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ORIGINAL RESEARCH

The Causal Association Analysis between Depression and Cerebrospinal Fluid: From the Perspective of Mendelian Randomization

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Background: Major depressive disorder (MDD) leads to significant distress and disruption across social, occupational, and other functional domains. Although cerebrospinal fluid (CSF) biomarkers have been identified as potential indicators and therapeutic targets for depression, their causal relationship with MDD remains unclear.

Methods: We analyzed publicly available CSF metabolomics and genotype data, quantifying 338 distinct metabolites. Among these, 296 were chemically validated and classified into eight major metabolic groups, while 38 remained undefined. To assess the genetic association with depression, we used summary statistics from a GWAS (F5_DEPRESSIO dataset, including 53,313 diagnosed cases and 394,756 controls from Finland). An integrated approach combining Mendelian randomization (MR), inverse variance weighting (IVW), and linkage disequilibrium score regression (LDSC) was applied to explore the causal impact of CSF metabolites on depression risk.

Results: Our analysis identified 62 metabolites significantly associated with depression ($p < 0.05$). Sensitivity tests revealed heterogeneity in five metabolites: 5-hydroxyindoleacetic acid, X-19438, ethylmalonic acid, γ-glutamylglutamine, and β-alanine. A focused analysis on 14 metabolites further supported a potential causal link with depression. LDSC confirmed significant genetic heritability for metabolites such as creatinine, arginine succinate, N-acetylisourea, 3-amino-2-piperidone, and carboxyethyl-GABA. Systematic leave-one-out analyses demonstrated that these associations are driven by multiple interacting SNPs rather than a single variant.

Conclusion: This study provides novel insights into the potential causal relationship between CSF metabolites and depression, highlighting 14 key metabolites with significant associations. The robustness of these findings is supported by MR and sensitivity analyses. Further longitudinal studies are warranted to confirm the clinical relevance of these CSF biomarkers in MDD.

Keywords: depression, cerebrospinal fluid, Mendelian randomization, LDSC, causal association

Introduction

As stated by the World Health Organization, depression impacts 5% of adults globally.[1] Major depressive disorder (MDD) is not only closely associated with increased suicide risk and comorbidities such as cardiovascular diseases and metabolic syndrome but also severely impairs social functioning.[2] Despite ongoing research into the pathophysiological mechanisms of MDD, which include theories such as neurotransmitter imbalances, neuroinflammation, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, these theories fail to fully explain the complex heterogeneity and

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dynamic progression of MDD.[3] To further understand the etiology of depression, there is a need for more biochemical and genetic studies on its pathogenesis.

In exploring disease etiology and diagnosis, the analysis of bodily fluids plays a crucial role. Cerebrospinal fluid (CSF), in particular, holds unique value in the study of neuropsychiatric disorders due to its direct connection with the nervous system and its metabolites, which reflect physiological changes in the central nervous system[4,5]. CSF metabolomics, through the systematic analysis of small molecules such as lipids, amino acids, and neurotransmitter precursors, has successfully identified potential biomarkers for neurodegenerative diseases (eg, Alzheimer's disease), cancers (eg, glioblastoma), and immune-mediated diseases (eg, multiple sclerosis).[6,7] For instance, a recent two-sample Mendelian randomization (MR) study found that 12 CSF metabolites (eg, α-tocopherol, valine) were causally associated with the risk of glioblastoma multiforme (GBM), suggesting that metabolic pathway abnormalities may be central to CNS diseases.[6] Additionally, CSF metabolites have been shown to correlate with the severity and prognosis of traumatic brain injury (TBI), further highlighting their distinctive role in neuropsychiatric research.[7] However, there remains a significant gap in CSF metabolomics research related to MDD: most existing studies are limited to small sample cross-sectional analyses, making it difficult to distinguish between causal relationships and confounding effects, and lacking a systematic analysis of the dynamic regulatory networks of metabolites.

Mendelian randomization (MR) utilizes genetic variations as instrumental variables to effectively mitigate confounding biases inherent in traditional observational studies. It has become a core method for exploring causal relationships between exposure factors and diseases.[8,9] In the field of neuropsychiatric disorders, MR studies have yielded meaningful findings. For example, in Parkinson's disease research, elevated levels of dimethylglycine and glucuronates in CSF were positively associated with PD risk, while plasma metabolites such as tryptophan exhibited protective effects.[10] In psychiatric disorders, MR studies have further confirmed that blood metabolites (eg, acetylornithine) mediate the causal impact on bipolar disorder through neurocognitive functions, providing new targets for metabolic interventions.[9] Nevertheless, the causal role of CSF metabolites in MDD remains unclear, partly due to the following challenges: (1) the difficulty of obtaining CSF samples and the scarcity of large-scale GWAS data; (2) the need for multi-omics support in metabolite functional annotation and pathway integration; (3) the sensitivity of existing MR methods to horizontal pleiotropy and heterogeneity requires optimization.

This study aims to systematically assess the causal effects of CSF metabolites on MDD and explore their underlying mechanisms by integrating CSF metabolomics with MR methods. First, using the latest GWAS summary data (eg, from FinnGen and UK Biobank), we included 338 CSF metabolites and MDD-related genetic instrumental variables, employing multiple methods such as inverse variance weighting (IVW) and MR-Egger regression to validate the robustness of the results.[7,9] Second, we explored the mediating role of neurocognitive functions (eg, the g-factor) in the metabolite-MDD association through mediation analysis, aiming to elucidate the "metabolism-brain function-psychiatric phenotype" cascade pathway.[9] Finally, through metabolic pathway enrichment analysis (eg, KEGG and Reactome), we identified core metabolic modules associated with MDD (eg, tryptophan-kynurenine pathway, lipid remodeling pathway), providing a theoretical basis for developing targeted intervention strategies. This research will not only fill the knowledge gap regarding the causal mechanisms of CSF metabolites in MDD but also promote the development of precision diagnostic and therapeutic strategies based on metabolic regulation.

Materials

Study Design

Figure 1 depicts the research framework. MR is a methodological approach that employs genetic instruments, particularly SNPs, to evaluate the effects of exposures on diverse outcomes and to elucidate causal connections among these variables. The genetic variants chosen as instruments in MR must adhere to three fundamental assumptions: relevance, independence, and exclusion. The two-stage MR analysis requires the fulfillment of the following conditions: (1) a causal link between the exposure and the outcome; (2) a causal association between the mediator and the outcome, independent of the exposure; (3) a causal relationship between the exposure and the mediator. Reverse MR analysis is performed at each stage to ensure that the final positive findings are free from reverse causality.

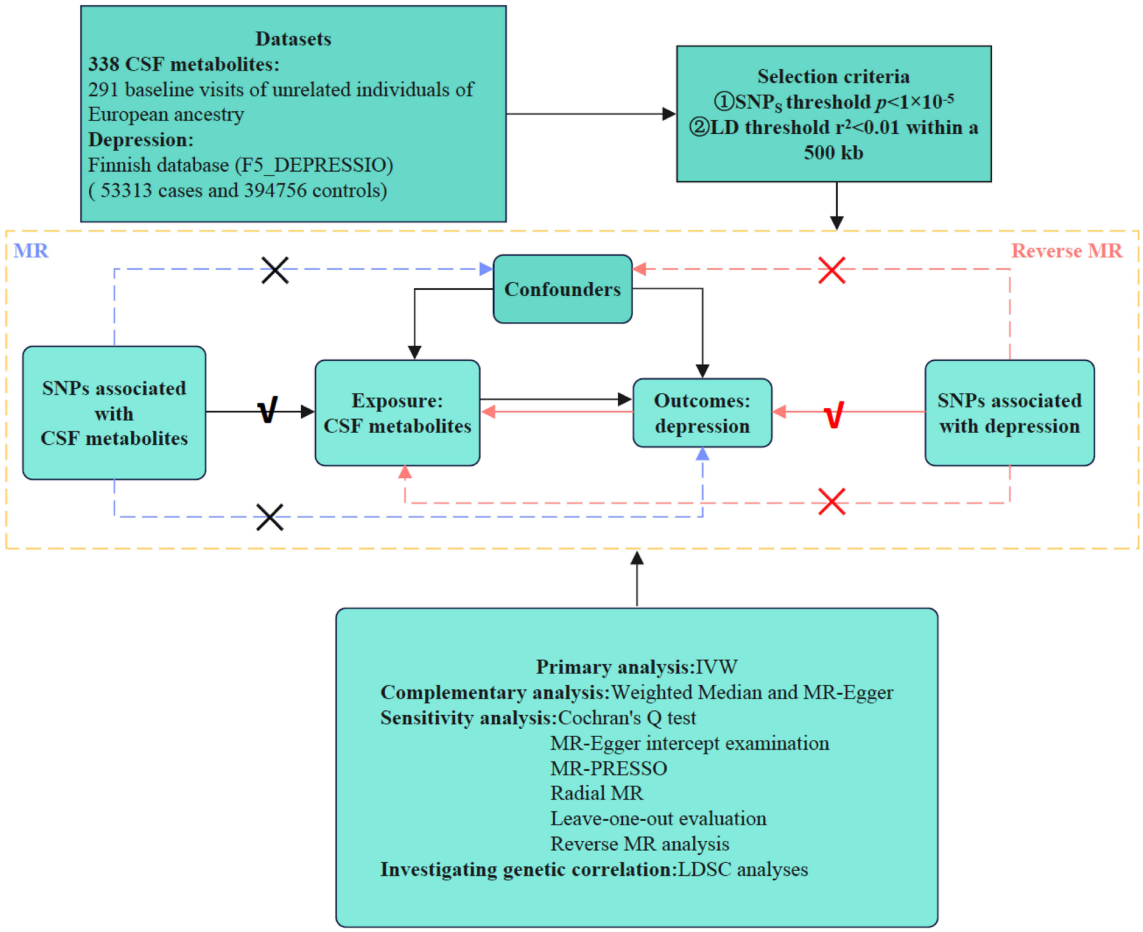

Figure 1 Flow Chart for MR Study. The comprehensive process involves MR, employing methods like IVW and LDSC for analysis.

In our research on metabolic responses related to major depressive disorder, we utilized a dataset encompassing CSF metabolite data and outcomes associated with depression. As illustrated in Figure 1, we extracted CSF metabolite data from publicly available sources of CSF metabolomics and genotype information. This approach resulted in a robust final dataset comprising 291 baseline visits from unrelated individuals of European ancestry. Within this dataset, we identified and quantified a total of 338 distinct CSF metabolites, a process thoroughly documented in the work of Daniel J. Panyard et al.[11] Among the 338 metabolites, 38 are still chemically undefined, whereas 296 have undergone chemical validation and are categorized into eight primary metabolic groups, encompassing amino acid, carbohydrate, cofactor and vitamin, energy, lipid, nucleotide, peptide, and xenobiotic metabolism. Additionally, in order to examine the genetic linkages with depression, we obtained the summary statistics from a genome-wide association study Furthermore, to analyze the genetic associations with depression, we accessed the genome-wide association study (GWAS)(https://www.ebi.ac.uk/gwas/) conducted on the Finnish database (https://www.finngen.fi/en), particularly the F5_DEPRESSIO dataset. For our analysis, we employed the database's most current iteration (R11), which includes a substantial number of participants—53,313 cases of diagnosed depression and 394,756 controls.[12] The categorization of depression followed the guidelines set forth in Tenth Revision (ICD-10), particularly code F32. The categorization of depression followed the guidelines set forth in Tenth Revision (ICD-10), particularly code F32.

Instrumental Variable Selection & Verification

SNPs, which represent genetic variations arising from single-base alterations at the genomic level, are frequently employed in MR analyses to reflect DNA sequence diversity.[13] In this study, we systematically developed a distinct set of instrumental variables (IVs) for each of the 338 CSF metabolites. This methodological approach was adopted to

accurately capture the genetic associations unique to each metabolite. Initially, recognizing the scarcity of SNPs achieving genome-wide significance for metabolites, we adjusted the significance threshold by permitting a p-value of less than 5×10^{-8}. Subsequently, to maintain the independence of the selected SNPs, we applied stringent linkage disequilibrium (LD) criteria, excluding SNPs with an r2 value greater than 0.001 and a genetic distance of less than 10,000 kilobases. Additionally, to address potential bias arising from weak instrument strength, we calculated the F-statistic for each SNP, defining those with an F-value below 10 as weak instruments. The F-statistic was computed using the formula $F = R^2(N - 2)/(1 - R^2)$, where R^2 represents the proportion of variance explained by the SNP, and N denotes the sample size of the GWAS for the SNP. Furthermore, we leveraged the IEU OpenGWAS database to meticulously screen and exclude any SNPs exhibiting significant associations with potential confounders. Finally, we mapped the SNPs associated with CSF metabolites onto the merged GWAS dataset for depression and extracted the relevant statistical parameters.

Statistical Analysis

In the statistical analysis section of our study, which investigates the potential causal relationship between cerebrospinal fluid metabolites and the risk of depression, all analyses were conducted using R software, version 4.2.2. We utilized several methods, including IVW, MR-Egger, Weighted Median, Weighted Mode, and Simple Mode, to estimate the causal effects. Given the higher statistical power of the IVW method compared to other MR techniques, it was chosen as the primary method. The IVW method assumes that all genetic variants serve as valid instrumental variables. It calculates the causal effects for each instrumental variable using the ratio method and then combines these estimates through weighted linear regression to obtain the overall effect. However, the presence of unmeasured confounders may result in genetic pleiotropy and bias in effect size estimation. To address this, MR-Egger regression and the weighted median method were used as secondary approaches to validate the causal relationship between the exposure and the outcome. The "leave-one-out" approach was implemented to identify any instrumental variables that could potentially distort the estimation of causal effects. Horizontal pleiotropy was evaluated using the Egger intercept, and the MR-PRESSO test was conducted to detect and exclude SNPs that might be affected by pleiotropy. Additionally, heterogeneity among SNPs was assessed using the Cochran Q test to evaluate the variability in the data.

Investigating Genetic Linkage and Causal Direction

To address the potential genetic correlation between exposure and outcome variables that may distort MR estimations, ancillary analyses were conducted. It remains plausible that combinations of SNPs, which do not exhibit significant associations with depression, could still contribute to the genetic susceptibility to this disorder. Hence, in order to gauge the possible influence of the shared genetic architecture on the perceived causal relationship, we assessed the genetic correlations between the pinpointed metabolites and depression traits through linkage disequilibrium score regression (LDSC).[14] This approach evaluates the joint inheritance of two traits using SNP-based Chi-squared tests, ensuring causal effects are not confounded by coheritability. Additionally, a reverse MR analysis was conducted to explore causality direction and gauge the effect of depression traits on potential metabolites, reducing reverse causality bias and improving causal insight.

Ethical Pronouncement

This MR study employed GWAS summary stats and shared datasets. All anonymized data were freely accessible and unrestricted, obviating the need for an ethics statement or consent. Approval was granted by the hospital's IRB (Ethics Committee of The Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine, ID: 2024–173).

Results

Analyzing the Association of CSF With Depression

We synthesized IVs for the remaining 338 metabolites related to depression, as detailed in Supplementary Table 1. To explore causal links between metabolites and depression, the IVW method was utilized, leveraging GWAS summary data. Our study revealed 62 robust significant causal associations ($p<0.05$) (Figure 2, Supplementary Table 2).

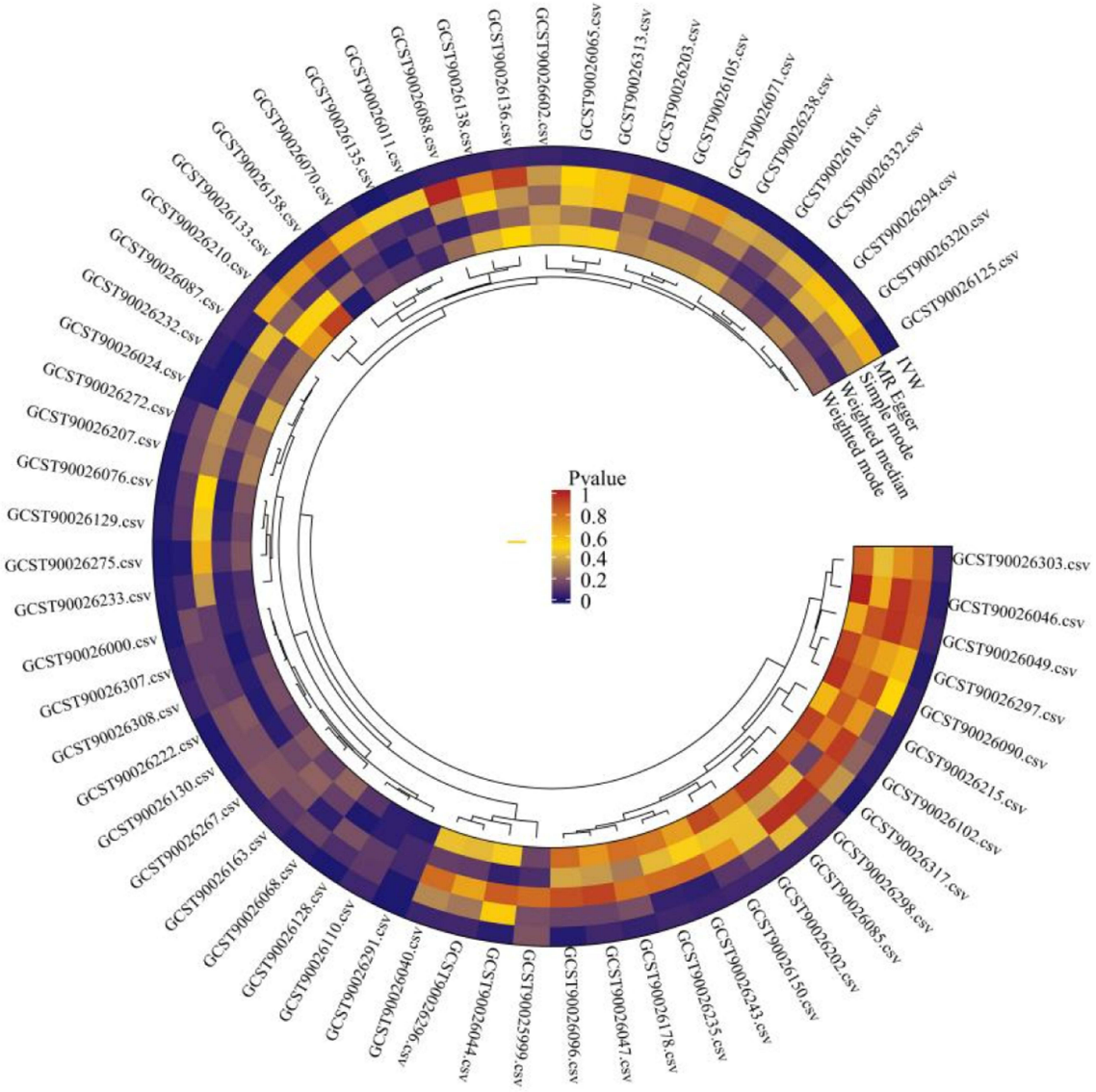

Figure 2 Circular heatmap for CSF metabolites' MR analysis in depression. This figure depicts causal links between 62 identified CSF metabolites and depression, as revealed by MR analysis. Each concentric ring signifies a distinct MR technique: the outermost ring stands for IVW, succeeded by MR-Egger, and the innermost ring denotes weighted median (WMe). The importance of the link between each metabolite and depression is demonstrated by the negative logarithm of the p-value (−log P).

Although the IVW approach successfully uncovers causal relationships, we acknowledged its vulnerability to weak instrument bias. In order to bolster our findings, we undertook further sensitivity analyses and examined pleiotropy. The Cochran's Q test revealed notable heterogeneity across five metabolites: 5-hydroxyindoleacetate, X-19438, Ethylmalonate, Gamma-glutamylglutamine, and Beta-alanine (p<0.05). Horizontal pleiotropy was assessed using MR-Egger regression(Supplementary Table 3), and no identifiable pleiotropic effects were found in the recognized CSF metabolites.

After the initial analysis, we used MR-PRESSO to explore heterogeneity further, revealing outliers in five identical metabolites (p > 0.05) (Figure 3 and Supplementary Tables 4 and 5).

These results indicate a possible link between particular CSF metabolites and depression. These findings do not conclusively demonstrate a direct influence on disease progression. Further investigation, especially longitudinal studies, is essential for deeper insight into these relationships and their implications.

Trails	method	nsnp	pval	OR(95%CI)
Creatinine levels	Inverse variance weighted	98	0.0712	0.9766 (0.9518−1.0020)
Kynurenine levels	Inverse variance weighted	98	0.0819	0.9453 (0.8873−1.0071)
Sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1) levels	Inverse variance weighted	98	0.9172	0.9932 (0.8728−1.1301)
5−oxoproline levels	Inverse variance weighted	98	0.2005	1.0216 (0.9887−1.0557)
1−linoleoyl−gpc (18:2) levels	Inverse variance weighted	98	0.1652	0.9146 (0.8062−1.0375)
2,3−dihydroxyisovalerate levels	Inverse variance weighted	98	0.1362	1.1658 (0.9528−1.4266)
2−hydroxy−3−methylvalerate levels	Inverse variance weighted	43	0.8928	0.9994 (0.9903−1.0085)
2−piperidinone levels	Inverse variance weighted	98	0.2837	1.1259 (0.9064−1.3986)
3−methoxytyrosine levels	Inverse variance weighted	98	0.5095	0.9437 (0.7944−1.1210)
3−methyl−2−oxobutyrate levels	Inverse variance weighted	98	0.8711	1.0029 (0.9684−1.0387)
3−methylglutaconate levels	Inverse variance weighted	43	0.5347	1.0025 (0.9946−1.0105)
4−methyl−2−oxopentanoate levels	Inverse variance weighted	98	0.2379	0.9747 (0.9341−1.0171)
Acetylcarnitine (c2) levels	Inverse variance weighted	98	0.3852	0.9635 (0.8860−1.0478)
Argininosuccinate levels	Inverse variance weighted	98	0.3420	0.9244 (0.7860−1.0871)
Benzoate levels	Inverse variance weighted	98	0.9714	0.9983 (0.9112−1.0938)
Beta−alanine levels	Inverse variance weighted	98	0.4173	0.9817 (0.9387−1.0266)
Beta−citrylglutamate levels	Inverse variance weighted	98	0.6353	1.0153 (0.9537−1.0808)
Carboxyethyl−gaba levels	Inverse variance weighted	98	0.2068	0.9666 (0.9170−1.0189)
Carnitine levels	Inverse variance weighted	98	0.5903	0.9826 (0.9220−1.0473)
Choline levels	Inverse variance weighted	98	<0.05	0.9421 (0.9072−0.9784)
Diglycerol levels	Inverse variance weighted	98	0.4207	0.9705 (0.9022−1.0439)
Ethylmalonate levels	Inverse variance weighted	98	0.3664	1.0321 (0.9637−1.1053)
Gamma−glutamylglutamine levels	Inverse variance weighted	98	0.0578	0.9549 (0.9105−1.0015)
Hippurate levels	Inverse variance weighted	98	0.6405	1.0361 (0.8927−1.2026)
Homocarnosine levels	Inverse variance weighted	98	0.7909	1.0191 (0.8860−1.1723)
Myo−inositol levels	Inverse variance weighted	98	0.1977	0.9440 (0.8647−1.0305)
N−acetyl−isoputreanine levels	Inverse variance weighted	98	0.4535	0.9818 (0.9357−1.0301)
N−acetylputrescine levels	Inverse variance weighted	98	0.8928	0.9969 (0.9528−1.0431)
N1−methyladenosine levels	Inverse variance weighted	98	0.1337	0.9540 (0.8970−1.0146)
N1−methylinosine levels	Inverse variance weighted	98	<0.05	0.9407 (0.8864−0.9983)
N6,n6,n6−trimethyllysine levels	Inverse variance weighted	98	0.2448	0.9701 (0.9217−1.0210)
Nicotinamide riboside levels	Inverse variance weighted	98	0.9236	0.9972 (0.9413−1.0564)
Oxalate (ethanedioate) levels	Inverse variance weighted	98	0.5780	0.9895 (0.9534−1.0270)
Stearoyl sphingomyelin (d18:1/18:0) levels	Inverse variance weighted	98	0.7607	0.9910 (0.9349−1.0504)
Theobromine levels	Inverse variance weighted	98	0.1912	1.1592 (0.9289−1.4465)
Threonate levels	Inverse variance weighted	98	0.6730	0.9906 (0.9480−1.0351)
X−12007 levels	Inverse variance weighted	98	0.1510	1.1841 (0.9402−1.4914)
X−12101 levels	Inverse variance weighted	98	0.0882	0.9163 (0.8288−1.0132)
Ascorbic acid 3−sulfate levels	Inverse variance weighted	98	0.4803	1.0581 (0.9046−1.2376)
X−12906 levels	Inverse variance weighted	98	0.4662	0.9786 (0.9234−1.0372)
X−18887 levels	Inverse variance weighted	98	0.1849	0.9142 (0.8006−1.0439)
X−19438 levels	Inverse variance weighted	98	0.2509	0.8482 (0.6404−1.1235)
X−23587 levels	Inverse variance weighted	98	0.5099	0.9168 (0.7080−1.1872)
X−23639 levels	Inverse variance weighted	98	0.1066	0.8797 (0.7530−1.0279)
3−amino−2−piperidone levels	Inverse variance weighted	98	0.2618	0.9678 (0.9139−1.0248)

Figure 3 The Forest plot displays the MR of depression and CSF. Inverse variance weighting derived OR & 95% CI. OR < 1 indicated protection; OR > 1 suggested causation.

Abbreviations: OR, odds ratio; CI, confidence interval; nsnp, number of single nucleotide polymorphisms.

Exploring Specific CSF Metabolite Links in Depression

In relation to CSF metabolites, 14 metabolites were found to have a suggestive causal relationship with the risk of depression. CSF metabolites 14 were recognized to possess an indicative causal link to depression risk (Figure 4).Among these, X−12007 and X−23587 are classified as unknown products.

The following are the 95% confidence intervals (CI) and odds ratios (OR) associated with the identified metabolites: Creatinine levels (95% CI 0.1816 to 0.7596, OR 0.37, p= 0.006), 2−piperidinone levels (95% CI 0.7040 to 0.9491, OR 0.82,

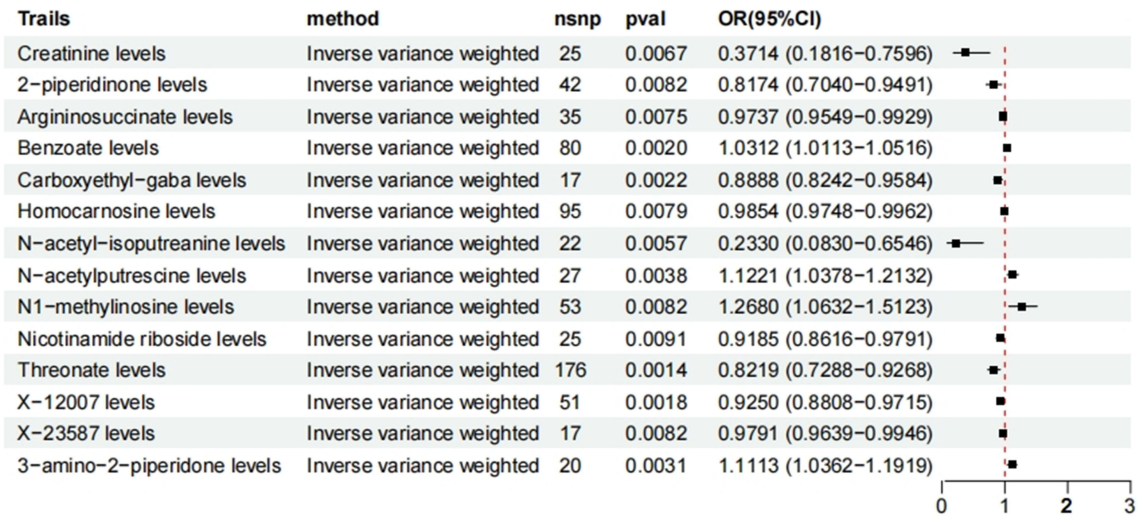

Figure 4 Forest plot illustrating causal estimations between depression and CSF metabolites. Using inverse variance weighting, we calculated the OR with a 95% CI. OR values <1 indicated protective effects, while values >1 suggested pathogenic links.
Abbreviations: OR, odds ratio; CI, confidence interval; nsnp, number of single nucleotide polymorphisms.

p= 0.008), Argininosuccinate levels (95% CI 0.9549 to 0.9929, OR 0.97, *p*=0.007), Benzoate levels (95% CI 1.0113 to 1.0516, OR 1.03, *p*=0.002), Carboxyethyl−GABA levels (95% CI 0.8242 to 0.9584, OR 0.89, *p*=0.002), Homocarnosine levels (95% CI 0.9748 to 0.9962, OR 0.99, *p*=0.008), N−acetyl−isoputreanine levels (95% CI 0.0830 to 0.6546, OR 0.23, *p*=0.006), N−acetylputrescine levels (95% CI 1.0378 to 1.2132, OR 1.12, *p* = 0.004), N1−methylinosine levels (95% CI 1.0632 to 1.5123, OR 1.27, p = 0.008), Nicotinamide riboside levels (95% CI 0.8616 to 0.9791, OR 0.92, *p*=0.009), Threonate levels (95% CI 0.7288 to 0.9268, OR 0.82, *p*=0.001), X−12007 levels (95% CI 0.8808 to 0.9715, OR 0.93, *p*=0.002), X−23587 levels (95% CI 0.9639 to 0.9946, OR 0.98, *p*=0.008), and 3−amino−2−piperidone levels (95% CI 1.0362 to 1.9946, OR 1.11, *p*=0.003) were also recognized as factors that contribute to the risk of depression. Significant insights into the associations between CSF metabolites and depression are provided by these findings.

Assessing Genetic Impacts on Depression and CSF Metabolites

In order to alleviate the potential confounding factors that may arise due to the alignment between exposure and outcomes, we utilized the method of LDSC. This was done to explore the genetic correlation between the screened metabolites and depression. CSF metabolites demonstrated notable heritability in the LDSC analyses conducted to assess their genetic underpinnings (Supplementary Table 6). Such as creatinine, argininosuccinate, N-acetyl-isoputreanine, 3-amino-2-piperidone and carboxyethyl-gaba. Notably, 3-amino-2-piperidone demonstrated an exceptionally high heritability, with a single nucleotide polymorphism (SNP)-based liability-scale heritability (h^2) value of 2.535 (*p*=0.01). Carboxyethyl-gaba also exhibited a pronounced genetic impact, Indicating by the h^2 measurement of 2.441 (*p*=0.01) (Supplementary Table 7). To provide further evidence of the causal link between five metabolites and depression, a systematic leave-one-out analysis was performed.

To provide further evidence of the causal link between five metabolites and depression, a systematic leave-one-out analysis was performed. It was clearly indicated that the links were not due to a single SNP, but instead originated from the combined effect of multiple SNPs.

Furthermore, scatter plots were utilized to visually depict the conclusions derived from every sensitivity examination, offering an instinctual and graphical comprehension of the analytical procedures (Figure 5). These findings additionally strengthen the validity of our MR assessments and highlight the discovered links between CSF metabolites and depression.

Discussion

In this study, we systematically investigated the potential causal relationship between cerebrospinal fluid (CSF) metabolites and depression susceptibility from a genetic epidemiology perspective using a Mendelian randomization

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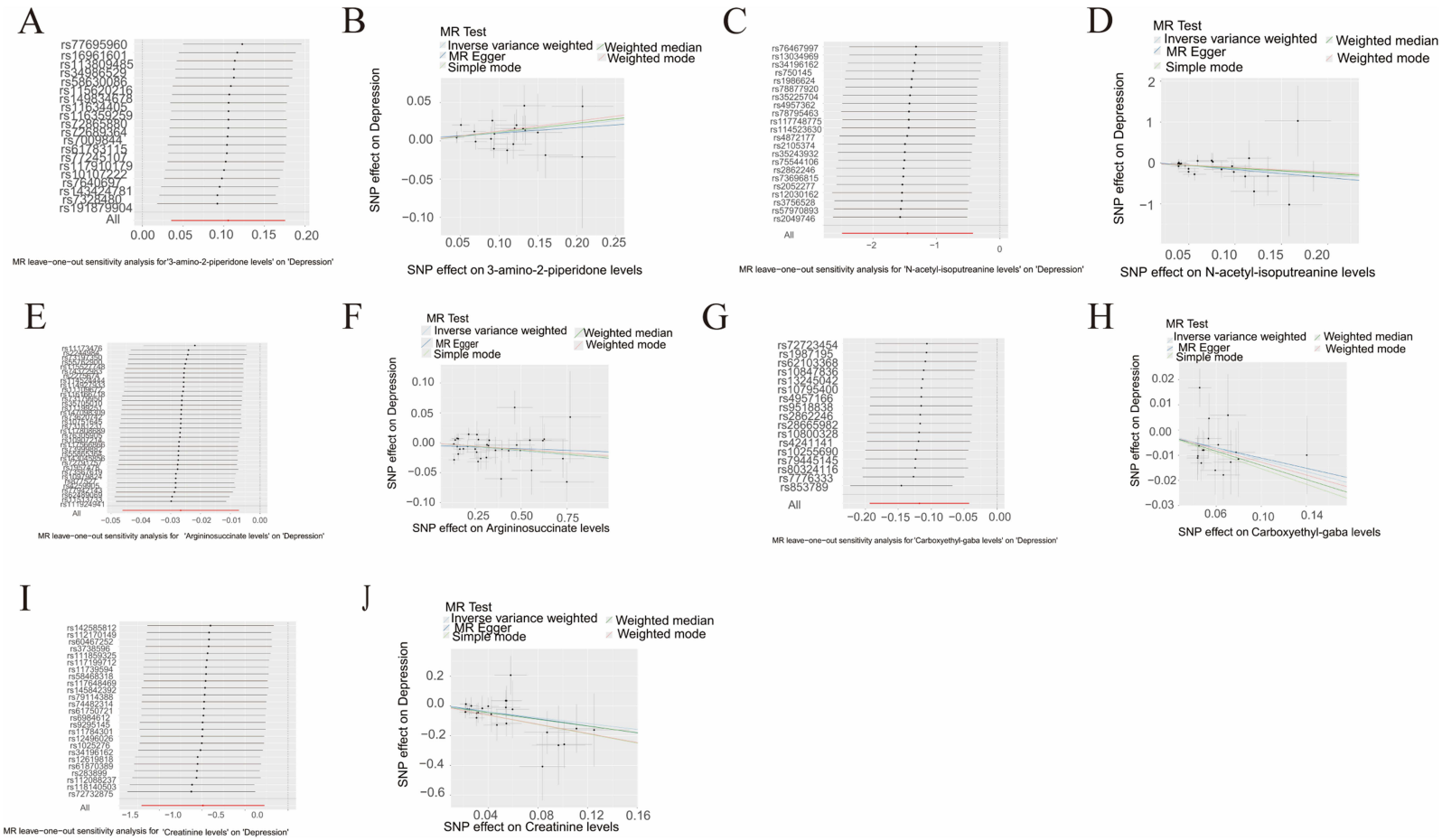

Figure 5 The risk of developing depression is causally associated with five different CSF metabolites.3-amino-2-piperidone and depression: (**A**) Leave one out, (**B**) scatter plot; N−acetylputrescine and depression: (**C**) Leave one out, (**D**) scatter plot; argininosuccinate and depression: (**E**) Leave one out, (**F**) scatter plot; carboxyethyl−GABA and depression: (**G**) Leave one out, (**H**) scatter plot; N−acetylputrescine and depression: (**I**) Leave one out, (**J**) scatter plot.

(MR) approach. Initially, 62 CSF metabolites associated with depression were screened, and after rigorous sensitivity analyses—including inverse variance weighted (IVW) analysis, MR-Egger regression, weighted median, and weighted mode methods—we confirmed that 12 metabolites exhibited statistically significant associations with depression Table 1). These findings not only reveal the multidimensional role of CSF metabolites in the pathophysiology of depression but also provide a new theoretical basis for biomarker-based precision diagnosis and personalized interventions (Figure 6).

Biological Significance of CSF Metabolites in Depression

Our results indicate that metabolites such as creatinine, 2-piperidinone, succinylarginine, benzoate, carboxyethyl-γ-aminobutyric acid, high muscle peptide, N-acetyl-isocytosine, N-acetylcorhamine, N1-methylmyosine, nicotinamide riboside, sucrose acid, and 3-amino-2-piperidinone are closely related to depression. These metabolites are involved in several critical biological processes including neurotransmitter metabolism, inflammatory regulation, and neuroplasticity. For instance, N1-Methylinosine primarily influences the formation and consolidation of cognitive processes through the modulation of specific receptors, particularly muscarinic acetylcholine receptors.[15,16] Furthermore, the mechanism by which N1-Methylinosine is correlated with interleukin-6 (IL-6) and lipopolysaccharides (LPS) has been highlighted.[15,17] Additionally, magnesium L-threonate has been shown to prevent depressive behavior and synaptic alteration.[18] The

Table 1 The Potential Relationship Between Cerebrospinal Fluid Metabolites and Depression

Metabolite	Relationship with Depression	Related Pathways/Influences
Creatinine	Associated with depression, may affect immune - inflammatory responses	Related to the levels of immune responses and inflammatory markers
2 - Pyrrolidone	Positively correlated with the risk of depression	Associated with cognitive impairment and inflammatory responses
Argininosuccinic Acid	Correlated with the severity of depression, with decreased plasma arginine levels	Amino acid metabolism, immune imbalance
Benzoate	Associated with depression, affects neurotransmitter balance	Influence on neurotransmitter regulation and BDNF
N-(2 - Carboxyethyl) -gamma-aminobutyric Acid (GABA)	(GABA)Significantly associated with depression, may affect the homeostasis of inhibitory neurotransmitters	GABA metabolism, neurotransmitter regulation
Homoarginine	Associated with depression, may affect the regulation of excitatory transmission in the GABA system	GABA metabolism, neurotransmitter regulation
N-Acetylalloisoleucine	Associated with depression, may affect cognitive and behavioral functions	Cognitive function, neurotransmitter pathway
N - Acetylornithine	Associated with depression, may affect cellular energy metabolism and amino acid balance	Cellular energy metabolism, immune regulation
N1- - Methylnicotinamide	Associated with depression, may affect cognitive processes by regulating acetylcholine receptors	Acetylcholine system, immune - inflammatory responses
Nicotinamide Riboside	Associated with depression, may affect neuroinflammation and synaptic plasticity	Neural plasticity, anti - inflammation, anti - apoptosis
Taurine	Associated with depression, may affect neuroinflammatory responses through the regulation of astrocytes	Neuroinflammation, immune regulation, astrocytes
3 - Amino - 2 - pyrrolidone	Associated with depression, may affect the levels of inflammatory factors and immune responses	Inflammatory responses, immune regulation
5- - Hydroxyindoleacetic Acid	Associated with depression, affects the function of the limbic system	5 - HT metabolism, emotional regulation

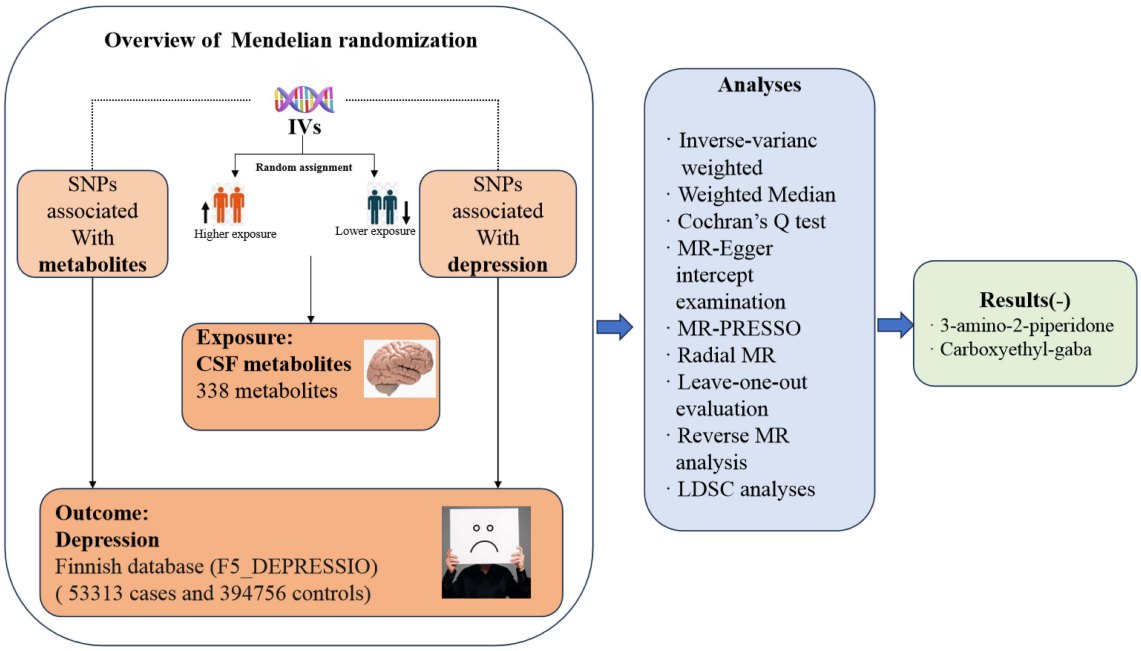

Figure 6 Visual depiction of Mendelian randomization outcomes. Schematic of Mendelian randomization outcomes. A red plus signifies risk factors.
Abbreviations: MR, Mendelian Randomization; LDSC, Linkage Disequilibrium Score Regression.

mechanism potentially underlying the metabolite's impact on depression entails suppressing IL-1β expression in glial cells through ERK1/2 and PPARγ signaling.[19] Amino acids are vital not only as protein building blocks, but also for immune system function. Compounds such as benzoates, N-Acetyl-isoputreanine, argininosuccinic acid, N-acetyl putrescine, 3-amino-2-piperidone, and threonate are closely related to amino acids. Imbalances in amino acid metabolism may contribute to depression's immunopathogenesis.

Moreover, benzoates participate in the regulatory processes of glycine within the central nervous system.[20] Recent studies suggest that benzoate boosts BDNF and protein kinase A levels in the prefrontal cortex, possibly aiding in alleviating depressive symptoms.[20] N-acetylisopurine, an amino acid derivative, plays a role in various aspects of neurotransmitter transmission, metabolic pathway regulation, and cognitive and behavioral effects.[21] The mechanism underlying cognitive impairment may be associated with the enzymatic action of aldehyde dehydrogenase (ALDH) and polyamine metabolism.[22] Argininosuccinic acid, known for its neurotoxic properties, along with its metabolites such as arginine, is negatively correlated with the severity of depression. The research report indicates that plasma arginine levels are significantly reduced in those suffering from MDD.[23] The underlying cause of depression might be associated with reduced levels of arginine, leading to decreased concentrations of glutathione (GSH) and elevated production of reactive oxygen species within both the cerebral cortex and striatum.[24] In-depth pathway analysis has identified N-acetyl putrescine (NAP) as a metabolite produced during cells' utilization of primary energy sources like glucose and specific amino acids for growth and protein synthesis.[25] Studies suggest that depression and anxiety, evaluated via HADS, can be diagnosed using clinical measurements. Furthermore, 3-amino-2-piperidone, a derivative of ornithine, is associated with both ornithine and interleukin-8 (IL-8).[26] Its effect on depression may be linked to inflammation. Previous research has also established connections between gamma-aminobutyric acid (GABA), nicotinamide riboside (NR), and creatinine with depression.[27–29] Carboxyethyl-GABA and homocarnosine, GABA derivatives detected in human CSF, play a role as inhibitory neurotransmitters, regulating excitatory transmission.[30] NR has been shown to reduce DNA damage, neuroinflammation, and apoptosis while enhancing hippocampal synaptic plasticity in mouse models.[31] It also protects against axonal degeneration and sensory neuropathy, significantly alleviating depression-like behaviors in mice.[32] Creatinine levels in CSF of depressive patients positively correlate with inflammation, immune responses.[33] In conclusion, we speculate that the biological mechanisms linking CSF and depression may involve the modulation of inflammatory

factors. Additional studies, both ex vivo and in vivo, are needed to elucidate the roles of metabolites in depression, potentially guiding new treatments.

Integrated Regulation of Inflammation, Neurotransmitters, and Neural Networks

The development of depression is closely associated with inflammatory responses, and previous studies have demonstrated a tight link between various metabolites and inflammatory processes. In our study, several amino acids and their derivatives (eg, N-acetyl-isocytosine, N-acetylcorhamine, and succinylarginine) not only play crucial roles in protein synthesis but may also influence immune system function, thereby participating in the immunopathogenesis of depression. Furthermore, alterations in neurotrophic factors in the CSF reflect the state of neuroplasticity. Notably, decreased levels of 5-hydroxyindoleacetic acid (5-HIAA) in the CSF of depressed patients are closely associated with limbic system dysfunction. When blood–brain barrier permeability is increased, peripheral inflammatory factors (eg, IL-6) may enter the CSF, further triggering neuroinflammation and affecting the survival and function of neurons in both the limbic system and the prefrontal cortex. Additionally, changes in CSF composition may disrupt the functional connectivity of the default mode network (DMN) and salience network, thereby exerting far-reaching effects on self-referential processing, introspection, and responses to external stimuli. Collectively, these findings indicate that alterations in CSF metabolites are not only a key component of the pathophysiology of depression but also critical regulators of neural network dysfunction.

Clinical Applications and Future Research Directions

Currently, the diagnosis of depression relies predominantly on psychological assessment tools such as the Hospital Anxiety and Depression Scale (HADS) and the Hamilton Depression Rating Scale (HAMD), which have limitations in capturing the subjective symptoms of patients. We propose that future studies integrate CSF metabolites as objective biomarkers with traditional psychological assessments to construct a multimodal diagnostic system, thereby improving diagnostic accuracy and early warning capabilities. Moreover, based on the key metabolites identified in this study, subsequent research should focus on functional studies and clinical trials to validate their causal roles in the onset and treatment of depression. Specifically, future research should focus on the following aspects:

Causal Validation and Clinical Trial Design: Conduct randomized controlled trials (RCTs) to further validate the causal relationship between CSF metabolites and depression, and to explore the impact of interventions targeting specific metabolites on disease progression and treatment outcomes. Construction of a Multimodal Diagnostic System: Integrate CSF biomarkers with existing psychological diagnostic tools to develop comprehensive evaluation models for early warning, risk stratification, and monitoring treatment response. Exploration of Novel Drug Targets: Elucidate the mechanisms by which key metabolites regulate neuroinflammation, neurotransmitter balance, and neural network function to provide molecular targets and theoretical foundations for the development of novel antidepressants.

Study Limitations

Although this study employed rigorous statistical methods and sensitivity analyses to ensure the robustness of the results, several limitations remain. First, the participant data were derived from a specific population, and the geographical and ethnic composition of the sample may limit the generalizability of the findings. Second, while MR methods can effectively reduce confounding bias and reverse causality, further in vitro and in vivo experiments as well as clinical trials are needed to validate the biological significance and translational potential of these associations.

Conclusion

In summary, this study, using a Mendelian randomization approach, revealed complex genetic associations between CSF metabolites and depression, providing a new perspective for exploring the pathogenesis of depression. By delineating the roles of key metabolites in neuroinflammation, neurotransmitter regulation, and neural network function, our findings not only indicate potential directions for early diagnosis and personalized treatment of depression but also offer robust evidence for further research in related fields. We look forward to future multicenter studies with larger sample sizes to validate these findings and facilitate their translation into clinical practice.

Data Sharing Statement

The original contributions presented in the study are included in the article/supplementary material. For further inquiries, please contact the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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