

Mendelian randomization identifies the characteristic plasma metabolite profile of meningioma

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Abstract

Introduction: Meningioma, a prevalent intracranial tumor, presents diagnostic and therapeutic challenges due to its heterogeneous nature. Metabolic profiling has emerged as a promising approach to elucidate its underlying molecular mechanisms and discover potential biomarkers.

Material and methods: This study employed bidirectional Mendelian randomization (MR) analysis to investigate the causal relationship between plasma metabolites and meningioma risk. Genetic instruments were used as surrogates for both plasma metabolites and meningioma, allowing MR analysis in both directions to assess the impact of metabolites on meningioma risk and vice versa. This study encompassed data on 1400 plasma metabolites and 314,708 participants (1316 individuals diagnosed with meningioma and 313,392 individuals without meningioma).

Results: Initially, 46 plasma metabolites/metabolite ratios were found to be associated with meningioma risk ($p < 0.05$), with 23 associated with a decreased risk and 23 associated with an increased risk of meningioma. Furthermore, the identified relationships between the 46 plasma metabolites/metabolite ratios and meningioma showed no significant horizontal pleiotropy ($p > 0.05$), suggesting that the results are not influenced by other confounding factors. Reverse MR analysis revealed that meningioma has no significant impact on the levels of 24 plasma metabolites/metabolite ratios, and is unaffected by confounding factors. In addition, the identified plasma metabolites influence the occurrence of meningioma through nine metabolic pathways.

Conclusions: The findings of this bidirectional MR study indicate that 24 plasma metabolites/metabolite ratios lead to a significantly increased/decreased risk of meningioma, suggesting that the plasma metabolite profile characteristics serve as important serological tools for the early diagnosis of meningioma.

Key words: Mendelian randomization, characteristic, plasma metabolite, profile, meningioma.

Introduction

Meningioma [1–3], a prevalent intracranial tumor originating from the meninges, represents a significant clinical challenge due to its varied presentation and heterogeneous nature. It accounts for a substantial pro-

portion of central nervous system (CNS) tumors, representing 37.6% of primary tumors within the CNS and 53.3% of benign neoplasms in this region [4]. Additionally, its incidence tends to escalate with advancing age, indicating that the likelihood of diagnosis increases as individuals grow older. The median age at diagnosis for meningioma is reported to be 66 years [4]. The common clinical manifestations of meningioma include headaches resulting from increased intracranial pressure, as well as generalized and partial seizures triggered by focal neurological deficits or local mass effects affecting the central nervous system [5]. Numerous factors can contribute to the development of meningioma, including hormonal factors [6] and head trauma [7]. Despite typically being classified as benign, certain subtypes of meningioma [8–10] exhibit aggressive behavior, which underscores the importance of prompt diagnosis and the implementation of tailored treatment strategies. While traditional diagnostic modalities, such as neuroimaging techniques, are indispensable in clinical practice, they may sometimes lack specificity and fail to capture the underlying molecular complexities that drive meningioma progression, highlighting the need for more advanced diagnostic approaches.

In recent years, there has been a growing interest in utilizing metabolomics [11, 12], a high-throughput approach for profiling small molecule metabolites in biological samples, to elucidate the intricate metabolic alterations linked to

a wide array of diseases [13, 14], including cancer [15]. Metabolic profiling provides a comprehensive snapshot of cellular physiology and has the potential to reveal metabolic dysregulations that may precede obvious pathological changes, thus offering considerable promise for early detection, prognosis, and the development of targeted therapeutic interventions. Plasma metabolites refer to the diverse array of small molecules found in the blood plasma that are the products of various metabolic processes occurring within the body. These metabolites include sugars, amino acids, lipids, hormones, and other organic compounds that play essential roles in cellular metabolism and physiological functions. The profiling of plasma metabolites provides valuable insights into the metabolic status of an individual and can be used to identify metabolic dysregulations associated with diseases, such as type 2 diabetes [16], colorectal cancer [17], gut microbiome [18] and cardiometabolic health [19]. However, the relationship between the characteristic plasma metabolite profile and meningioma remains largely unknown.

Mendelian randomization (MR) [20–25], an innovative analytical method, capitalizes on genetic variants as instrumental variables (IVs) to infer causal relationships between modifiable exposures and disease outcomes. By mimicking the random allocation of alleles during meiosis, MR enables researchers to assess the potential causal effects of plasma metabolites on meningioma risk

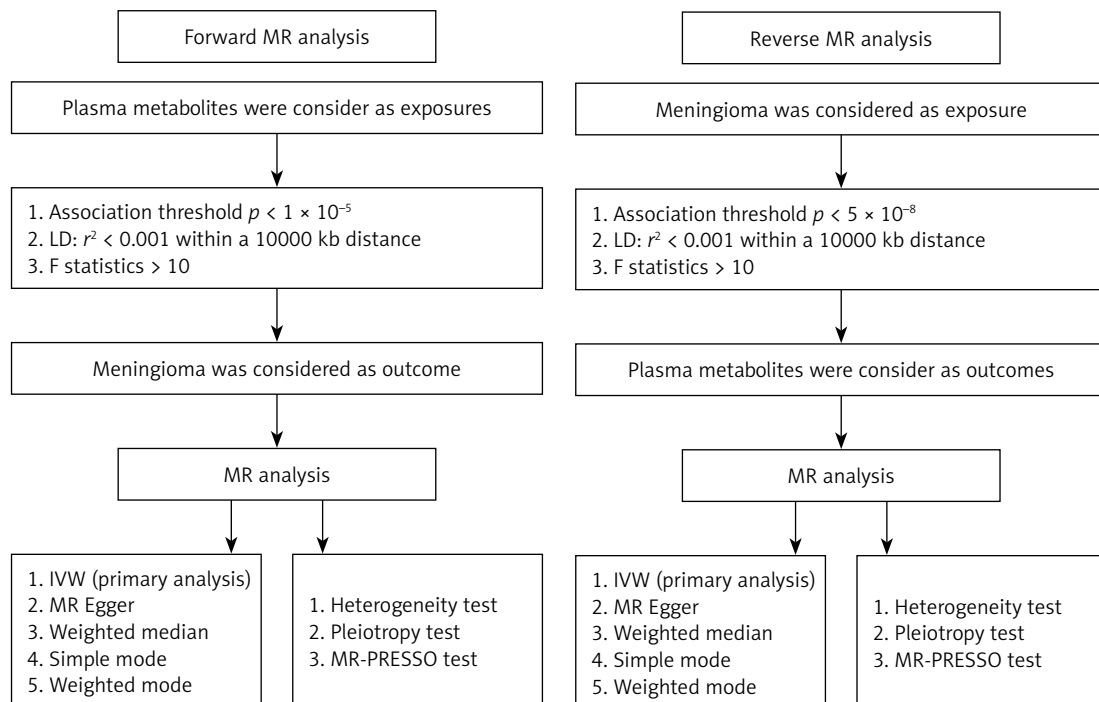


Figure 1. Study flowchart

MR – Mendelian randomization, LD – linkage disequilibrium, IVW – inverse variance weighted.

and vice versa, providing insights into the underlying biological mechanisms. In this study, we employed MR analysis aiming to elucidate the causal relationship between plasma metabolites and meningioma risk.

Material and methods

Study design

We employed a two-sample MR analysis, leveraging large-scale genome-wide association studies (GWAS), to accurately investigate the causal relationship between plasma metabolites and the risk of meningioma. Subsequently, reverse MR analysis was conducted to demonstrate the causal impact of meningioma on plasma metabolites, providing a comprehensive understanding of the bidirectional relationship between these variables. This study is built upon three foundational assumptions of MR [20, 26, 27]: (1) genetic variants, specifically IVs, display a strong association with the exposure; (2) IVs are devoid of any correlation with confounding factors; and (3) the effect of IVs on the outcome is solely mediated through the exposure, excluding involvement in alternative pathways. This study was performed according to the relevant MR guidelines, and Figure 1 provides a brief overview of the process of this bidirectional MR study.

Ethical considerations

This study used GWAS data that had been previously published. In each study, participants provided informed consent and obtained ethical approval from their respective institutional review boards. Consequently, ethical approval was deemed unnecessary, as the study exclusively used summarized data and did not contain any patient information.

GWAS data for blood metabolites

The GWAS data for plasma metabolites were obtained from the study by Chen *et al.* [28], which included approximately 8,000 participants of European descent. These plasma metabolite GWAS data are accessible through the GWAS catalog (<https://www.ebi.ac.uk/gwas/>), with accession numbers ranging from GCST90199621 to GCST90201020. This extensive dataset provides

a wealth of information on the genetic associations underlying plasma metabolite profiles in individuals of European ancestry. The information regarding blood metabolites GWAS is described in Table I.

GWAS data for meningioma

The data for the meningioma GWAS were obtained from the FinnGen database (<https://www.finnngen.fi/>), a comprehensive repository encompassing a cohort of 314,708 participants of European descent. Among these participants, 1,316 individuals were diagnosed with meningioma, while 313,392 individuals were without meningioma. This extensive dataset offers valuable insights into the genetic factors contributing to meningioma susceptibility in individuals of European ancestry. Table I provides information regarding meningioma GWAS.

IV selection

Following the three fundamental assumptions of MR analysis, we used publicly available GWAS databases to select IVs for our study. A thorough screening process was conducted to address issues of linkage disequilibrium (LD) among genetic variants and to explore the causal relationship between plasma metabolites and meningioma. This involved employing clump window sizes of $r^2 = 0.001$ and $\text{kb} = 10\,000$ to mitigate LD issues. Additionally, we applied a significance threshold of $p < 1 \times 10^{-5}$ to filter IVs strongly associated with plasma metabolites, aiming for comprehensive coverage of relevant genetic variants. Furthermore, we examined the correlation of selected IVs with potential confounding factors. The screening process for confounding factors primarily involved searching the IEU OpenGWAS project (<https://gwas.mrcieu.ac.uk/>) and the GWAS catalog (<https://www.ebi.ac.uk/gwas/>), where single nucleotide polymorphisms (SNPs) associated with factors such as age, obesity, smoking, alcohol consumption, renal dysfunction, cardiovascular diseases, medication use, and other tumors were excluded from our study to ensure the robustness and accuracy of our analysis. In the reverse MR analysis, aimed at elucidating the causal association between meningioma and plasma metabolites, we implemented a rigorous threshold of $p < 5 \times 10^{-8}$.

Table I. Genome-wide association studies (GWAS) data included in this Mendelian randomization study

GWAS data	Journal/source	Sample size
Plasma metabolites	Nature Genetics	Approximately 8000 participants of European ancestry.
Meningioma	FinnGen	A total of 314,708 participants of European descent (1,316 with meningioma and 313,392 without meningioma).

to meticulously identify IVs strongly correlated with meningioma. The other screening criteria were consistent with the criteria specified above. Following this selection process, we conducted an exploration of the causal relationship between the identified IVs associated with meningioma and plasma metabolites.

Furthermore, we calculated the F-statistic to identify and eliminate weak IVs. Those with an F-statistic below 10 were considered weak and consequently removed from the analysis. The F-statistic was calculated using the following formula [29-31]: $F\text{-statistics} = R^2 \times (N - 2) / (1 - R^2)$, $R^2 = 2 \times \beta^2 \times \text{EAF} \times (1 - \text{EAF}) / [2 \times \beta^2 \times \text{EAF} \times (1 - \text{EAF}) + 2 \times \text{SE}^2 \times N \times \text{EAF} \times (1 - \text{EAF})]$. N – sample size for exposure; EAF – effect allele frequency for exposure; β – estimated effect.

Metabolic pathway analysis

We used the online platform MetaboAnalyst 6.0 (<https://www.metaboanalyst.ca/>) to conduct a comprehensive analysis of the metabolic pathways through which plasma metabolites may influence the occurrence of meningioma. This process predominantly incorporates the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, providing a robust framework for identifying and elucidating the specific biochemical pathways implicated in the pathogenesis of meningioma.

Statistical analysis

This study extensively investigated the causal relationships between plasma metabolites and meningioma, as well as the bidirectional causal association between meningioma and plasma metabolites. The primary method used for estimating causal effects was the inverse variance-weighted (IVW) method [29–32]. In instances of substantial heterogeneity, random-effects IVW analysis was performed, while fixed-effects IVW was employed when heterogeneity was absent. Additionally, four supplementary MR methods – MR-Egger, weighted median, simple mode, and weighted mode – were applied to conduct sensitivity analyses and assess the causal connection between plasma metabolites and meningioma, and vice versa. With the inclusion of 1400 plasma metabolites in this investigation, consistent findings across IVW, MR Egger, weighted median, simple mode, and weighted mode were considered significant only when estimated values, whether positive or negative, consistently indicated a notable association between plasma metabolites and meningioma, as well as vice versa. The results were presented using odds ratios (OR) or β coefficients and their respective 95% confidence intervals (CI).

Moreover, to ensure the robustness of our findings, we conducted supplementary sensitivity analyses, which included assessing potential heterogeneity and horizontal pleiotropy. Heterogeneity was evaluated using IVW and MR Egger regression techniques, with Cochran's Q statistic serving as the primary measure. A p -value surpassing 0.05 for both IVW and MR Egger Cochran's Q tests indicated the absence of significant heterogeneity, while values below 0.05 suggested its presence. Additionally, we examined the intercept in MR Egger regression to gauge the impact of horizontal pleiotropy on our results. An intercept approaching 0 with a p -value exceeding 0.05 suggested a lack of horizontal pleiotropy, indicating that confounding factors did not influence the causal relationship. Conversely, a markedly deviated intercept with a p -value below 0.05 indicated potential confounding effects. Furthermore, we employed MR-PRESSO analysis to identify and address significant outliers. The analytical procedures for this MR investigation were conducted using RStudio statistical software (version 4.2.2) and the TwoSampleMR package (version 0.5.6). Results were deemed statistically significant when p -values were less than 0.05.

Results

Causal relationships between plasma metabolites and meningioma risk

According to the criteria outlined above, a total of 46 plasma metabolites and metabolite ratios were ultimately found to be associated with the risk of meningioma. Among these, 23 were linked to a decreased risk, including: glycerophosphorylcholine (GPC) levels (OR = 0.792, 95% CI: 0.632 to 0.992), 3-methyl-2-oxovalerate levels (OR = 0.733, 95% CI: 0.541 to 0.992), kynurenine levels (OR = 0.826, 95% CI: 0.687 to 0.992), 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels (OR = 0.764, 95% CI: 0.588 to 0.992), glutamine degradant levels (OR = 0.764, 95% CI: 0.628 to 0.928), pregnenediol sulfate ($\text{C}_{21}\text{H}_{34}\text{O}_5\text{S}$) levels (OR = 0.807, 95% CI: 0.664 to 0.980), 2,3-dihydroxy-2-methylbutyrate levels (OR = 0.723, 95% CI: 0.523 to 0.999), 3-phosphoglycerate levels (OR = 0.751, 95% CI: 0.594 to 0.949), plasma lactate levels (OR = 0.751, 95% CI: 0.583 to 0.968), X-12216 levels (OR = 0.794, 95% CI: 0.634 to 0.995), X-13507 levels (OR = 0.776, 95% CI: 0.606 to 0.995), X-12844 levels (OR = 0.805, 95% CI: 0.689 to 0.941), X-16087 levels (OR = 0.819, 95% CI: 0.693 to 0.968), X-21742 levels (OR = 0.786, 95% CI: 0.628 to 0.983), S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio (OR = 0.764, 95% CI: 0.614 to 0.951), adenosine 5'-diphosphate (ADP) to creatine ratio

(OR = 0.853, 95% CI: 0.731 to 0.994), arginine to ornithine ratio (OR = 0.817, 95% CI: 0.692 to 0.965), aspartate to citrulline ratio (OR = 0.721, 95% CI: 0.564 to 0.923), palmitate (16:0) to myristate (14:0) ratio (OR = 0.670, 95% CI: 0.468 to 0.958), histidine to pyruvate ratio (OR = 0.761, 95% CI: 0.636 to 0.911), adenosine 5'-monophosphate (AMP) to valine ratio (OR = 0.779, 95% CI: 0.638 to 0.950), tryptophan to tyrosine ratio (OR = 0.807, 95% CI: 0.668 to 0.976), and threonine to pyruvate ratio (OR = 0.850, 95% CI: 0.725 to 0.995). Conversely, 23 plasma metabolites and metabolite ratios were associated with an increased risk of meningioma, including: tartronate (hydroxymalonate) levels (OR = 1.305, 95% CI: 1.103 to 1.543), 1-linoleoylglycerol (18:2) levels (OR = 1.409, 95% CI: 1.015 to 1.954), 2-hydroxyglutarate levels (OR = 1.271, 95% CI: 1.053 to 1.535), 6-oxopiperidine-2-carboxylate levels (OR = 1.252, 95% CI: 1.056 to 1.485), sphingomyelin (d18:2/14:0, d18:1/14:1) levels (OR = 1.351, 95% CI: 1.059 to 1.722), 1-dihomo-linolenylglycerol (20:3) levels (OR = 1.343, 95% CI: 1.050 to 1.717), 4-hydroxychlorothalonil levels (OR = 1.280, 95% CI: 1.061 to 1.545), methylsuccinoylcarnitine levels (OR = 1.197, 95% CI: 1.043 to 1.374), carotene diol (1) levels (OR = 1.206, 95% CI: 1.022 to 1.423), methyl vanillate sulfate levels (OR = 1.191, 95% CI: 1.018 to 1.394), arachidonate (20:4n6) levels (OR = 1.269, 95% CI: 1.085 to 1.486), cystathionine levels (OR = 1.263, 95% CI: 1.061 to 1.504), serine levels (OR = 1.238, 95% CI: 1.063 to 1.442), arachidate (20:0) levels (OR = 1.216, 95% CI: 1.014 to 1.458), X-11315 levels (OR = 1.262, 95% CI: 1.069 to 1.489), X-12221 levels (OR = 1.273, 95% CI: 1.023 to 1.583), X-12680 levels (OR = 1.362, 95% CI: 1.052 to 1.764), X-23654 levels (OR = 1.195, 95% CI: 1.024 to 1.395), X-25957 levels (OR = 1.351, 95% CI: 1.024 to 1.781), 3-methylcytidine levels (OR = 1.145, 95% CI: 1.033 to 1.270), adenosine 5'-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio (OR = 1.157, 95% CI: 1.011 to 1.325), phosphate to acetoacetate ratio (OR = 1.209, 95% CI: 1.008 to 1.449), and paraxanthine to linoleate (18:2n6) ratio (OR = 1.293, 95% CI: 1.014 to 1.648). The relationships between the 46 plasma metabolites/metabolite ratios and meningioma elucidated by IVW are depicted in Figure 2, while the relationships between the 46 plasma metabolites/metabolite ratios and meningioma elucidated by the five methods are presented in Supplementary Table S1.

Heterogeneity test of plasma metabolites and meningioma

The heterogeneity test results for the 46 plasma metabolites/metabolite ratios and meningi-

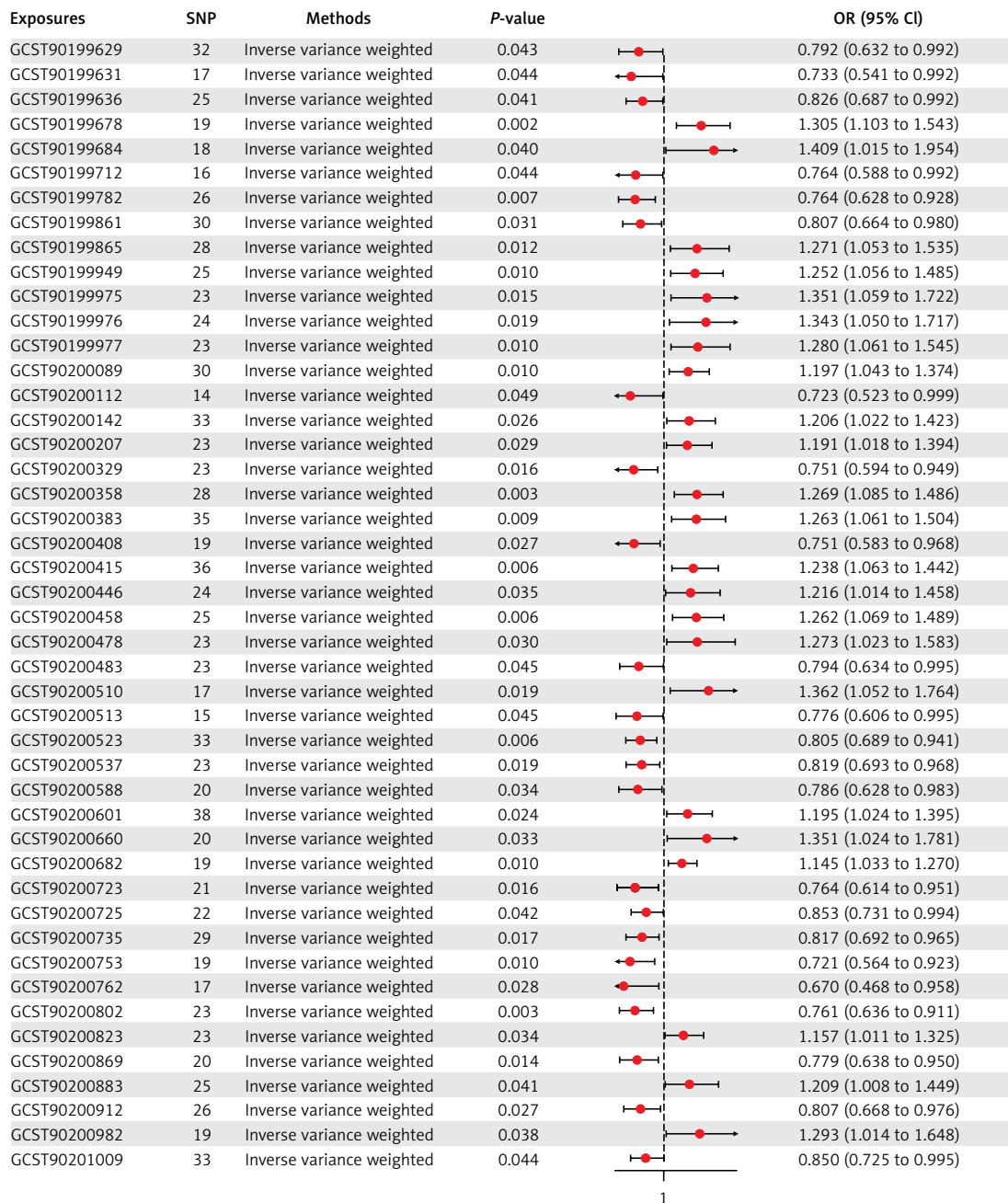
oma are presented in Table II. The IVW method revealed significant heterogeneity in the relationships between glycerophosphorylcholine (GPC) levels (Cochran's Q test = 46.694, $p = 0.035$) and the palmitate (16:0) to myristate (14:0) ratio (Cochran's Q test = 26.455, $p = 0.048$) with meningioma. Similarly, the MR Egger method indicated significant heterogeneity in the relationship between 1-dihomo-linolenylglycerol (20:3) levels and meningioma (Cochran's Q test = 34.449, $p = 0.044$). Interestingly, regardless of whether the IVW or MR Egger method was employed, a significant association was detected between the S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio and meningioma ($p < 0.05$). Furthermore, no significant heterogeneity was observed in the relationship between meningioma and the remaining plasma metabolites ($p > 0.05$).

Horizontal pleiotropy testing of plasma metabolites and meningioma

The assessment of horizontal pleiotropy for the 46 plasma metabolites and meningioma is presented in Table III. As depicted, the intercepts for the relationships between the 46 plasma metabolites/metabolite ratios and meningioma tended towards 0, indicating minimal evidence of horizontal pleiotropy. The scatter plot illustrating the relationships between the 46 plasma metabolites/metabolite ratios and meningioma is presented in Supplementary Figure S1. Moreover, all p -values associated with these intercepts exceeded 0.05, further suggesting the absence of significant horizontal pleiotropy. This implies that the relationships between the 46 plasma metabolites/metabolite ratios and meningioma are unlikely to be influenced by other confounding factors.

Causal relationship between meningioma and plasma metabolites

We further investigated the impact of meningioma on the identified 46 plasma metabolites/metabolite ratios using reverse MR analysis. Based on the established criteria, we found no significant effect of meningioma on 24 plasma metabolites/metabolite ratios, including 3-methyl-2-oxovalerate levels, kynurenine levels, tartronate (hydroxymalonate) levels, CMPF levels, glutamine degradant levels, 1-dihomo-linolenylglycerol (20:3) levels, 4-hydroxychlorothalonil levels, 2,3-dihydroxy-2-methylbutyrate levels, carotene diol (1) levels, methyl vanillate sulfate levels, plasma lactate levels, serine levels, arachidate (20:0) levels, X-11315 levels, X-12216 levels, X-13507 levels, X-23654 levels, 3-methylcytidine levels, adenosine 5'-diphosphate (ADP) to creatine ratio, arginine to ornithine ratio, palmitate (16:0) to myristate

**Figure 2.** Causal relationship between plasma metabolites and meningioma risk

MR – Mendelian randomization, SNP – single nucleotide polymorphisms, OR – odds ratio, CI – confidence interval. GCST90199629: glycerophosphorylcholine (GPC) levels; GCST90199631: 3-methyl-2-oxovalerate levels; GCST90199636: kynurenine levels; GCST90199678: tartronate (hydroxymalonate) levels; GCST90199684: 1-linoleoylglycerol (18:2) levels; GCST90199712: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels; GCST90199782: glutamine degradant levels; GCST90199861: pregnenediol sulfate ($C_{21}H_{34}O_5S$) levels; GCST90199865: 2-hydroxyglutarate levels; GCST90199949: 6-oxopiperidine-2-carboxylate levels; GCST90199975: sphingomyelin (d18:2/14:0, d18:1/14:1) levels; GCST90199976: 1-dihomo-linolenylglycerol (20:3) levels; GCST90199977: 4-hydroxychlorothalonil levels; GCST90200089: methylsuccinoylcarnitine levels; GCST90200112: 2,3-dihydroxy-2-methylbutyrate levels; GCST90200142: carotene diol (1) levels; GCST90200207: methyl vanillate sulfate levels; GCST90200329: 3-phosphoglycerate levels; GCST90200358: arachidonate (20:4n6) levels; GCST90200383: cystathionine levels; GCST90200408: plasma lactate levels; GCST90200415: serine levels; GCST90200446: arachidate (20:0) levels; GCST90200458: X-11315 levels; GCST90200478: X-12221 levels; GCST90200483: X-12216 levels; GCST90200510: X-12680 levels; GCST90200513: X-13507 levels; GCST90200523: X-12844 levels; GCST90200537: X-16087 levels; GCST90200588: X-21742 levels; GCST90200601: X-23654 levels; GCST90200660: X-25957 levels; GCST90200682: 3-methylcytidine levels; GCST90200723: S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio; GCST90200725: adenosine 5'-diphosphate (ADP) to creatine ratio; GCST90200735: arginine to ornithine ratio; GCST90200753: aspartate to citrulline ratio; GCST90200762: palmitate (16:0) to myristate (14:0) ratio; GCST90200802: histidine to pyruvate ratio; GCST90200823: adenosine 5'-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio; GCST90200869: adenosine 5'-monophosphate (AMP) to valine ratio; GCST90200883: phosphate to acetoacetate ratio; GCST90200912: tryptophan to tyrosine ratio; GCST90200982: paraxanthine to linoleate (18:2n6) ratio; GCST90201009: threonine to pyruvate ratio.

Table II. Heterogeneity test of plasma metabolites and meningioma

Outcome	Exposures	Methods	Cochran's Q test	P-value
Meningioma	Glycerophosphorylcholine (GPC) levels	MR Egger	46.436	0.028
Meningioma	Glycerophosphorylcholine (GPC) levels	IVW	46.694	0.035
Meningioma	3-Methyl-2-oxovalerate levels	MR Egger	12.702	0.625
Meningioma	3-Methyl-2-oxovalerate levels	IVW	12.720	0.693
Meningioma	Kynurenine levels	MR Egger	12.558	0.961
Meningioma	Kynurenine levels	IVW	14.299	0.940
Meningioma	Tartronate (hydroxymalonate) levels	MR Egger	19.789	0.285
Meningioma	Tartronate (hydroxymalonate) levels	IVW	19.801	0.344
Meningioma	1-Linoleoylglycerol (18:2) levels	MR Egger	22.691	0.122
Meningioma	1-Linoleoylglycerol (18:2) levels	IVW	23.330	0.139
Meningioma	3-Carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels	MR Egger	13.445	0.492
Meningioma	3-Carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels	IVW	13.603	0.556
Meningioma	Glutamine degradant levels	MR Egger	17.604	0.822
Meningioma	Glutamine degradant levels	IVW	19.450	0.775
Meningioma	Pregnenediol sulfate (C ₂₁ H ₃₄ O ₅ S) levels	MR Egger	22.965	0.735
Meningioma	Pregnenediol sulfate (C ₂₁ H ₃₄ O ₅ S) levels	IVW	23.265	0.764
Meningioma	2-Hydroxyglutarate levels	MR Egger	28.896	0.316
Meningioma	2-Hydroxyglutarate levels	IVW	29.050	0.358
Meningioma	6-Oxopiperidine-2-carboxylate levels	MR Egger	20.562	0.608
Meningioma	6-Oxopiperidine-2-carboxylate levels	IVW	20.668	0.658
Meningioma	Sphingomyelin (d18:2/14:0, d18:1/14:1) levels	MR Egger	14.215	0.860
Meningioma	Sphingomyelin (d18:2/14:0, d18:1/14:1) levels	IVW	14.860	0.868
Meningioma	1-Dihomo-linolenylglycerol (20:3) levels	MR Egger	34.449	0.044
Meningioma	1-Dihomo-linolenylglycerol (20:3) levels	IVW	35.206	0.050
Meningioma	4-Hydroxychlorothalonil levels	MR Egger	24.802	0.256
Meningioma	4-Hydroxychlorothalonil levels	IVW	25.104	0.292
Meningioma	Methylsuccinoylcarnitine levels	MR Egger	22.350	0.765
Meningioma	Methylsuccinoylcarnitine levels	IVW	22.692	0.790
Meningioma	2,3-Dihydroxy-2-methylbutyrate levels	MR Egger	9.365	0.671
Meningioma	2,3-Dihydroxy-2-methylbutyrate levels	IVW	9.747	0.715
Meningioma	Carotene diol (1) levels	MR Egger	20.824	0.916
Meningioma	Carotene diol (1) levels	IVW	24.056	0.842
Meningioma	Methyl vanillate sulfate levels	MR Egger	22.518	0.370
Meningioma	Methyl vanillate sulfate levels	IVW	22.761	0.415
Meningioma	3-Phosphoglycerate levels	MR Egger	20.988	0.460
Meningioma	3-Phosphoglycerate levels	IVW	21.803	0.472
Meningioma	Arachidonate (20:4n6) levels	MR Egger	25.389	0.497
Meningioma	Arachidonate (20:4n6) levels	IVW	25.799	0.530
Meningioma	Cystathionine levels	MR Egger	29.022	0.666
Meningioma	Cystathionine levels	IVW	30.553	0.637
Meningioma	Plasma lactate levels	MR Egger	21.155	0.219
Meningioma	Plasma lactate levels	IVW	22.601	0.206
Meningioma	Serine levels	MR Egger	22.176	0.941
Meningioma	Serine levels	IVW	22.590	0.948
Meningioma	Arachidate (20:0) levels	MR Egger	13.963	0.903

Table II. Cont.

Outcome	Exposures	Methods	Cochran's Q test	P-value
Meningioma	Arachidate (20:0) levels	IVW	14.623	0.908
Meningioma	X-11315 levels	MR Egger	24.225	0.391
Meningioma	X-11315 levels	IVW	24.250	0.447
Meningioma	X-12221 levels	MR Egger	22.779	0.356
Meningioma	X-12221 levels	IVW	23.081	0.397
Meningioma	X-12216 levels	MR Egger	25.696	0.218
Meningioma	X-12216 levels	IVW	25.865	0.258
Meningioma	X-12680 levels	MR Egger	16.543	0.347
Meningioma	X-12680 levels	IVW	16.563	0.414
Meningioma	X-13507 levels	MR Egger	10.951	0.615
Meningioma	X-13507 levels	IVW	11.457	0.650
Meningioma	X-12844 levels	MR Egger	28.184	0.612
Meningioma	X-12844 levels	IVW	28.258	0.657
Meningioma	X-16087 levels	MR Egger	19.999	0.521
Meningioma	X-16087 levels	IVW	20.040	0.581
Meningioma	X-21742 levels	MR Egger	22.658	0.204
Meningioma	X-21742 levels	IVW	22.742	0.249
Meningioma	X-23654 levels	MR Egger	32.570	0.633
Meningioma	X-23654 levels	IVW	32.586	0.676
Meningioma	X-25957 levels	MR Egger	23.381	0.176
Meningioma	X-25957 levels	IVW	23.383	0.221
Meningioma	3-Methylcytidine levels	MR Egger	18.733	0.344
Meningioma	3-Methylcytidine levels	IVW	19.225	0.378
Meningioma	S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio	MR Egger	30.885	0.042
Meningioma	S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio	IVW	32.894	0.035
Meningioma	Adenosine 5'-diphosphate (ADP) to creatine ratio	MR Egger	14.648	0.796
Meningioma	Adenosine 5'-diphosphate (ADP) to creatine ratio	IVW	16.074	0.765
Meningioma	Arginine to ornithine ratio	MR Egger	20.007	0.830
Meningioma	Arginine to ornithine ratio	IVW	21.400	0.808
Meningioma	Aspartate to citrulline ratio	MR Egger	13.147	0.726
Meningioma	Aspartate to citrulline ratio	IVW	14.054	0.726
Meningioma	Palmitate (16:0) to myristate (14:0) ratio	MR Egger	23.169	0.081
Meningioma	Palmitate (16:0) to myristate (14:0) ratio	IVW	26.455	0.048
Meningioma	Histidine to pyruvate ratio	MR Egger	12.219	0.934
Meningioma	Histidine to pyruvate ratio	IVW	12.363	0.949
Meningioma	Adenosine 5'-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio	MR Egger	22.387	0.378
Meningioma	Adenosine 5'-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio	IVW	24.166	0.339
Meningioma	Adenosine 5'-monophosphate (AMP) to valine ratio	MR Egger	18.403	0.429
Meningioma	Adenosine 5'-monophosphate (AMP) to valine ratio	IVW	19.119	0.449
Meningioma	Phosphate to acetoacetate ratio	MR Egger	22.120	0.513
Meningioma	Phosphate to acetoacetate ratio	IVW	22.374	0.557
Meningioma	Tryptophan to tyrosine ratio	MR Egger	24.368	0.441

Table II. Cont.

Outcome	Exposures	Methods	Cochran's Q test	P-value
Meningioma	Tryptophan to tyrosine ratio	IVW	24.557	0.487
Meningioma	Paraxanthine to linoleate (18:2n6) ratio	MR Egger	13.325	0.714
Meningioma	Paraxanthine to linoleate (18:2n6) ratio	IVW	13.749	0.745
Meningioma	Threonine to pyruvate ratio	MR Egger	34.732	0.295
Meningioma	Threonine to pyruvate ratio	IVW	34.732	0.339

IVW – inverse variance weighted, MR – Mendelian randomization.

(14:0) ratio, tryptophan to tyrosine ratio, paraxanthine to linoleate (18:2n6) ratio, and threonine to pyruvate ratio, suggesting that the occurrence of meningioma has no notable influence on the levels of these 24 plasma metabolites/metabolite ratios. The results are depicted in Table IV and Supplementary Table SII.

Heterogeneity test of meningioma and plasma metabolites

Supplementary Table SIII presents the results of the heterogeneity test examining the association between meningioma and plasma metabolites/metabolite ratios. According to the MR Egger method, a notable level of heterogeneity was observed in the relationship between meningioma and serine levels (Cochran's Q test = 5.252, $p = 0.022$), indicating significant variability in this association. Similarly, the IVW method also revealed significant heterogeneity in the relationship between meningioma and adenosine 5'-diphosphate (ADP) to creatine ratio (Cochran's Q test = 6.005, $p = 0.050$). However, no significant heterogeneity was detected in the relationship between meningioma and other plasma metabolites, suggesting a more consistent association in those cases.

Horizontal pleiotropy testing of meningioma and plasma metabolites

Supplementary Table SIV provides an overview of the assessment of horizontal pleiotropy between meningioma and 24 plasma metabolites/metabolite ratios. Importantly, the analysis revealed no significant horizontal pleiotropy in the relationship between meningioma and these 24 plasma metabolites/metabolite ratios. This suggests that the association between meningioma and the examined plasma metabolites remains unaffected by potential confounding factors.

Metabolic pathway analysis

The KEGG analysis indicates that the identified plasma metabolites influence the occurrence of meningioma through nine metabolic pathways: valine, leucine, and isoleucine biosynthesis; butanoate metabolism; ether lipid metabolism; gly-

cine, serine, and threonine metabolism; cysteine and methionine metabolism; glycerophospholipid metabolism; biosynthesis of unsaturated fatty acids; valine, leucine, and isoleucine degradation; and tryptophan metabolism (Figure 3).

Discussion

Key findings

Our bidirectional MR analysis initially revealed significant associations between 46 plasma metabolites/metabolite ratios and meningioma risk, with 23 associated with a decreased risk and 23 associated with an increased risk of meningioma. Importantly, these relationships showed no significant horizontal pleiotropy, indicating that they are not influenced by other confounding factors. Additionally, reverse MR analysis demonstrated that meningioma has no significant impact on the levels of 24 plasma metabolites/metabolite ratios and is unaffected by confounding factors. Finally, the main finding of this study is that 24 plasma metabolites/metabolite ratios are significantly associated with the occurrence of meningioma, with 13 associated with a decreased risk and 11 associated with an increased risk of meningioma. In addition, the identified plasma metabolites influence the occurrence of meningioma through nine metabolic pathways. These findings underscore the potential of plasma metabolite profiles as serological tools for the early diagnosis of meningioma and suggest implications for precision medicine and targeted therapeutic interventions.

Plasma metabolites and meningioma

The relationship between plasma metabolites and meningioma has been a subject of increasing interest due to its potential implications for both understanding the pathogenesis of meningioma and identifying biomarkers for early detection. The investigation conducted by Masalha *et al.* [33], involved a comparative analysis of 43 individuals diagnosed with either low- or high-grade meningiomas, including 28 cases of grade I meningiomas, 12 cases of grade II meningiomas, and 3 cases of grade III meningiomas. Their results

Table III. Horizontal pleiotropy testing of plasma metabolites and meningioma

Outcome	Exposures	Egger intercept	P-value
Meningioma	Glycerophosphorylcholine (GPC) levels	-0.013	0.687
Meningioma	3-methyl-2-oxovalerate levels	0.006	0.896
Meningioma	Kynurenine levels	0.044	0.200
Meningioma	Tartronate (hydroxymalonate) levels	0.002	0.921
Meningioma	1-Linoleoylglycerol (18:2) levels	-0.035	0.511
Meningioma	3-Carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels	-0.016	0.696
Meningioma	Glutamine degradant levels	0.029	0.187
Meningioma	Pregnenediol sulfate (C ₂₁ H ₃₄ O ₅ S) levels	-0.012	0.589
Meningioma	2-hydroxyglutarate levels	-0.009	0.712
Meningioma	6-oxopiperidine-2-carboxylate levels	0.006	0.748
Meningioma	Sphingomyelin (d18:2/14:0, d18:1/14:1) levels	0.019	0.431
Meningioma	1-Dihomo-linolenylglycerol (20:3) levels	-0.027	0.494
Meningioma	4-Hydroxychlorothalonil levels	-0.013	0.619
Meningioma	Methylsuccinoylcarnitine levels	0.012	0.563
Meningioma	2,3-dihydroxy-2-methylbutyrate levels	-0.027	0.548
Meningioma	Carotene diol (1) levels	-0.045	0.082
Meningioma	Methyl vanillate sulfate levels	-0.021	0.639
Meningioma	3-Phosphoglycerate levels	0.030	0.377
Meningioma	Arachidonate (20:4n6) levels	0.013	0.528
Meningioma	Cystathionine levels	-0.028	0.225
Meningioma	Plasma lactate levels	0.041	0.296
Meningioma	Serine levels	0.014	0.524
Meningioma	Arachidate (20:0) levels	0.021	0.425
Meningioma	X-11315 levels	-0.004	0.879
Meningioma	X-12221 levels	0.020	0.603
Meningioma	X-12216 levels	-0.014	0.714
Meningioma	X-12680 levels	-0.006	0.895
Meningioma	X-13507 levels	-0.022	0.489
Meningioma	X-12844 levels	-0.007	0.786
Meningioma	X-16087 levels	0.005	0.842
Meningioma	X-21742 levels	0.008	0.799
Meningioma	X-23654 levels	-0.002	0.901
Meningioma	X-25957 levels	0.002	0.968
Meningioma	3-methylcytidine levels	-0.013	0.513
Meningioma	S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio	-0.042	0.280
Meningioma	Adenosine 5'-diphosphate (ADP) to creatine ratio	-0.028	0.246
Meningioma	Arginine to ornithine ratio	-0.027	0.248
Meningioma	Aspartate to citrulline ratio	-0.052	0.354
Meningioma	Palmitate (16:0) to myristate (14:0) ratio	0.068	0.165
Meningioma	Histidine to pyruvate ratio	-0.008	0.708
Meningioma	Adenosine 5'-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio	0.030	0.210
Meningioma	Adenosine 5'-monophosphate (AMP) to valine ratio	0.019	0.414
Meningioma	Phosphate to acetoacetate ratio	0.013	0.619
Meningioma	Tryptophan to tyrosine ratio	-0.011	0.670
Meningioma	Paraxanthine to linoleate (18:2n6) ratio	-0.023	0.524
Meningioma	Threonine to pyruvate ratio	0.000	0.988

Table IV. Causal relationship between meningioma and plasma metabolites

Exposure	Outcomes	Method	Number of SNP	β	95% CI	P-value
Meningioma	3-Methyl-2-oxovalerate levels	IVW	3	0.013	−0.091 to 0.117	0.804
Meningioma	Kynurenine levels	IVW	3	0.018	−0.057 to 0.093	0.635
Meningioma	Tartronate (hydroxymalonate) levels	IVW	3	0.039	−0.039 to 0.117	0.331
Meningioma	3-Carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF) levels	IVW	3	−0.005	−0.120 to 0.109	0.926
Meningioma	Glutamine degradant levels	IVW	3	0.004	−0.079 to 0.087	0.923
Meningioma	1-Dihomo-linolenylglycerol (20:3) levels	IVW	3	−0.034	−0.120 to 0.052	0.437
Meningioma	4-Hydroxychlorothalonil levels	IVW	3	−0.025	−0.102 to 0.053	0.532
Meningioma	2,3-dihydroxy-2-methylbutyrate levels	IVW	3	−0.028	−0.104 to 0.049	0.479
Meningioma	Carotene diol (1) levels	IVW	3	−0.014	−0.092 to 0.063	0.715
Meningioma	Methyl vanillate sulfate levels	IVW	3	0.068	−0.048 to 0.183	0.249
Meningioma	Plasma lactate levels	IVW	3	0.022	−0.055 to 0.099	0.577
Meningioma	Serine levels	IVW	3	−0.026	−0.212 to 0.160	0.785
Meningioma	Arachidate (20:0) levels	IVW	3	0.046	−0.033 to 0.124	0.256
Meningioma	X-11315 levels	IVW	3	0.037	−0.041 to 0.116	0.352
Meningioma	X-12216 levels	IVW	3	0.073	−0.003 to 0.150	0.060
Meningioma	X-13507 levels	IVW	3	−0.017	−0.096 to 0.062	0.674
Meningioma	X-23654 levels	IVW	3	0.002	−0.079 to 0.082	0.969
Meningioma	3-methylcytidine levels	IVW	3	0.035	−0.054 to 0.123	0.442
Meningioma	Adenosine 5'-diphosphate (ADP) to creatine ratio	IVW	3	0.000	−0.182 to 0.182	0.998
Meningioma	Arginine to ornithine ratio	IVW	3	0.026	−0.063 to 0.115	0.566
Meningioma	Palmitate (16:0) to myristate (14:0) ratio	IVW	3	0.038	−0.036 to 0.113	0.315
Meningioma	Tryptophan to tyrosine ratio	IVW	3	−0.030	−0.136 to 0.077	0.587
Meningioma	Paraxanthine to linoleate (18:2n6) ratio	IVW	3	0.018	−0.062 to 0.097	0.665
Meningioma	Threonine to pyruvate ratio	IVW	3	−0.033	−0.112 to 0.045	0.407

IVW – inverse variance weighted, MR – Mendelian randomization, SNP – single nucleotide polymorphisms, CI – confidence interval.

revealed a marked decrease in the glycine/serine cluster in relation to both the disease grade and proliferation of meningiomas. Moreover, the study identified a significantly prolonged progression-free survival linked to the glycine/serine cluster, suggesting a potential association between metabolite levels and the differentiation and recurrence of meningiomas. Moreover, Talari *et al.* [34] conducted an investigation into the alterations in tryptophan metabolism in human meningiomas. Their findings revealed a preference for the kynurenine (KYN) pathway in tryptophan (TRP) metabolism in human meningiomas, potentially attributed to elevated levels of indoleamine 2,3-dioxygenase 2, with mRNA levels being upregulated in human meningiomas. Additionally, notable increases were observed in KYN and 5-hydroxy indole acetic acid (5-HIAA) levels in meningiomas compared to control meninges, while the levels of TRP, 5-hydroxy tryptamine (5-HT), 5-hydroxy

tryptophan (5-HTP), N-acetyl serotonin (NAS), and melatonin (MEL) were significantly decreased. Similarly, Petersen *et al.* [35], found in their study that meningioma tissues exhibit higher levels of 2-monoacylglycerols compared to human non-tumor brain tissue. Furthermore, they observed an enhanced capacity for phosphatidylcholine to convert into monoacylglycerol and suggested that 2-arachidonoylglycerol, anandamide, and other N-acylethanolamines may serve as endogenous anti-tumor mediators.

To our knowledge, this study represents the first exploration of the relationship between plasma metabolites and meningioma based on large-scale GWAS data, involving 1400 plasma metabolites, 1,316 diagnosed meningioma patients, and 313,392 non-meningioma patients. The results of this study reveal that 24 plasma metabolites/metabolite ratios – 3-methyl-2-oxovalerate levels, kynurenine levels, tartronate (hydroxymalonate)

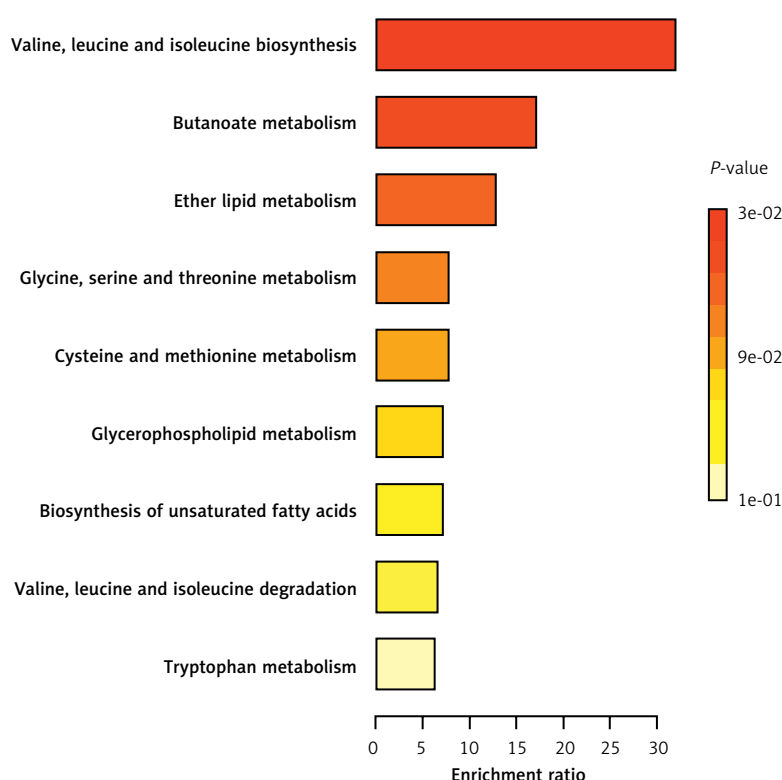


Figure 3. Metabolite sets enrichment overview

levels, CMPF levels, glutamine degradant levels, 1-dihomo-linolenylglycerol (20:3) levels, 4-hydroxy-chlorothalonil levels, 2,3-dihydroxy-2-methylbutyrate levels, carotene diol (1) levels, methyl vanillate sulfate levels, plasma lactate levels, serine levels, arachidate (20:0) levels, X-11315 levels, X-12216 levels, X-13507 levels, X-23654 levels, 3-methylcytidine levels, adenosine 5'-diphosphate (ADP) to creatine ratio, arginine to ornithine ratio, palmitate (16:0) to myristate (14:0) ratio, tryptophan to tyrosine ratio, paraxanthine to linoleate (18:2n6) ratio and threonine to pyruvate ratio – can serve as important serum markers for early prediction of meningioma occurrence. The conclusions of this study are consistent with previous research [33–35], demonstrating the significant predictive ability of meningioma occurrence risk from the perspective of plasma metabolites. Additionally, it is worth noting that while previous studies compared the characteristics of plasma metabolites between patients with high-grade and low-grade meningiomas, this study compared the plasma metabolite characteristics between patients with and without meningioma, providing novel insights for even earlier prediction of meningioma occurrence.

Clinical implications

The identification of specific plasma metabolites associated with meningioma occurrence holds significant clinical implications. Firstly, these findings

provide potential biomarkers for the early detection and diagnosis of meningioma, which could lead to improved patient outcomes through earlier intervention and treatment initiation. Additionally, understanding the metabolic profile characteristic of meningioma could aid in risk stratification and personalized treatment strategies. Furthermore, these findings may open avenues for the development of novel therapeutic targets aimed at modulating the metabolism of meningioma cells. Overall, the integration of plasma metabolite profiling into clinical practice has the potential to enhance the management and treatment of meningioma patients, ultimately contributing to better prognosis and quality of life. In addition, KEGG analysis revealed that the identified plasma metabolites influence the occurrence of meningioma through nine metabolic pathways: valine, leucine, and isoleucine biosynthesis; butanoate metabolism; ether lipid metabolism; glycine, serine, and threonine metabolism; cysteine and methionine metabolism; glycerophospholipid metabolism; biosynthesis of unsaturated fatty acids; valine, leucine, and isoleucine degradation; and tryptophan metabolism. This provides an important theoretical basis for subsequent meningioma treatment and drug development.

Limitations

Firstly, while bidirectional MR analysis provides insights into potential causal relationships,

it is essential to consider the assumptions and limitations of this method, including the reliance on genetic variants as IVs. Secondly, the study's reliance on data from GWAS databases may introduce bias or confounding factors, and the generalizability of the findings may be limited to the populations represented in these datasets. Thirdly, this study identified a series of plasma metabolites associated with the occurrence of meningioma. However, the underlying mechanisms driving these associations remain poorly understood due to a lack of related research. Therefore, there is a pressing need for further mechanistic studies to elucidate the potential pathways through which these metabolites may influence meningioma development, thereby validating the findings of this study and advancing our understanding of meningioma pathogenesis. Finally, we employed MR, which uses genetic variants as IVs to infer causal relationships between exposures (plasma metabolites) and outcomes (meningiomas). In this context, genetic conditions are considered, suggesting that the plasma metabolite profiles identified in this study might be useful for the early detection of meningiomas caused by genetic factors, such as neurofibromatosis type 2 [36, 37]. However, further prospective, multi-center studies are still needed to validate these findings.

In conclusion, our MR study demonstrates the complicated association between plasma metabolites and meningioma, offering potential insights into early diagnosis, risk stratification, and therapeutic interventions. The identification of specific plasma metabolites associated with meningioma occurrence underscores their potential utility as biomarkers for early detection and personalized treatment strategies. However, further research is warranted to elucidate the underlying mechanisms driving these associations and validate the findings in diverse populations.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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