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ORIGINAL RESEARCH

Potential Causal Relationship Between Plasma and Cerebrospinal Fluid Metabolites and Meningioma: Two-Sample Mendelian Randomization Study

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Background: Meningioma (MGM) is the most common benign intracranial tumor and ranks as the second most frequent intracranial tumor in terms of incidence, following malignant gliomas. Studying the metabolites in the serum and cerebrospinal fluid (CSF) of patients with MGM is crucial for understanding the underlying biological mechanisms, identifying new biomarkers, and developing novel therapeutic strategies.

Methods: Mendelian randomization (MR) is a powerful analytical approach that leverages genetic variants to assess potential causal relationships between exposures and outcomes. In this study, MR analysis was used to investigate the causal relationships between 486 serum metabolites, 338 CSF metabolites, and MGM. Our MGM data was derived from the genome wide association studies (GWASs) dataset in the FinnGen database, comprising 1,835 cases of European ancestry and 377,674 controls. The data for 486 plasma metabolites was obtained from the GWAS catalog, and the data for 338 CSF metabolites was obtained from the Wisconsin Alzheimer's Disease Research Center (WADRC) and Wisconsin Alzheimer's Disease Prevention Registry (WRAP) study collections. We mainly utilized the Inverse Variance Weighted (IVW) approach to evaluate the causal association between metabolites and MGMs, supplemented by four additional methods to further validate and strengthen our findings. False discovery rate (FDR) correction was applied ($q<0.05$) to control the false-positive rate.

Results: Through MR analysis, the study identified 19 plasma metabolites and 17 CSF metabolites demonstrating potential causal associations with MGMs. Among these, 14 metabolites indicated positive causality with MGMs, while 22 metabolites displayed a remarkable negative causality. In particular, plasma levels of Glycerol 3−phosphate (G3P) (OR=4.76, 95% CI=1.02–22.12, P=0.047) and Valine (OR=0.025, 95% CI=0.0020–0.42, P=0.010) were found to exhibit the optimal efficacy. Multiple sensitivity analyses confirm the robustness of the results. The study found no evidence of a reverse causality between MGMs and the plasma levels of Glycerol 3−phosphate (G3P) and Valine.

Conclusion: This study identified 36 metabolites associated with the incidence of MGMs, among which Glycerol 3-phosphate (G3P) and Valine are the most notable findings.

Keywords: plasma, cerebrospinal fluid, meningioma, Mendelian randomization, metabolites

Introduction

Meningiomas (MGMs) are among the most common primary central nervous system (CNS) tumor adults.[1] The incidence rate is approximately 36.4%, accounting for more than 50% of all benign primary central nervous system tumors. The incidence is higher in females (F:M ratio = 3.38:1) and increases with age, with a significant rise in individuals aged 65 and older. According to the statistical report from the Central Brain Tumor Registry of the United States (CBTRUS, 2009–2010), the prevalence of meningiomas is approximately 97.5 per 100,000. The age-standardized incidence rate of meningiomas (per 100,000) is estimated to be between 1.6 and 5.8 in Europe.[2] Therefore, the genome-wide association study (GWAS) data in this study were derived from cohorts of European ancestry to ensure homogeneity in genetic background. In 2021, the World Health Organization (WHO) classified MGMs into three grades based on

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histopathological features, genetic characteristics, and the risk of progression or recurrence: Grade 1 (benign), Grade 2 (atypical),s in and Grade 3 (malignant or anaplastic). Among these, Grade 1 MGMs are the most prevalent, accounting for over 80% of all cases.[3] The primary treatment modalities for MGMs include surgery and radiotherapy, with craniotomy being the standard therapeutic approach. However, complete surgical resection is often unachievable, and post-surgical adverse effects are frequently observed. In cases where cranial nerves are involved, neurological dysfunction is a common complication, significantly exacerbating patient morbidity.

With the rapid advancement of metabolomics, new avenues have emerged for elucidating the pathogenesis of meningiomas and identifying potential biomarkers.[4] Previous studies have demonstrated that specific high-abundance MGM metabolites, including Arginyl-Proline, can effectively distinguish metabolic alterations between low-grade and high-grade meningiomas.[5] Additionally, GATA-4 has been proposed as a potential therapeutic target through its regulation of miR-497, while miR-497 itself may serve as a promising circulating biomarker for high-grade MGMs.[6] Furthermore, a research team has identified unique DNA methylation biomarkers in the plasma of 155 MGM patients, distinguishing them from other CNS tumors.[7] Notably, the concentration of extracellular vesicles in plasma has also been found to be useful for meningioma grading and the evaluation of postoperative treatment responses.[8] However, due to limited sample sizes and heterogeneity in research methodologies, no clinically validated biomarkers for primary CNS tumors, including MGMs, have been established to date.[9] These findings highlight the need to elucidate the causal relationship between cerebrospinal fluid (CSF) and plasma metabolites and MGM development.

CSF and plasma are both critical biological compartments that reflect systemic and localized metabolic changes, providing complementary insights into tumor biology. CSF is particularly valuable for exploring molecular alterations at the tumor site, while plasma serves as a readily accessible source for investigating systemic metabolic disruptions. By integrating data from both compartments, we can achieve a more comprehensive understanding of MGM pathophysiology, which is crucial for identifying reliable biomarkers and potential therapeutic targets.

Mendelian randomization (MR) is a powerful analytical approach that leverages genetic variations to assess potential causal relationships between exposures and outcomes. Compared to traditional randomized controlled trials (RCTs), MR is not constrained by factors such as cost, time, or ethical concerns associated with interventional studies. Additionally, it effectively minimizes confounding bias and reduces the risk of reverse causality.[10] Therefore, our study aims to apply MR analysis to investigate which metabolites in CSF and plasma may have potential causal relationships with the occurrence and progression of MGMs.

Materials and Methods

Study Design

To ensure methodological rigor, this study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR, a guideline designed to strengthen the reporting standards for Mendelian randomization studies) guidelines.[11] We strictly adhered to the three fundamental instrumental variables (IVs) assumptions in MR analysis:

1. The genetic variations of the selected IVs must robustly represent the exposures of interest, which in this study are serum and CSF metabolites.
2. The IVs must be independent of confounding factors.
3. The IVs must influence the occurrence of meningiomas exclusively through the exposure factors (Figure 1).

CSF Metabolites Data Source

The dataset for CSF metabolites was derived from the study by Panyard et al, which focused on metabolomics research. The genome-wide association study (GWAS) dataset for CSF metabolites was obtained from CSF samples of 689 participants, including 532 individuals from the Wisconsin Alzheimer's Disease Research Center (WADRC) and 168 individuals from the Wisconsin Alzheimer's Disease Prevention Registry (WRAP) (After excluding individual data with

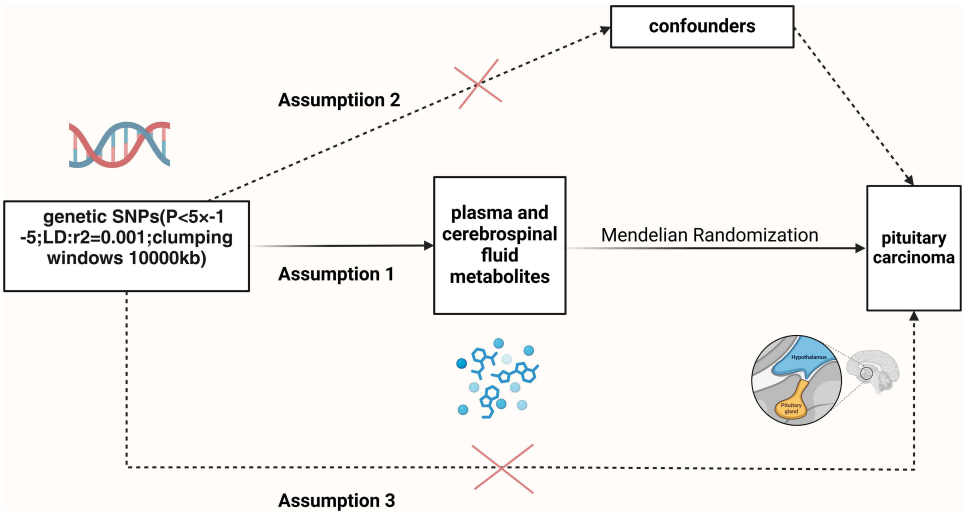

Figure 1 Schematic illustration of the study design. SNPs, single nucleotide polymorphisms. Created with BioRender.com.

missing values and data with duplicate counts, the number of participants available for further analysis was 689). Of the 338 CSF metabolites analyzed, 296 have been chemically validated, while 38 remain uncharacterized. The study received approval from the Institutional Ethics Review Board of the University of Wisconsin Health Sciences.[12]

Serum Metabolites Data Source

The dataset for serum metabolites was obtained from the study conducted by So-Youn Shin et al, which included 7,824 adult individuals from two large European population cohorts: the German KORA F4 study (n = 1,768 participants) and the UK TwinsUK study (n = 6,056 participants). Among the 486 serum metabolites analyzed, 309 have been chemically validated, while 177 remain uncharacterized.[13]

MGM Data Source

The GWAS dataset for MGMs was obtained from the Round 12 version of the FinnGen biobank documentation.[14] This dataset consists of 1,835 MGM patients of European ancestry and 379,509 European control participants, encompassing a total of 20,111,133 single nucleotide polymorphisms (SNPs).

Selection of Instrumental Variables

SNPs are commonly used genetic variations in MR analysis, reflecting DNA sequence diversity caused by single nucleotide changes at the genomic level. In our study, we constructed a unique set of instrumental variables for each of the CSF and plasma metabolites. This approach was adopted to ensure the accurate representation of the genetic associations specific to each metabolite. Instrumental variables were selected based on the following criteria:

1. Considering the limited number of SNPs available to achieve genome-wide significance for metabolites, we relaxed the significance threshold to $P < 1\times10^{-5}$ to increase statistical power. However, this raised concerns about the potential influence of weak-instruments.
2. To eliminate linkage disequilibrium, an $r^2<0.001$ threshold and a genetic distance of 10,000 kb were set, ensuring independence among selected SNPs.
3. The F-statistic for each SNP was calculated, and SNPs with F-values<10 were excluded to avoid weak instrument bias. Only SNPs with F-values>10 were retained.
4. SNPs located within palindromic sequences were removed. To ensure the alignment of alleles across exposure and outcome datasets, we employed the harmonise function from the TwoSampleMR R package. This function systematically compares the effect and non-effect alleles for each SNP in both datasets and harmonizes them to

a common reference strand. Specifically, it flips the sign of the beta coefficient when alleles are aligned in opposite directions and removes SNPs with ambiguous alignment that cannot be resolved reliably. For palindromic SNPs (ie, A/T or G/C variants), which are prone to strand ambiguity, the function excludes those with intermediate allele frequencies (typically between 0.42 and 0.58). This harmonization process is crucial for avoiding misclassification of effect directions.

5. SNPs associated with potential confounding factors were excluded.

Statistical Analysis

All statistical analyses were performed using the TwoSampleMR R package (Version 0.5.8) in R-Studio (Version 4.4.1).[15] The Inverse Variance Weighted (IVW) method has been reported as the most effective approach for detecting causal effects between exposures and outcomes in MR studies.[16] Therefore, IVW was chosen as the primary analytical method. Additionally, MR-Egger, weighted mode, weighted median, and simple mode methods were applied as supplementary analyses to ensure robustness. However, when fewer than 10 instrumental variables were available, the results from the MR-Egger analysis exhibited a degree of unreliability. A P-value < 0.05 was set as the threshold for statistical significance. Odds ratios (ORs) were used to quantify the effect of CSF and serum metabolites on MGM risk. To effectively control the false positive rate arising from multiple testing, false discovery rate (FDR) correction was applied to enhance the accuracy and reliability of the findings. The Benjamini–Hochberg method was utilized to apply a FDR for the results.

Sensitivity Analyses

To assess the robustness of the findings, various sensitivity analyses were conducted on the significant variants. Given that weak instrumental variables were used in this study to conduct the Mendelian randomization (MR) analysis, we considered performing a sensitivity analysis using only genome-wide significant variants. Cochran's Q test was used to evaluate heterogeneity, with a P-value <0.05 indicating significant heterogeneity.[17] Potential horizontal pleiotropy was assessed using MR-Egger regression by testing for a non-zero intercept (P<0.05) and by identifying outliers using the MR-PRESSO method.[18,19] Additionally, a leave-one-out analysis was performed to evaluate the potential influence of individual SNPs on the results and to mitigate bias[20] (Figure 1).

Results

Mendelian Randomization Analysis of 486 Plasma Metabolites and Their Impact on Meningiomas

A total of 19 metabolites were identified to exhibit putative causal associations (IVW $p < 0.05$) (Table 1). Specifically, plasma levels of Glycerol 3-phosphate (G3P) (OR = 4.759, 95% CI = 1.024 − 22.116, P = 0.0466), 1-stearoylglycerophosphocholine (OR = 4.752, 95% CI = 1.314 − 17.186, P = 0.0175), Eicosapentaenoate (EPA; 20:5n3) (OR = 2.948, 95% CI = 1.119 − 7.770, P = 0.0287), and Butyrylcarnitine (OR = 1.436, 95% CI = 1.009–2.045, P = 0.0445) were positively correlated with the risk of MGMs.

Conversely, several plasma metabolites exhibited negative correlations with MGM risk, including Epiandrosterone sulfate (OR = 0.612, 95% CI = 0.418–0.896, P = 0.0116), 1-linoleoylglycerol (1-monolinolein) (OR = 0.539, 95% CI = 0.315–0.923, P = 0.0243), Gamma-tocopherol (OR = 0.472, 95% CI = 0.273–0.816, P = 0.0072), Laurylcarnitine (OR = 0.219, 95% CI = 0.099–0.482, P = 0.0002), Creatinine (OR = 0.141, 95% CI = 0.022–0.903, P = 0.0387), and Valine (OR = 0.025, 95% CI = 0.002–0.423, P = 0.0105).

Additionally, nine unidentified metabolites exhibited a causal relationship with MGM occurrence (Figures 2–4). While, after FDR correction, no associations between metabolites and meningioma remained statistically significant ($q < 0.05$). Scatter plots were generated to visualize these causal associations (Figure 5). Moreover, reverse MR analysis confirmed that no causal relationship exists from MGMs to these metabolites (P < 0.05).

Table 1 The Significant IVW Results of Plasma Metabolites and MGMs

Exposure	Method	nSNP	b	se	OR (95% CI)	P_Val
Creatinine	IVW	25	−1.96	0.95	0.141	0.0387
Valine	IVW	6	−3.67	1.43	0.025	0.0105
Glycerol 3−phosphate (G3P)	IVW	13	1.56	0.78	4.759	0.0466
X−04495	IVW	11	−1.11	0.54	0.331	0.0403
Eicosapentaenoate (EPA; 20:5n3)	IVW	12	1.08	0.49	2.948	0.0287
1−linoleoylglycerol (1−monolinolein)	IVW	14	−0.62	0.27	0.539	0.0243
X−10810	IVW	15	0.75	0.38	2.126	0.0463
Butyrylcarnitine	IVW	24	0.36	0.18	1.436	0.0445
X−11540	IVW	8	−0.86	0.39	0.420	0.0245
X−12013	IVW	9	−0.38	0.16	0.683	0.0170
Gamma−tocopherol	IVW	13	−0.75	0.28	0.472	0.0072
X−12212	IVW	11	−0.66	0.30	0.518	0.0307
X−10346	IVW	14	0.34	0.15	1.402	0.0201
X−12435	IVW	26	−0.15	0.06	0.861	0.0124
1−stearoylglycerophosphocholine	IVW	12	1.56	0.66	4.752	0.0175
Epiandrosterone sulfate	IVW	12	−0.49	0.19	0.612	0.0116
Laurylcarnitine	IVW	13	−1.52	0.40	0.219	0.0002
X−13435	IVW	21	−1.12	0.46	0.325	0.0141
X−13553	IVW	8	1.47	0.55	4.368	0.0075

Mendelian Randomization Analysis of 338 CSF Metabolites and Their Impact on Meningiomas

A total of 17 metabolites were identified to exhibit putative causal associations (IVW $p < 0.05$) (Table 2). Notably, Creatine (OR = 1.865, 95% CI = 1.054–3.302, P = 0.0324), Homostachydrine (OR = 1.201, 95% CI = 1.003–1.439, P = 0.0465), Cortisol (OR = 1.122, 95% CI = 1.004–1.253, P = 0.0422), 2'-deoxyuridine (OR = 1.057, 95% CI = 1.003–1.113, P = 0.0369), and Theobromine (OR = 1.040, 95% CI = 1.001–1.080, P = 0.0453) were positively correlated with MGM risk.

Conversely, several CSF metabolites exhibited negative correlations with MGM risk, including Sphingomyelin (d18:1/20:0, d16:1/22:0) (OR = 0.939, 95% CI = 0.892–0.988, P = 0.0154), Ribulonate/xylulonate (OR = 0.899, 95% CI = 0.823–0.983, P = 0.0192), Gamma-glutamylvaline (OR = 0.884, 95% CI = 0.795–0.982, P = 0.0222), 1-palmitoyl-2-stearoyl-gpc (16:0/18:0) (OR = 0.852, 95% CI = 0.729–0.994, P = 0.0420), Guanosine (OR = 0.819, 95% CI = 0.687–0.976, P = 0.0257), Threonine (OR = 0.676, 95% CI = 0.500–0.912, P = 0.0105), Arabinose (OR = 0.657, 95% CI = 0.442–0.977, P = 0.0381), and 7-methylguanine (OR = 0.606, 95% CI = 0.374–0.981, P = 0.0414).

Additionally, four unidentified metabolites demonstrated causal associations with MGMs (Figures 3 and 4). Scatter plots were generated to illustrate these relationships (Figure 6). While, after FDR correction, no associations between metabolites and meningioma remained statistically significant ($q < 0.05$). Reverse MR analysis confirmed that no causal relationship exists from MGMs to these metabolites ($P < 0.05$).

Sensitivity Analyses

To ensure the robustness of our findings, several sensitivity analyses were conducted. The MR-Egger intercept test was performed to assess the presence of pleiotropy, while Cochran's Q test was used to evaluate heterogeneity.

For plasma metabolites and MGMs, no evidence of heterogeneity or pleiotropy was detected among the 19 plasma metabolites.

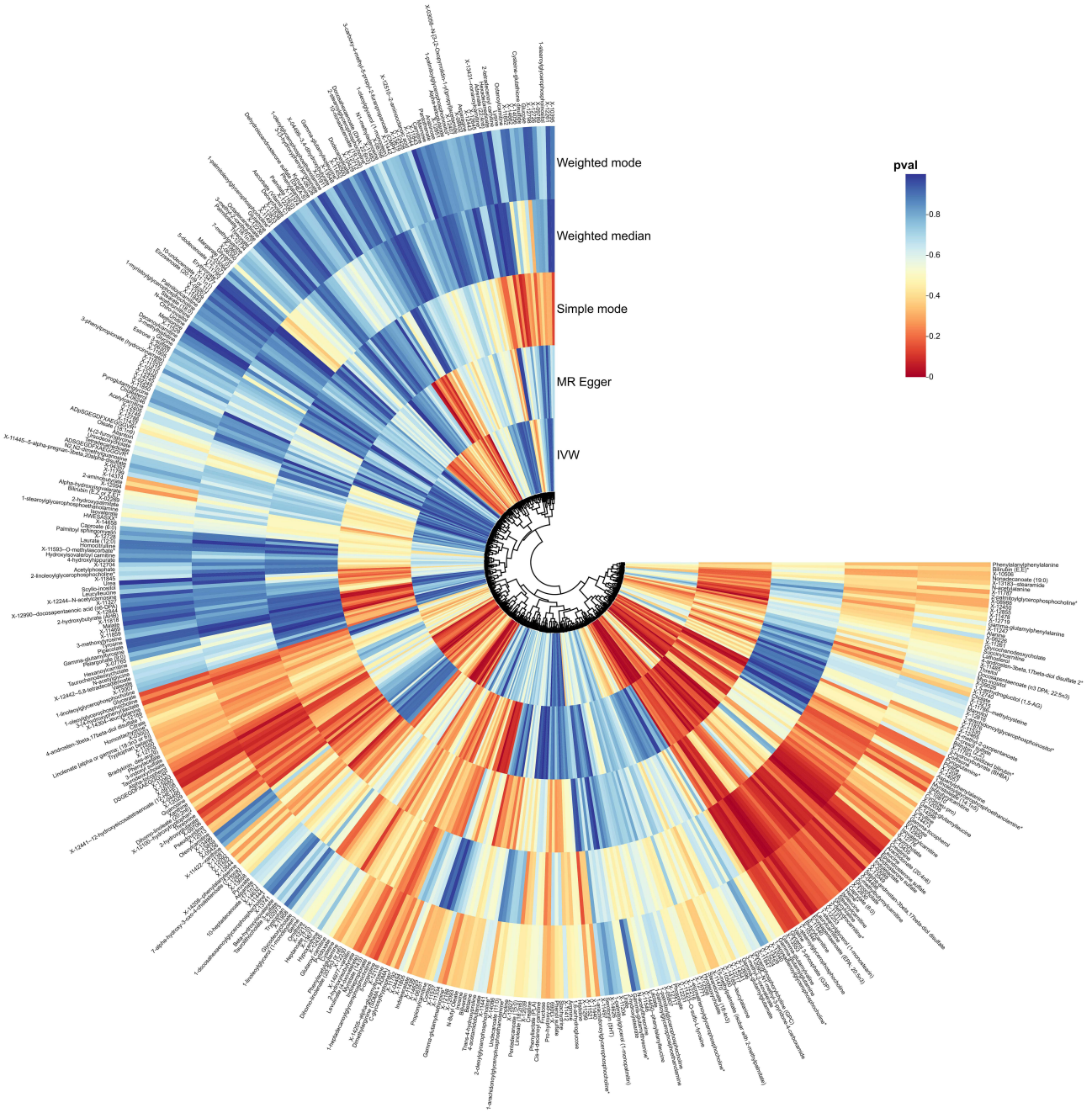

Figure 2 Summary of causal estimates regarding the impact of all plasma metabolites on MGMs in MR analysis. From outside to inside, the corresponding P-values of Weighted mode, Weighted median, Simple mode, MR Egger, IVW are represented, respectively.
Abbreviations: MR, Mendelian randomization; IVW, inverse-variance weighted.

For CSF metabolites and MGMs, with the exception of Sphingomyelin (d18:1/20:0, d16:1/22:0), no significant heterogeneity was observed in the other 16 CSF metabolites. Additionally, except for Cortisol, no significant pleiotropy was detected among the remaining CSF metabolites.

Furthermore, leave-one-out analysis identified no potential outliers, and after outlier correction, MR-PRESSO analysis did not yield any additional abnormal instrumental variables. These results collectively reinforce the robustness and reliability of our findings (Tables 3 and 4), while illustrations of leave-one-out analysis and funnel plots can be discovered in Supplementary Figure S1–S6.

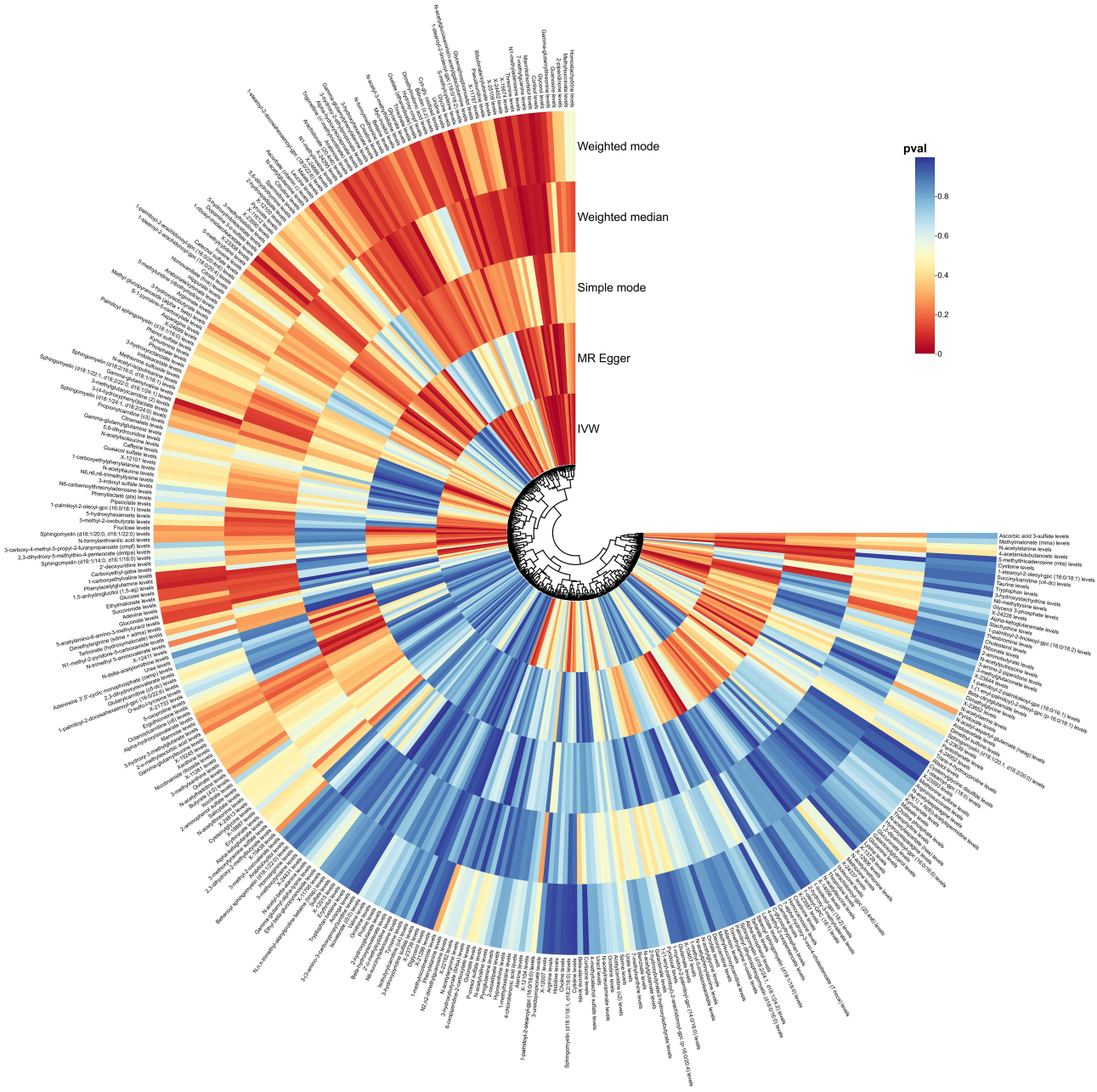

Figure 3 Summary of causal estimates regarding the impact of all CSF metabolites on MGMs in MR analysis. From outside to inside, the corresponding P-values of Weighted mode, Weighted median, Simple mode, MR Egger, IVW are represented, respectively.
Abbreviations: MR, Mendelian randomization; IVW, inverse-variance weighted.

Discussion

To elucidate the potential causal relationship between various metabolites and the occurrence of MGMs, we conducted a MR analysis utilizing serum and CSF metabolite datasets alongside MGM genetic data. Our study identified 17 CSF metabolites and 19 plasma metabolites associated with MGM occurrence. Among these, 14 metabolites exhibited a positive correlation, while 22 metabolites showed a negative correlation with MGMs. Among these metabolites, 13 remained unidentified ("X-"), a phenomenon attributed to the presence of features labeled as " unidentified metabolites" in the metabolomic dataset. In the metabolomics datasets, certain features were labeled as "unidentified metabolites", denoting signals detected via mass spectrometry that lacked confirmed structural annotation at the time of data release.

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Exposure	No.of SNP	Method	OR(95% CI)	P
		Plasma metabolites		
Creatinine	25	IVW	0.141 (0.022 to 0.903)	0.039
Valine	6	IVW	0.025 (0.002 to 0.423)	0.010
Glycerol 3−phosphate (G3P)	13	IVW	4.759 (1.024 to 22.116)	0.047
X−04495	11	IVW	0.331 (0.115 to 0.952)	0.040
Eicosapentaenoate (EPA; 20:5n3)	12	IVW	2.948 (1.119 to 7.770)	0.029
1−linoleoylglycerol (1−monolinolein)	14	IVW	0.539 (0.315 to 0.923)	0.024
X−10810	15	IVW	2.126 (1.012 to 4.463)	0.046
Butyrylcarnitine	24	IVW	1.436 (1.009 to 2.045)	0.045
X−11540	8	IVW	0.420 (0.197 to 0.895)	0.025
X−12013	9	IVW	0.683 (0.499 to 0.934)	0.017
Gamma−tocopherol	13	IVW	0.472 (0.273 to 0.816)	0.007
X−12212	11	IVW	0.518 (0.285 to 0.941)	0.031
X−10346	14	IVW	1.402 (1.054 to 1.865)	0.020
X−12435	26	IVW	0.861 (0.765 to 0.968)	0.012
1−stearoylglycerophosphocholine	12	IVW	4.752 (1.314 to 17.186)	0.017
Epiandrosterone sulfate	12	IVW	0.612 (0.418 to 0.896)	0.012
Laurylcarnitine	13	IVW	0.219 (0.099 to 0.482)	0.000
X−13435	21	IVW	0.325 (0.133 to 0.797)	0.014
X−13553	8	IVW	4.368 (1.483 to 12.864)	0.007
		Cerebrospinal fluid		
Cortisol levels	69	IVW	1.122 (1.004 to 1.253)	0.042
Sphingomyelin (d18:1/20:0, d16:1/22:0)	223	IVW	0.939 (0.892 to 0.988)	0.015
1−palmitoyl−2−stearoyl−gpc (16:0/18:0)	48	IVW	0.852 (0.729 to 0.994)	0.042
2'−deoxyuridine	130	IVW	1.057 (1.003 to 1.113)	0.037
7−methylguanine	24	IVW	0.606 (0.374 to 0.981)	0.041
Arabinose	26	IVW	0.657 (0.442 to 0.977)	0.038
Creatine	24	IVW	1.865 (1.054 to 3.302)	0.032
Gamma−glutamylvaline	66	IVW	0.884 (0.795 to 0.982)	0.022
Guanosine	58	IVW	0.819 (0.687 to 0.976)	0.026
Homostachydrine	28	IVW	1.201 (1.003 to 1.439)	0.046
Ribulonate/xylulonate	93	IVW	0.899 (0.823 to 0.983)	0.019
Theobromine	61	IVW	1.040 (1.001 to 1.080)	0.045
Threonine	37	IVW	0.676 (0.500 to 0.912)	0.011
X−11787	75	IVW	0.925 (0.864 to 0.990)	0.024
X−15674	59	IVW	1.183 (1.035 to 1.351)	0.013
X−24452	27	IVW	0.671 (0.496 to 0.908)	0.010
X−25109	64	IVW	1.135 (1.009 to 1.278)	0.036

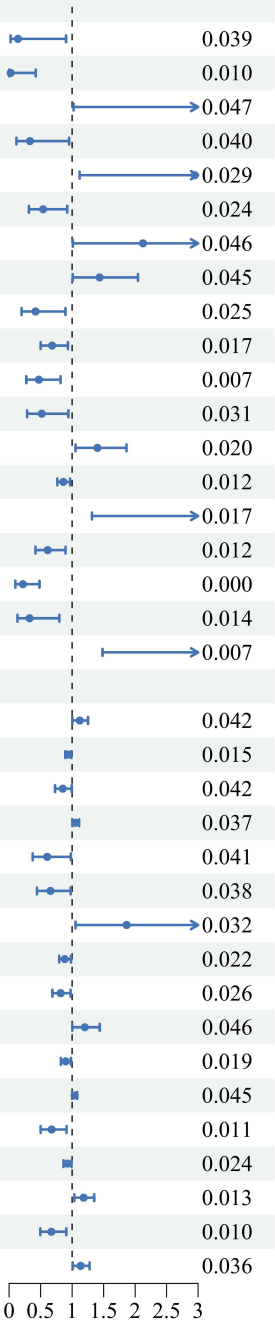

Figure 4 Forest plots illustrating the significant causal estimates of plasma and CSF metabolites on MGMs are presented.
Abbreviations: SNPs, single nucleotide polymorphisms; OR, odds ratio; IVW, inverse-variance weighted.

These entries were retained in the analysis to preserve potentially informative biological signals. These findings provide valuable insights into potential novel biomarkers for MGM diagnosis and prognosis.

The IV method is a statistical approach designed to address endogeneity issues, particularly in regression analyses, by leveraging external variables—termed IVs—to infer causal relationships.[21] The IVW method, a widely adopted statistical approach in IV analysis, is commonly employed for the combined analysis of multiple instrumental variables to enhance the reliability of causal inference.

The MR framework is based on Mendel's second law, which posits that alleles are randomly distributed during meiosis. This method exploits genetic variations, such as SNPs, as IVs for exposure factors that are indezatiopendent of outcome risk, unaffected by confounding factors, and not influenced by acquired characteristics. This enables robust causal inference between exposure variables and health outcomes.[22,23]

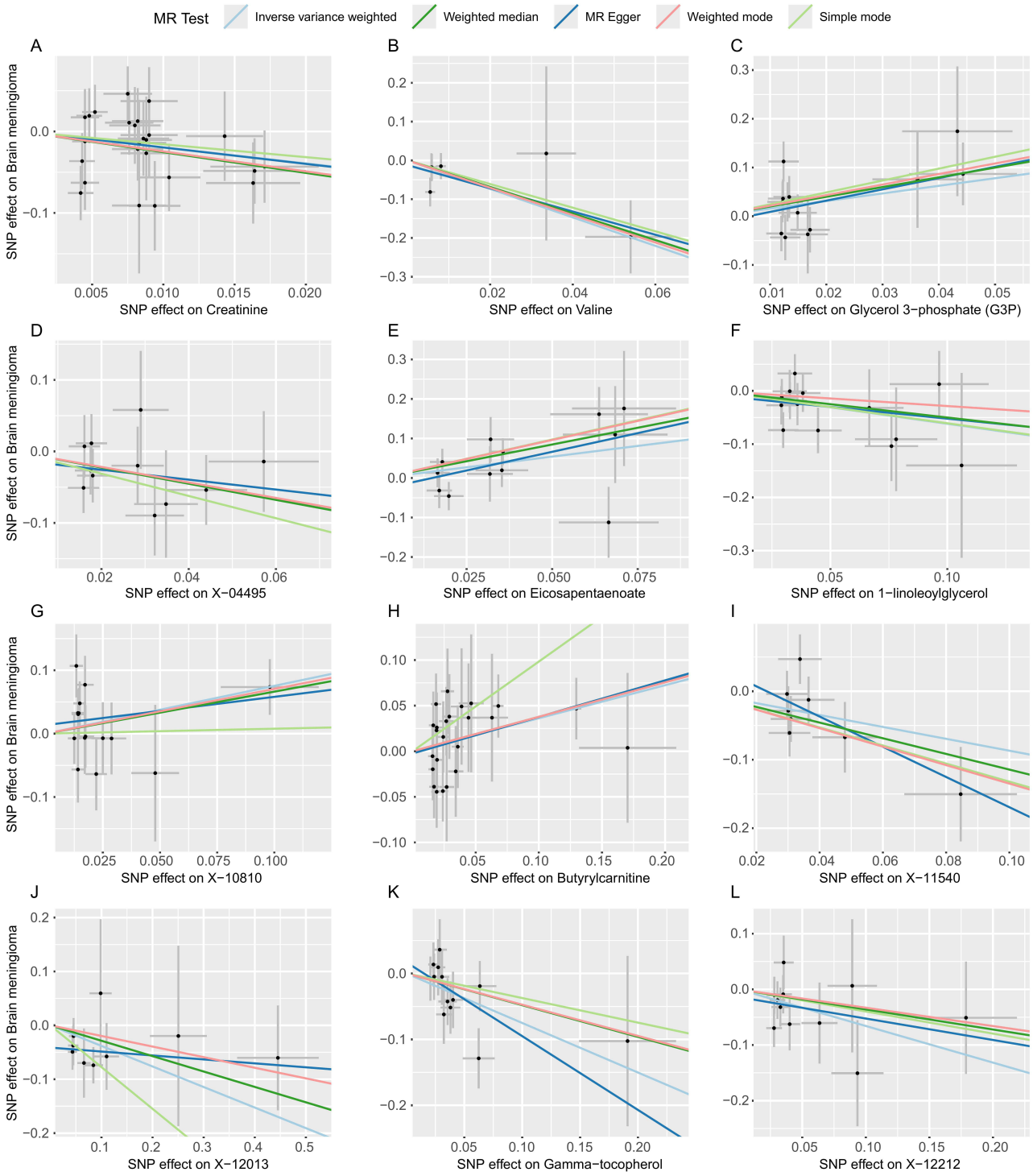

Figure 5 Continued.

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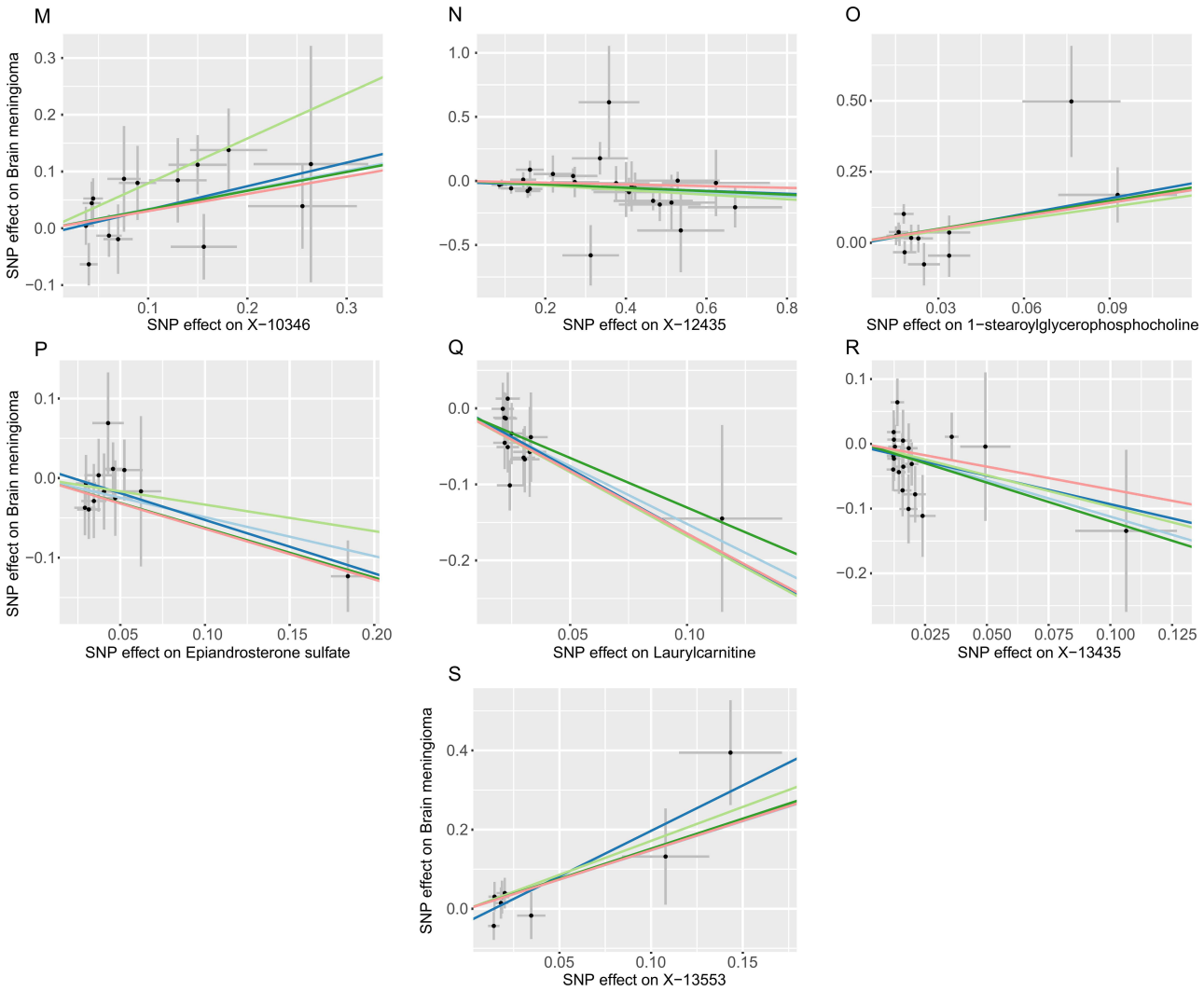

Figure 5 Scatter plots for the causal association between plasma metabolites and MGMs.(**A**) Creatinine (**B**) Valine (**C**) Glycerol 3−phosphate (G3P) (**D**) X−04495 (**E**) Eicosapentaenoate (**F**) 1−linoleoylglycerol (**G**) X−10810 (**H**) Butyrylcarnitine (**I**) X−11540 (**J**) X−12013 (**K**) Gamma−tocopherol (**L**) X−12212 (**M**) X−10346 (**N**) X−12435 (**O**) 1−stearoylglycerophosphocholine (**P**) Epiandrosterone sulfate (**Q**) Laurylcarnitine (**R**) X−13435 (**S**) X−13553.

Although several treatment modalities exist for CNS tumors, they are often accompanied by substantial limitations. Identifying biomarkers for early diagnosis and prognosis assessment is therefore of paramount importance. Advances in metabolomics research within neurosurgery have provided novel insights and methodologies for biomarker discovery.[24]

Table 2 The Significant IVW Results of CSF Metabolites and MGMs

Exposure	Method	nSNP	b	se	OR (95% CI)	P_Val
Cortisol	IVW	69	0.11	0.06	1.122	0.0422
Sphingomyelin (d18:1/20:0, d16:1/22:0)	IVW	223	−0.06	0.03	0.939	0.0154
1−palmitoyl−2−stearoyl−gpc (16:0/18:0)	IVW	48	−0.16	0.08	0.852	0.0420
2'−deoxyuridine	IVW	130	0.06	0.03	1.057	0.0369
7−methylguanine	IVW	24	−0.50	0.25	0.606	0.0414
Arabinose	IVW	26	−0.42	0.20	0.657	0.0381
Creatine	IVW	24	0.62	0.29	1.865	0.0324

(*Continued*)

Table 2 (Continued).

Exposure	Method	nSNP	b	se	OR (95% CI)	P_Val
Gamma−glutamylvaline	IVW	66	−0.12	0.05	0.884	0.0222
Guanosine	IVW	58	−0.20	0.09	0.819	0.0257
Homostachydrine	IVW	28	0.18	0.09	1.201	0.0465
Ribulonate/xylulonate	IVW	93	−0.11	0.05	0.899	0.0192
Theobromine	IVW	61	0.04	0.02	1.040	0.0453
Threonine	IVW	37	−0.39	0.15	0.676	0.0105
X−11787	IVW	75	−0.08	0.03	0.925	0.0238
X−15674	IVW	59	0.17	0.07	1.183	0.0135
X−24452	IVW	27	−0.40	0.15	0.671	0.0098
X−25109	IVW	64	0.13	0.06	1.135	0.0356

However, metabolomics-based research on MGMs remains in its infancy. Nonetheless, accumulating evidence underscores the promising potential of metabolomics in elucidating the mechanisms underlying MGMs, as well as in their clinical staging and prognostic evaluation.[4]

Metabolomics and the Pathophysiology of Meningiomas

Recent metabolomics researches had yielded crucial insights into the interplay between metabolic pathways and the biological behavior of MGMs. The anaplerotic role of glutamine facilitates the replenishment of tricarboxylic acid (TCA) cycle intermediates, supporting amino acid synthesis and thereby influencing tumor cell growth and survival. This pathway appears particularly critical in high-grade MGMs.[25]

Advanced analytical approaches, such as liquid chromatography-high resolution mass spectrometry (LC-HRMS) and machine learning algorithms, have enabled the effective differentiation between aggressive and low-grade tumors based on their metabolic and lipidomic profiles.[26] Additionally, High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance (HR-MAS NMR) has been instrumental in distinguishing metabolic alterations across different meningioma grades, with metabolites such as glutamate and alanine emerging as key determinants of tumor invasiveness and therapeutic response.[27]

Collectively, these findings indicate that metabolic reprogramming plays a pivotal role in MGM progression, with metabolic profiles serving as biomarkers for tumor aggressiveness, aiding in prognostic prediction and therapeutic decision-making. Notably, as tumor grade increases, the clinical utility of metabolic alterations becomes increasingly pronounced.[28]

Glycerol-3-Phosphate (G3P) as Potential Biomarkers

In our MR analysis results, G3P exhibited the highest OR (4.759) among all plasma and CSF metabolites associated with MGM occurrence, warranting further investigation. G3P, a central metabolic intermediate, participates in glycolysis and gluconeogenesis, two essential pathways for cellular energy homeostasis. Dysregulated glucose metabolism is a hallmark of meningiomas, often manifesting as significantly enhanced glycolysis to support the rapid proliferation of tumor cells.[28]

Although most studies on G3P have focused on renal metabolism, emerging evidence suggests that G3P is involved in multiple metabolic pathways, including NAD^+ regeneration, oxidative stress regulation, and fatty acid metabolism. In chronic kidney disease (CKD), G3P enhances gluconeogenesis, mitigates oxidative stress-induced cell damage, and aids in restoring cellular energy balance.[29,30] Additionally, G3P modulates phosphate metabolism by regulating FGF23 synthesis, which in turn affects vascular calcification and phosphate reabsorption.[31,32]

Intriguingly, the cross-regulation between glycolysis and phosphate metabolism is particularly relevant in MGMs. Lactate, a key glycolytic product, is known to regulate renal phosphate transporters, influencing phosphate homeostasis.[33]

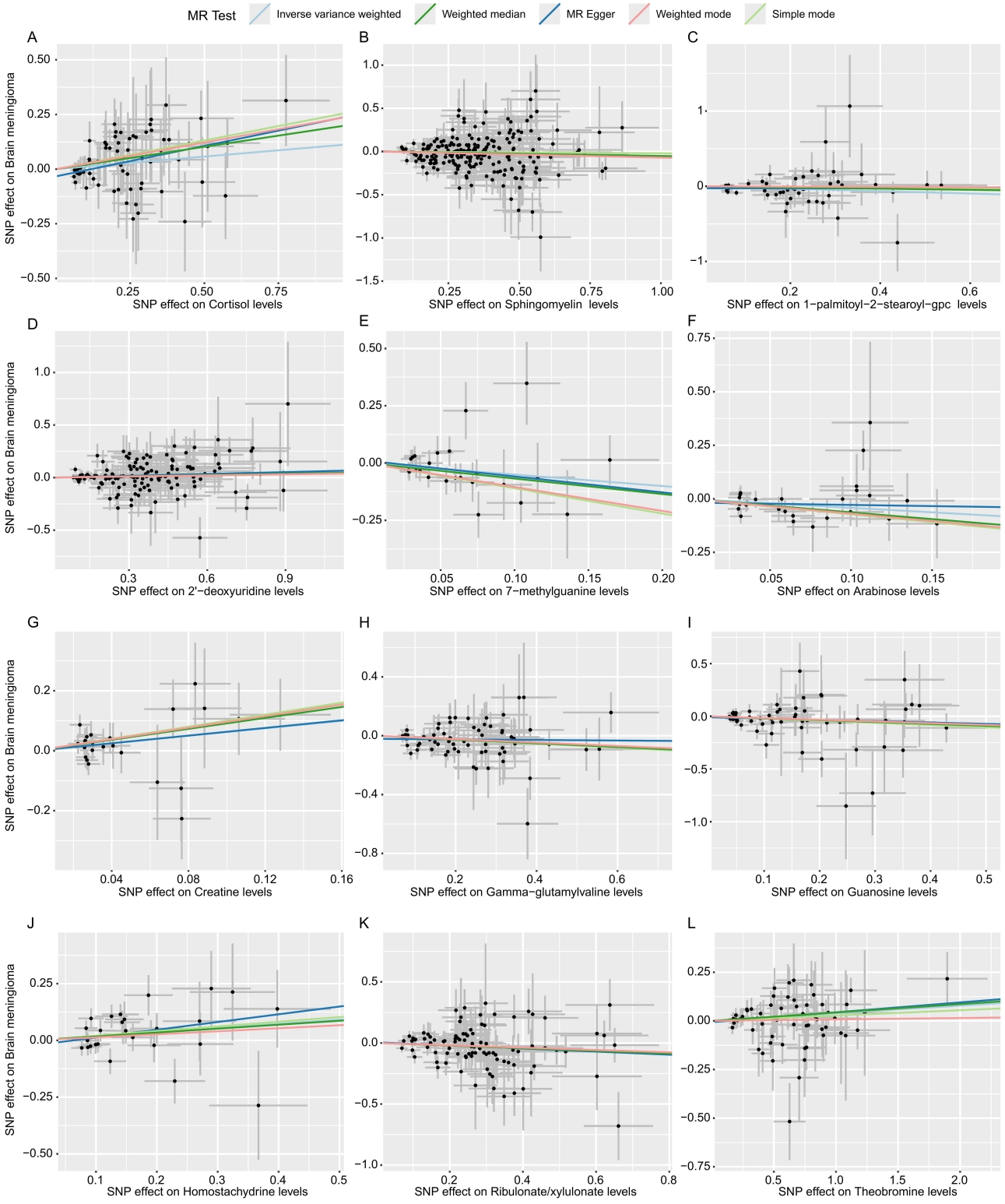

Figure 6 Continued.

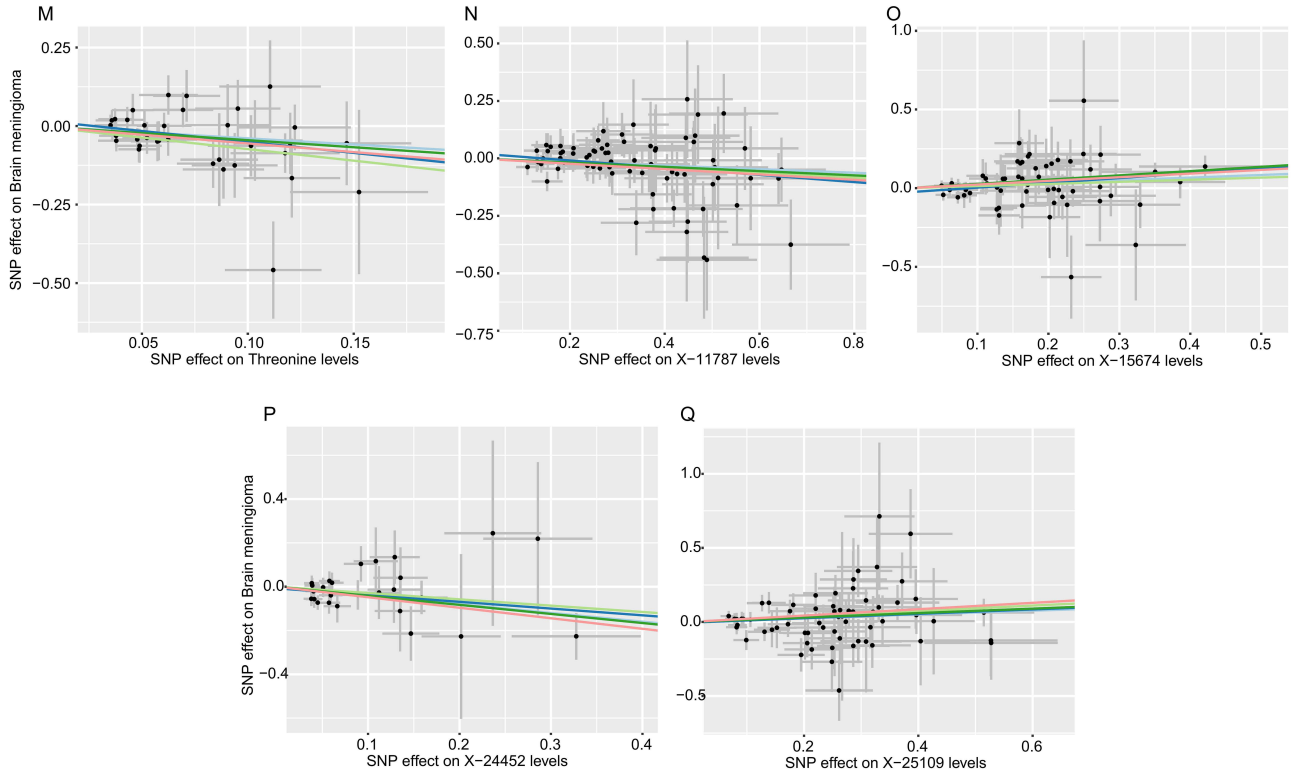

Figure 6 Scatter plots for the causal association between cerebrospinal fluid metabolites and MGMs.(**A**) Cortisol (**B**) Sphingomyelin (**C**) 1−palmitoyl−2−stearoyl −gpc (**D**) 2′−deoxyuridine (**E**) 2′−deoxyuridine (**F**) Arabinose (**G**) Creatine (**H**) Gamma−glutamylvaline (**I**) Guanosine (**J**) Homostachydrine (**K**) Ribulonate/ xylulonate (**L**) Theobromine (**M**) Threonine (**N**) X−11787 (**O**) X−15674 (**P**) X−24452 (**Q**) X−25109 and IVW results of plasma metabolites and MGMs.

Similarly, during aerobic glycolysis (Warburg effect), lactate accumulation may promote malignant transformation in MGMs, allowing tumors to adapt to hypoxic conditions.[27] Recent metabolomic analyses have linked hyperphosphatemia to MGM progression and calcification, highlighting the importance of phosphate metabolism in tumor biology.[25]

Table 3 The Sensitivity Analysis Results of Plasma Metabolites and MGMs

Exposure	Method	Q	Q_pval	Ple_pval	Presso_pval
Creatinine	MR Egger	20.15	0.633		
	IVW	20.15	0.688	0.978	0.033
Valine	MR Egger	3.04	0.552		
	IVW	3.30	0.653	0.632	0.025
Glycerol 3-phosphate (G3P)	MR Egger	12.34	0.338		
	IVW	12.57	0.401	0.660	0.070
X-04495	MR Egger	4.74	0.856		
	IVW	4.87	0.900	0.729	0.015
Eicosapentaenoate (EPA; 20:5n3)	MR Egger	13.21	0.212		
	IVW	14.06	0.229	0.441	0.051
1-linoleoylglycerol (1-monolinolein)	MR Egger	9.19	0.687		
	IVW	9.26	0.753	0.793	0.019
X-10810	MR Egger	12.55	0.483		
	IVW	13.17	0.513	0.445	0.059
Butyrylcarnitine	MR Egger	14.41	0.886		
	IVW	14.45	0.913	0.844	0.019

(*Continued*)

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Table 3 (Continued).

Exposure	Method	Q	Q_pval	Ple_pval	Presso_pval
X-11540	MR Egger	6.54	0.365		
	IVW	7.84	0.347	0.318	0.059
X-12013	MR Egger	2.07	0.956		
	IVW	5.35	0.720	0.113	0.019
Gamma-tocopherol	MR Egger	7.95	0.718		
	IVW	8.45	0.749	0.495	0.008
X-12212	MR Egger	6.76	0.662		
	IVW	7.05	0.721	0.604	0.028
X-10346	MR Egger	13.50	0.333		
	IVW	13.66	0.398	0.716	0.037
X-12435	MR Egger	23.45	0.494		
	IVW	23.68	0.538	0.632	0.017
1-stearoylglycerophosphocholine	MR Egger	15.21	0.125		
	IVW	15.28	0.170	0.832	0.037
Epiandrosterone sulfate	MR Egger	5.12	0.883		
	IVW	5.67	0.894	0.477	0.005
Laurylcarnitine	MR Egger	8.30	0.687		
	IVW	8.32	0.760	0.885	0.001
X-13435	MR Egger	17.45	0.559		
	IVW	17.53	0.619	0.785	0.016
X-13553	MR Egger	5.00	0.544		
	IVW	6.83	0.447	0.225	0.030

Table 4 The Sensitivity Analysis Results of CSF Metabolites and MGM

Exposure	Method	Q	Q_pval	Ple_pval	Presso_pval
Cortisol	MR Egger	47.06	0.969		
	IVW	52.07	0.924	0.029	0.023
Sphingomyelin (d18:1/20:0, d16:1/22:0)	MR Egger	277.51	0.006		
	IVW	277.57	0.007	0.829	0.016
1-palmitoyl-2-stearoyl-gpc (16:0/18:0)	MR Egger	41.70	0.653		
	IVW	43.86	0.604	0.149	0.041
2'-deoxyuridine	MR Egger	131.77	0.392		
	IVW	131.79	0.415	0.893	0.039
7-methylguanine	MR Egger	25.25	0.285		
	IVW	25.43	0.328	0.694	0.053
Arabinose	MR Egger	22.81	0.531		
	IVW	23.44	0.552	0.435	0.042
Creatine	MR Egger	21.45	0.493		
	IVW	21.45	0.553	0.982	0.037
Gamma-glutamylvaline	MR Egger	56.97	0.721		
	IVW	58.43	0.705	0.233	0.019
Guanosine	MR Egger	53.23	0.580		
	IVW	53.75	0.598	0.473	0.025
Homostachydrine	MR Egger	36.92	0.076		
	IVW	37.51	0.086	0.526	0.057
Ribulonate/xylulonate	MR Egger	95.45	0.354		
	IVW	95.53	0.380	0.775	0.021

(*Continued*)

Table 4 (Continued).

Exposure	Method	Q	Q_pval	Ple_pval	Presso_pval
Theobromine	MR Egger	55.28	0.614		
	IVW	55.46	0.642	0.670	0.042
Threonine	MR Egger	32.50	0.589		
	IVW	33.25	0.600	0.392	0.012
X-11787	MR Egger	60.87	0.844		
	IVW	62.18	0.835	0.256	0.016
X-15674	MR Egger	43.90	0.898		
	IVW	46.01	0.872	0.152	0.007
X-24452	MR Egger	21.52	0.663		
	IVW	21.67	0.706	0.701	0.009
X-25109	MR Egger	66.44	0.327		
	IVW	66.50	0.358	0.820	0.040

Amino Acid Metabolism and Meningiomas

The reprogramming of amino acid metabolism has emerged as a major focus in cancer research. Amino acid dysregulation plays a critical role in tumor initiation and progression, with diagnostic, prognostic, and therapeutic implications.

Our MR analysis revealed that valine exhibited the lowest OR (0.025) among both plasma and CSF metabolites, indicating a negative association with MGM occurrence. In contrast, creatine demonstrated the highest OR (1.865) among CSF metabolites, suggesting a positive correlation with MGM risk. Retrospective analysis of 62 MGM samples using HRMAS spectroscopy revealed that high-grade MGMs (WHO grade II and III) are associated with lower valine concentrations, which correlate with poorer histopathological prognostic markers.[27]

Similarly, creatine, a key metabolite in energy metabolism, has been identified as a potential CSF biomarker for MGMs. Creatine levels are significantly associated with MGM presence, with plasma creatine and creatinine levels demonstrating strong discriminatory power in distinguishing MGM patients from healthy individuals.[34] Postoperative metabolic profiling reveals elevated glutamine-to-creatinine ratios following extensive tumor resections,[35] while CSF ribulonate/xylulonate and arabinose levels demonstrate negative correlations with MGM development - patterns mirroring hepatocellular carcinoma metabolomes.[36]

Lipid Metabolism and Meningiomas

Lipid metabolic dysregulation is implicated in the pathogenesis of multiple cancers, including MGMs.[37] Our MR analysis identified four lipid metabolites with causal relationships to MGM occurrence. Plasma 1-stearoylglycerophosphocholine and eicosapentaenoate (EPA; 20:5n3) were positively correlated, whereas plasma 1-linoleoylglycerol (1-monolinolein) and CSF 1-palmitoyl-2-stearoyl-glycerophosphocholine (16:0/18:0) were negatively correlated with MGM occurrence.

Interestingly, EPA exhibits neuroprotective and anti-tumor properties,[38,39] but its susceptibility to oxidative stress may compromise these effects. Vitamin E, a potent antioxidant, may help preserve EPA's biological activity, thereby modulating its role in tumor biology. Our MR analysis identified plasma gamma-tocopherol levels as inversely associated with MGM occurrence, further supporting this hypothesis.

Nucleotide Metabolism and Meningiomas

Nucleotide metabolism dysregulation emerges through CSF biomarkers: 2'-deoxyuridine shows positive correlation, contrasting with negative associations for guanosine, threonine, and 7-methylguanine. The proliferative marker 5-ethynyl-2'-deoxyuridine (EdU) derivatives and guanosine catabolites like neopterin warrant further investigation.[40] Threonine-mediated tRNA modification mechanisms observed in glioblastoma suggest parallel metabolic reprogramming in meningiomas.[41]

Peptide Metabolism and Meningiomas

Peptide metabolism alterations manifest through plasma epiandrosterone sulfate (inverse correlation) and CSF homostachydrine/cortisol (positive correlations). The sexual dimorphism in meningioma incidence and cortisol's modulation of steroid hormone receptors suggest endocrine-metabolic crosstalk in tumorigenesis.[42] Acylcarnitine profiling reveals contrasting associations for short-chain (butyrylcarnitine, positive) versus long-chain (laurylcarnitine, negative) species, implicating fatty acid metabolism in MGM pathophysiology.

Study Limitations

While our study provides novel insights into metabolite-associated MGM pathogenesis, several limitations must be acknowledged.

1. Population Specific Bias – Our MR analysis was conducted using GWAS data exclusively from European cohorts, potentially limiting generalizability across ethnic groups.
2. Lack of Experimental Validation – The causal relationships identified require further validation through experimental and clinical studies.
3. Statistical Adjustments – As an exploratory study, multiple testing adjustments were limited, although we employed multiple MR methodologies to ensure robustness.

An important limitation of the two-sample MR analysis conducted herein lies in the pronounced sample size disparity between the exposure and outcome datasets (689/7,824: 379,509). As a result, we applied a more relaxed threshold and used weaker instruments for the analysis ($P<1\times10^{-5}$). This imbalance may introduce multiple methodological concerns.

Firstly, the difference in sample sizes may inflate the FDR, as the large outcome sample size amplifies the significance of instrument bias, thereby significantly increasing the probability of type I errors and potentially reducing the likelihood of type II errors.

Secondly, the relatively small sample size of the exposure dataset may lead to the "winner's curse" phenomenon—due to sampling variability, the effect sizes of genetic variants associated with the exposure may be overestimated. This issue is particularly evident when the exposure GWAS lacks sufficient statistical power to robustly detect true associations. The winner's curse can further inflate the instrument-exposure association, thereby exacerbating the bias in MR causal effect estimates, especially when the outcome sample size is large.

Thirdly, despite implementing sensitivity analyses such as MR-Egger regression and MR-PRESSO, the imbalance in sample sizes may exacerbate residual pleiotropy, where genetic instruments influence the outcome through non-target exposure pathways, leading to confounding effects. Although these biases were assessed and mitigated through sensitivity analyses, the risk of overestimated causal effects and potential residual pleiotropy due to unequal sample sizes cannot be entirely ruled out.

Therefore, due to the presence of these potential sources of bias, the Mendelian randomization approach may not completely rule out the possibility of vertical pleiotropy or violations of the exclusion restriction assumption. Consequently, interpretations of the results should be approached with caution, particularly for metabolites exhibiting notably strong OR, as further in-depth experimental validation is warranted to clarify their true biological relevance and research potential.

Conclusions

In this study, we investigated the potential causal relationships between metabolites in cerebrospinal fluid and plasma and the development of meningioma. Provides evidence consistent with a causal role for the identified metabolites. These findings aim to further advance the application of metabolomics in elucidating meningioma the pathogenic mechanisms of meningioma and underscore the potential utility of plasma and CSF metabolites as valuable diagnostic and prognostic indicators.

This study provides novel insights into the metabolic landscape of meningiomas, providing indicative value for early detection, tumor grading, and prognosis assessment. Future investigations, including large-scale validation studies and mechanistic explorations, are warranted to confirm these findings and facilitate their translation into clinical applications.

Abbreviations

MGM, Meningioma; CNS, Central nervous system; WHO, World Health Organization; CSF, Cerebrospinal fluid; MR, Mendelian randomization; RCT, Randomized controlled trial; IV, Instrumental variable; IVW, Inverse Variance Weighted, GWAS, Genome-wide association study; SNP, Single nucleotide polymorphism; ORs, Odds ratios; G3P, Glycerol-3-phosphate; TCA, Tricarboxylic acid; LC-HRMS, Liquid chromatography-high resolution mass spectrometry; HR-MAS NMR, High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance; CKD, Chronic kidney disease; EdU, 5-ethynyl-2'-deoxyuridine; STROBE-MR, Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University (Approval No. QYFYwzll30212).

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Disclosure

The authors declare no competing interests.

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