2.80E-02	0.398 (0.175–0.907)
Triacylglycerol (54:7)	Glioblastoma	IVW	3	3.60E-02	0.358 (0.137–0.934)
Phosphatidylcholine (16:0_18:2)	Glioblastoma	IVW	5	2.20E-02	1.694 (1.080–2.658)
Phosphatidylcholine (18:1_18:1)	Glioblastoma	IVW	4	1.80E-02	2.236 (1.146–4.363)
Phosphatidylcholine (18:1_18:2)	Glioblastoma	IVW	5	2.30E-02	1.613 (1.069–2.434)
Phosphatidylcholine (18:2_18:2)	Glioblastoma	IVW	3	2.20E-02	2.247 (1.122–4.501)
Phosphatidylcholine (O-16:0_18:1)	Glioblastoma	IVW	3	1.90E-02	3.325 (1.223–9.036)
Phosphatidylcholine (O-18:1_16:0)	Glioblastoma	IVW	3	2.50E-02	2.980 (1.144–7.762)
Phosphatidylethanolamine (16:0_18:2)	Glioblastoma	IVW	6	2.60E-02	1.478 (1.048–2.084)
Phosphatidylethanolamine (16:0_20:4)	Glioblastoma	IVW	5	2.40E-03	1.671 (1.199–2.328)
Phosphatidylethanolamine (18:1_18:1)	Glioblastoma	IVW	6	2.60E-02	1.751 (1.071–2.862)
Phosphatidylcholine (16:0_18:2)	Meningioma	IVW	5	3.80E-02	0.872 (0.766–0.993)
Phosphatidylcholine (16:0_20:2)	Meningioma	IVW	6	1.40E-02	0.824 (0.706–0.962)
Phosphatidylcholine (O-16:0_18:1)	Meningioma	IVW	3	2.50E-02	0.723 (0.544–0.961)
Phosphatidylcholine (O-18:1_16:0)	Meningioma	IVW	3	2.20E-02	0.723 (0.547–0.955)
Phosphatidylethanolamine (16:0_20:4)	Meningioma	IVW	5	4.40E-02	0.906 (0.822–0.997)
Sphingomyelin (d34:0)	Meningioma	IVW	3	2.90E-02	0.841 (0.720–0.982)
Ceramide (d42:1)	Pituitary tumor craniopharyngioma	IVW	3	2.30E-02	0.730 (0.577–0.957)
Phosphatidylinositol (18:0_20:3)	Pituitary tumor craniopharyngioma	IVW	4	2.20E-02	1.208 (1.027–1.422)
Phosphatidylcholine (15:0_18:1)	Cranial neuroma	IVW	9	3.10E-02	0.612 (0.392–0.956)
Triacylglycerol (48:3)	Cranial neuroma	IVW	14	3.70E-02	0.692 (0.489–0.979)
Phosphatidylcholine (O-16:2_18:0)	Cranial neuroma	IVW	7	1.10E-02	1.538 (1.102–2.147)
Phosphatidylinositol (18:0_20:4)	Spinal cord tumor	IVW	6	1.50E-02	0.672 (0.488–0.924)
Phosphatidylcholine (O-16:0_20:3)	Spinal cord tumor	IVW	3	4.70E-03	2.274 (1.287–4.019)

IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; nSNP, number of single nucleotide polymorphism.

Causal Effects of Lipid Groups on Pituitary Tumors and Craniopharyngiomas

Regarding pituitary tumors and craniopharyngiomas, the MR study identified ceramide (d42:1) (OR, 0.730; 95% CI, 0.577–0.957; P = 2.3E-02) as a protective factor, whereas phosphatidylinositol (18:0–20:3) (OR, 1.208; 95% CI, 1.027–1.422; P = 2.2E-02) was identified as a risk factor (Table 1).

Causality of Lipid Groups for Cranial Neuromas

For cranial neuromas, phosphatidylcholine (15:0–18:1) (OR, 0.612; 95% CI, 0.392–0.956; P = 3.1E-02) and triacylglycerol (48:3) (OR, 0.692; 95% CI, 0.489–0.979; P = 3.7E-02) were protective factors, while phosphatidylcholine (O-16:2_18:0) (OR, 1.538; 95% CI, 1.102–2.147; P = 1.1E-02) was identified as a risk factor (Table 1).

Causal Effect of Lipid Groups on Spinal Cord Tumors

In the context of spinal cord tumors, phosphatidylinositol (18:0_20:4) (OR, 0.672; 95% CI, 0.488–0.924; P = 1.5E-02) emerged as a protective factor, whereas phosphatidylcholine (O-16:0_20:3) (OR, 2.274; 95% CI, 1.287–4.019; P = 4.7E-03) was identified as a risk factor (Table 1).

Sensitivity Analyses

Using alternative methods besides the IVW approach, we acquired insightful findings that enriched our study. Based on Q statistics, we found no heterogeneity in the results. Moreover, our results withstood the double test of the MR-Egger intercept and MR-PRESSO regarding horizontal multivariate validity and were exceptionally reasonable (Table 2). Meanwhile, the "leave one out" method demonstrated that a single SNP did not affect our results, which increased their reliability.

DISCUSSION

This groundbreaking study represents the first exploration of basic and clinical research on CNS tumors using MR to establish the links between 5 standard classes of neurological tumors and 179 lipids, thereby investigating causal associations. Our findings will contribute significantly to identifying and addressing critical issues within this domain, prompting further inquiry and resolution. Our investigation yielded intriguing results, notably revealing that while different isoforms of the same lipid class exert similar effects on a particular tumor, phosphatidylcholine exhibits contrasting behaviors in cranial nerve tumors. Moreover, we observed divergent responses of identical lipids across different neurological tumors. For instance, sphingomyelin emerged as a protective factor against glioblastoma and meningioma, whereas phosphatidylcholine and phosphatidylethanolamine served as protective factors against glioblastoma but emerged as risk factors for meningioma. These observations suggest that the underlying molecular pathways, such as sphingomyelin-ceramide metabolism and phosphatidylcholine-related signaling, may modulate tumor-specific responses and highlight potential targets for therapeutic intervention.

Glycerolipids and triglycerides are vital lipid components in the human body. Triglycerides, which function as crucial energy storage substances, are vital in metabolic processes, and alterations in their production and metabolism can precipitate various diseases, including cardiovascular and digestive disorders.[39] Glycerol lipids, which are synthesized from triglycerides by diacylglycerol acyltransferase-2,[40] are closely intertwined. Research indicates that energy vital for the growth and development of glioblasts originates from lipid droplets. Triglycerides are crucial components for lipid droplet formation and act as primary fatty acids aggregated by these droplets.[41,42]

Additionally, lipid droplets have been identified as reservoirs in various tumors,[43,44] although their roles have not been thoroughly investigated. In our study, we found that glycerol lipids and triglycerides were protective factors against glioblastoma. This finding suggests that the formation of lipid droplets in glioblastomas may be a defense mechanism against the lipotoxic effects of glycerol lipids and triglycerides. These findings suggest a genetic association between glioblastomas and the lipids mentioned above, offering novel insights for glioblastoma targeting strategies beyond singularly focusing on diacylglycerol acyltransferase-1.[17] Conversely, some studies have found that inhibiting triglyceride synthesis increases the lipotoxicity of lipids in glioblastoma, thereby accelerating tumor cell death.[45] This phenomenon may stem from a decrease in lipid droplet formation, which favors higher triglyceride concentrations. Moreover, targeting lipid droplet formation or triglyceride metabolism could represent a promising therapeutic avenue in glioblastoma treatment. As for cranial nerve tumors, the different lipid compositions of the cranial nerves and their contents can change,[46] which can be used as a basis for the influence of lipid type and content on the development of cranial nerve tumors. However, unraveling the precise mechanisms requires further exploration through foundational studies.

Phospholipids are crucial for maintaining the stability of human cell membranes, with lecithin and ceruloplasmin species comprising most phospholipid species,[47] thus holding indispensable functions. Moreover, they, along with sphingolipids, which are vital surface components of plasma lipoproteins,[48] play important roles in several pathophysiological processes. Notably, sphingolipids, an essential component of cell membranes, are important targets for temozolomide treatment in glioblastoma cells because of their susceptibility to breakdown by sphingomyelinase.[49] We believe the protective effect of sphingomyelin against glioblastoma can be attributed to 2 main mechanisms. First, sphingomyelin is metabolized to ceramide, which induces apoptosis in glioblastoma. One study found that highly aggressive glioblastomas contain less ceramide.[50] However, a definite genetic link between ceramides and glioblastoma remains elusive, suggesting the potential involvement of alternative pathways. Secondly, elevated levels of sphingomyelin inhibit the development of glioblastoma, and the inhibitory effect of fluoxetine on glioblastoma is caused by the inhibition of sphingosine phosphodiesterase 1, thereby elevating sphingomyelin levels.[51] An experimental model showed that ceramides inhibit pituitary hormone secretion,[52] possibly serving as a pathway for their effects on pituitary and craniopharyngiomas. These mechanistic insights indicate that modulating sphingomyelin-ceramide metabolism could provide targeted strategies for glioblastoma and other CNS tumors.

Table 2. Heterogeneity and Multiple Validity Tests

		Heterogeneity Test		Pleiotropy Test	
		Q Test		*P* Value	
Exposure	Outcome	IVW	MR-Egger	Egger Intercept	MR-PRESSO
Diacylglycerol (18:1_18:1)	Glioblastoma	0.22	0.11	0.89	0.13
Diacylglycerol (18:1_18:2)	Glioblastoma	0.42	0.29	0.78	0.19
Sphingomyelin (d36:1)	Glioblastoma	0.62	0.51	0.87	0.59
Sphingomyelin (d38:2)	Glioblastoma	0.7	0.58	0.65	0.52
Triacylglycerol (51:3)	Glioblastoma	0.12	0.1	0.53	0.05
Triacylglycerol (52:6)	Glioblastoma	0.98	0.93	0.9	0.24
Triacylglycerol (54:7)	Glioblastoma	0.8	0.95	0.88	0.35
Phosphatidylcholine (16:0_18:2)	Glioblastoma	0.39	0.45	0.31	0.61
Phosphatidylcholine (18:1_18:1)	Glioblastoma	0.6	0.54	0.52	0.55
Phosphatidylcholine (18:1_18:2)	Glioblastoma	0.42	0.79	0.22	0.39
Phosphatidylcholine (18:2_18:2)	Glioblastoma	0.37	0.87	0.39	NA
Phosphatidylcholine (O-16:0_18:1)	Glioblastoma	0.35	0.46	0.43	NA
Phosphatidylcholine (O-18:1_16:0)	Glioblastoma	0.41	0.42	0.48	NA
Phosphatidylethanolamine (16:0_18:2)	Glioblastoma	0.39	0.8	0.13	0.54
Phosphatidylethanolamine (16:0_20:4)	Glioblastoma	0.93	0.86	0.74	0.94
Phosphatidylethanolamine (18:1_18:1)	Glioblastoma	0.47	0.36	0.7	0.6
Phosphatidylcholine (16:0_18:2)	Meningioma	0.66	0.72	0.38	0.68
Phosphatidylcholine (16:0_20:2)	Meningioma	0.78	0.81	0.41	0.7
Phosphatidylcholine (O-16:0_18:1)	Meningioma	0.77	0.51	0.81	NA
Phosphatidylcholine (O-18:1_16:0)	Meningioma	0.74	0.53	0.73	NA
Phosphatidylethanolamine (16:0_20:4)	Meningioma	0.29	0.43	0.87	0.55
Sphingomyelin (d34:0)	Meningioma	0.49	0.26	0.78	0.26
Ceramide (d42:1)	Pituitary tumor Craniopharyngioma	0.66	0.36	0.93	NA
Phosphatidylinositol (18:0_20:3)	Pituitary tumor Craniopharyngioma	0.7	0.57	0.66	0.7
Phosphatidylcholine (15:0_18:1)	Cranial neuroma	0.19	0.19	0.38	0.05
Triacylglycerol (48:3)	Cranial neuroma	0.24	0.25	0.33	0.47
Phosphatidylcholine (O-16:2_18:0)	Cranial neuroma	0.7	0.61	0.67	0.79
Phosphatidylinositol (18:0_20:4)	Spinal cord tumor	0.51	0.37	0.95	NA
Phosphatidylcholine (O-16:0_20:3)	Spinal cord tumor	0.33	0.66	0.39	0.19

IVW, inverse-variance weighted.

Although lecithin is considered a structural phospholipid owing to its abundance, its significance extends beyond mere structural support.[53] Current studies suggest that abnormalities in lecithin metabolism are a novel hallmark of tumor development. In glioblastomas, elevated expression of choline kinase α[54] results in the production of more lecithin, a finding corroborated by our study, demonstrating a genetic causal association between lecithin and glioblastoma. Furthermore, lecithin is not only highly expressed in glioblastoma but also tends to aggregate in other tumors,[55,56] suggesting its potential as a therapeutic target for various cancers, thereby guiding future clinical trials and basic research. Phosphatidylcholine oxide may mediate neurodegenerative diseases,[57] with studies in mouse models indicating its predominant action in the spinal cord,[58] which is possibly closely related to spinal cord tumorigenesis. However, our observations in meningiomas presented contrasting results,

suggesting that lecithin acts as a protective factor. We found that lecithin promoted meningioma transformation in mice,[59] a discrepancy that may be attributed to species differences.

Further investigation is warranted to elucidate the role of lecithin in human meningioma formation. It has also been found that lecithin supplementation can mitigate inflammatory damage in the CNS via the brain-gut axis,[60] potentially serving as a pathway through which lecithin reduces the risk of certain neurological tumors. These findings underscore the importance of phosphatidylcholine metabolism in CNS tumor biology and suggest potential avenues for therapeutic modulation. As one of the most abundant lipids in the human body, lecithin plays a pivotal role in various pathophysiological processes and is particularly abundant in the nervous system.[61] In the development of glioblastoma, ceruloplasmin has been identified as a lipid bioactive center.[62] Studies have linked ceruloplasmin to various diseases and found that higher expression of ethanolamine kinase 2 correlates with poorer patient prognosis, leading to increased ceruloplasmin production,[63] consistent with our findings of a causal association between ceruloplasmin and glioblastoma. This association may be attributed to the fact that ceruloplasmin is involved in the production of reactive oxygen species by mitochondria, which is involved in the development of several diseases.[61]

Conversely, one study found that elevated expression of ceruloplasmin-binding protein 4 was associated with meningioma recurrence,[64] which was not consistent with our results. Therefore, we believe that the protective effect of ceruloplasmin against meningiomas may stem from its antitumor effects as a lipid receptor.[65] Phosphatidylinositol, a unique phospholipid, plays an indispensable role in the normal physiological activities of cells.[66] Increasingly, it has been found to play a significant role in the formation of tumor cells and in the fight against apoptosis and evasion of immunity.[67] Future studies focusing on phosphatidylinositol signaling pathways may provide insights into mechanisms of tumor progression and immune evasion.

However, our study has several limitations. Although MR can reduce confounding and reverse causality, residual polygenic effects cannot be completely ruled out. As this study is based on a European population, the generalizability of our findings to other populations may be limited. Reverse MR analyses were not performed due to the limited number of genetic instruments, so we cannot fully exclude the possibility that tumors influence lipid profiles. For tumor subtypes with very low case counts, statistical power is limited and causal estimates may be unstable. Finally, our results are exploratory and should not be interpreted as definitive evidence of causal mechanisms; inherent limitations such as pleiotropy, limited statistical power, and residual confounding must be considered.

CONCLUSIONS

This study represents the first attempt to assess the association between the lipidome and the CNS using MR, thereby circumventing confounding interference from multiple factors. Consequently, we deem our results reliable and groundbreaking, offering new directions for clinical trials and basic research, while facilitating the development of novel treatments. Our findings promise disease prevention, risk avoidance, and guidance in high-risk groups.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Wenhui Zhang: Conceptualization, Data curation, Investigation, Visualization, Writing — review & editing. **Yongxue Li:** Data curation, Methodology, Validation. **Lihao Lin:** Formal analysis, Validation. **Yan Wang:** Writing — original draft. **Yi Guan:** Conceptualization, Funding acquisition, Resources, Supervision, Validation, Writing — original draft, Writing — review & editing.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the genome-wide association study (GWAS) repository at https://gwas.mrcieu.ac.uk. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the GWAS repository.

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Conflict of interest statement: This study was supported by the Natural Science Fund Project of the Jilin Province Science and Technology Department (No. YDZJ202501ZYTS046).

Received 10 September 2025; accepted 17 October 2025

Citation: World Neurosurg. (2025) 204:124590. http://doi.org/10.1016/j.wneu.2025.124590

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