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Relationship of metabolites and metabolic ratios with schizophrenia: a mendelian randomization study

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Abstract

Background This study aims to investigate the causal relationship of human plasma metabolites and metabolic ratios with schizophrenia (SCZ).

Methods We employed Mendelian Randomization (MR) approach to comprehensively analyze two large-scale metabolomics and schizophrenia Genome-Wide Association Study (GWAS) datasets, incorporating a total of 1091 metabolites and 309 metabolic ratios, with 52017 schizophrenia patients and 75889 healthy controls. The inverse variance-weighted (IVW) method was utilized to estimate the causal relationship between exposure and outcome. To provide a more comprehensive evaluation, additional Mendelian Randomization (MR) approaches were employed, including MR-Egger regression, weighted median, simple mode, and weighted mode methods. These analyses assessed the causal effects between blood metabolites, metabolic ratios, and schizophrenia. Tests for pleiotropy and heterogeneity were conducted. False Discovery Rate (FDR) correction was applied to account for multiple comparisons and heterogeneity, ensuring the robustness and reliability of our findings. Consistent with previous studies, an FDR threshold of < 0.2 was considered suggestive of a causal relationship, while an FDR of < 0.05 was considered to indicate a significant causal relationship.

Results The final results revealed that a significant causal association was found between the levels of two metabolites and schizophrenia, Alliin (OR = 0.915, 95%CI = 0.879–0.953, $P = 1.93 \times 10^{-5}$, FDR = 0.013) was associated with a decreased risk of schizophrenia, N-actylcitrulline (OR = 1.058, 95%CI = 1.034–1.083, $P = 1.4 \times 10^{-6}$, FDR = 0.002) was associated with increased risk of schizophrenia. When adjusting FDR to 0.2, the results showed that 4 metabolite levels and 2 metabolite ratios were suggestively causally associated with a reduced risk of schizophrenia including 2-aminooctanoate (OR = 0.904, 95%CI = 0.847–0.964, $P = 0.002$, FDR = 0.160), N-lactoylvaline (OR = 0.853, 95%CI = 0.775–0.938, $P = 0.001$,FDR = 0.122), X − 21310 (OR = 0.917, 95%CI = 0.866–0.971, $P = 0.003$,FDR = 0.195), X − 26111 (OR = 0.932, 95%CI = 0.890–0.976, $P = 0.003$,FDR = 0.189), Arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio (OR = 0.945, 95%CI = 0.914–0.977, $P = 8.2 \times 10^{-4}$, FDR = 0.104), and Citrulline to ornithine ratio (OR = 0.924, 95%CI = 0.881–0.969, $P = 0.001$, FDR = 0.122), while 4 metabolite levels and 2 metabolite ratios were suggestively causally associated with an increased risk of schizophrenia including N2, N5-diacetylornithine (OR = 1.090, 95%CI = 1.031–1.153, $P = 0.003$, FDR = 0.185), N − acetyl − 2–aminooctanoate (OR = 1.069, 95%CI=(1.027–1.114, $P = 0.001$, FDR = 0.127), N − acetyl − 2–

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aminoadipate (OR = 1.081, 95%CI = 1.030–1.133, *P* = 0.001, FDR = 0.128), X – 13844 (OR = 1.110, 95%CI = 1.036–1.190, *P* = 0.003, FDR = 0.196), X – 24556 (OR = 1.083, 95%CI = 1.036–1.132, $P = 4.5 \times 10^{-4}$, FDR = 0.098), X – 24736 (OR = 1.065, 95%CI = 1.028–1.104, $P = 5.6 \times 10^{-4}$, FDR = 0.098), N – acetylasparagine (OR = 1.048, 95%CI = 1.021–1.075, $P = 4.5 \times 10^{-4}$, FDR = 0.098), N – acetylarginine (OR = 1.060, 95%CI = 1.028–1.092, $P = 1.8 \times 10^{-4}$, FDR = 0.083), Cysteine to alanine ratio (OR = 1.086, 95%CI = 1.036–1.138, $P = 6.5 \times 10^{-4}$, FDR = 0.101), and Benzoate to linoleoyl – arachidonoyl – glycerol (18:2 to 20:4) ratio (OR = 1.070, 95%CI = 1.025–1.117, *P* = 0.002, FDR = 0.158).

Conclusion Our study results provide valuable insights for identifying diagnostic biomarkers related to schizophrenia and offer preliminary research findings for further exploration of the mechanisms linking schizophrenia and metabolism.

Introduction

Schizophrenia (SCZ) is a severe mental disorder, with a lifetime prevalence of approximately 1% and a suicide rate of around 5% among patients [1]. The symptoms of SCZ are typically divided into positive symptoms (such as hallucinations and delusions) and negative symptoms (such as social dysfunction and emotional withdrawal) [2]. Additionally, some patients may experience depressive moods and cognitive impairments [3, 4]. Patients with SCZ typically have a lifelong illness, and even those with well-controlled symptoms face adverse outcomes such as social isolation, stigma, and increased unemployment rates [5]. In consequence, treatment for SCZ is particularly important. Currently, antipsychotic medication remains the preferred method, while non-pharmacological therapies such as psychological interventions have relatively minor effects on symptoms [1]. Currently, there are still many issues with antipsychotic drugs in clinical practice [6], so early diagnosis and treatment of SCZ may help control symptoms and improve prognosis [7]. Nevertheless, the diagnosis of SCZ still relies on subjective interpretation of symptoms and social functioning, without an objective biological marker as a diagnostic standard [8]. Therefore, this study makes the link between biomarkers and treatment of SCZ clearer.

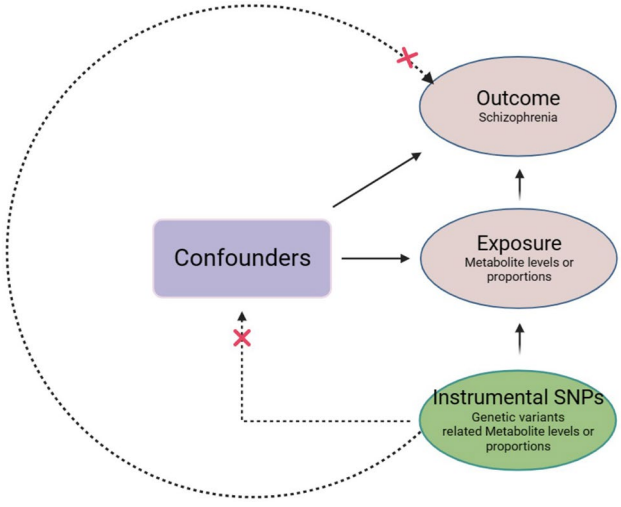

Fig. 1 Flowchart of Mendelian randomization study

There are some studies on SCZ and metabolites to prove that there is an important link between the two. One study showed that serum samples of patients with SCZ had elevated levels of branched chain amino acids, phenylalanine and tyrosine, proline, glutamic, lactic acid, and pyruvic acids compared with those of patients with other psychiatric disorders. This study may potentially provide assistance in the diagnosis of SCZ [9]. Another retrospective systematic study showed that some metabolites may be involved in the pathogenesis of SCZ. The increased levels of peroxide metabolites, arachidonic acid and pyruvate in patients with SCZ [8]. may be related to oxidative stress, PUFA metabolism and glucose metabolism malfunction in SCZ. The decrease of phospholipid level is closely related to the membrane phospholipid hypothesis. However, these studies appear to have relatively small sample sizes and appear to lack evidence of relevance to the wider population.

Mendelian randomization (MR) uses genetic variation as an instrumental variable to infer whether risk factors causally influence health outcomes and has been used to combine summary data from genome-wide association studies (GWAS) involving a large number of genetic variations [10]. MR studies use single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) based on the assumption that the SNP is associated with the risk factor but not with the disease or confounding factors [11]. In recent years, several MR studies have been conducted in the field of mental illness, and some progress has been made [12]. Jia et al. [13]. investigated the association between 92 blood metabolites and the risk of various mental illnesses, finding associations between eight metabolites and psychiatric disorders. However, the study results seem to be limited in their relevance to SCZ due to constraints related to the types of metabolites and the specific types of disorders. Yang et al. [14] further investigated the relationship between 486 metabolites and psychiatric disorders using MR methods, identifying 22 metabolites with potential causal associations with SCZ. In contrast, the present study utilized new metabolite GWAS data based on previous studies to investigate the association of a wider range of metabolites (1091) with schizophrenia. Additionally, for the first time,301

metabolite ratios were included in the study.This study aims to determine the causal relationship of human blood metabolites and metabolic ratios with SCZ through comprehensive two-sample MR analysis.

Materials and methods

GWAS data sources and IV selection

In this study, we consider metabolites and metabolic ratios as the exposure factors, and disease (SCZ) as the outcome factor, and follow the two-sample Mendelian randomization (2SMR) method (Fig. 1).

Summary statistics for each metabolite were obtained from the GWAS Catalog (accession numbers from GCST90199621 to GCST90201020) [15]. The data comes from Cheng et al.and is published in Nat.Genet in 2023.01, in the largest human metabolomics GWAS study to date, comprising 1,091 metabolites and 309 metabolite ratios in 8,299 individuals from the Canadian Longitudinal Study on Aging (CLSA) cohort. These metabolites were detected by biomarker analysis in biological samples, such as blood and urine, using a variety of assays including mass spectrometry, nuclear magnetic resonance, immunoassay and liquid chromatography. A total of 248 loci associated with 690 metabolites and 69 loci associated with 143 metabolite ratios were identified. After integrating metabolic genes and gene expression information, 94 effector genes were identified, involving 109 metabolites and 48 metabolite proportions. Of the 1,091 plasma metabolites tested, 850 had known properties in eight super pathways (i.e., lipids, amino acids, xenobiotics, nucleotides, cofactors and vitamins, carbohydrates, peptides and energy). The remaining 241 molecules were classified as unknown or "partially" characteristic molecules. The current study included 81 metabolites, which had not been detected in previously representative large metabolomic GWAS [16–20]. These metabolites may include previously unnamed metabolites. Detailed information on this GWAS cohort (mean age, BMI, sex) and metabolites compared with previously published metabolite GWAS data is available in Supplementary Table 1.

Based on a large number of recent studies of the same type [21–24] the significance level of IVs for each metabolite was set to 1×10^{-5}. For the inverse MR analysis, the IV significance threshold for schizophrenia was defined as $5\times10^{-8}$and linkage disequilibrium (LD) was mainly determined by $R^2=0.001$ and distance (kb=10000) [25]. Further, F values were calculated, and only those with F>10 were retained as instrumental variables (IV) [26]. Based on these criteria, we conducted the screening using R software (version 4.3.2).

Recently, Trubetskoy et al. [27] conducted a comprehensive analysis of the GWAS data from the Psychiatric Genomics Consortium (PGC). This study utilized GWAS data from a cohort of 127,906 participants of European ((N_{case} = 52,017 $N_{control}$ = 75,889) from their dataset. The original data can be downloaded from the IEU Open GWAS project at https://gwas.mrcieu.ac.uk/ (ID: ieu-b-5102). Detailed information on study design, phenotype definition, quality control, and genetic data estimation has been previously described in a prior study by Trubetskoy et al. [27].

Mendelian randomization analysis

MR analyses were performed using the 2SMR approach with the "TwoSampleMR" (version 0.5.7) package of R software 4.3.2. The analysis was performed using the IVW, MR-Egger, simple mode, weighted median, and weighted mode methods. The inverse variance weighting (IVW) method is currently the most important method in two-sample MR analysis, providing an overall estimate of the causal effect [28]. The MR-Egger regression method is mainly used to address horizontal pleiotropy, with an intercept<0.05 being considered as evidence of horizontal pleiotropy [29]. Simple mode, weighted median, and weighted mode are used to assess the stability of MR results [30]. This study primarily uses the IVW method to infer the causal relationship between metabolites and SCZ, with other methods serving as supplementary analyses to the IVW method. The obtained results are subjected to FDR correction to ensure stability, including: (1) IVW with $P<0.05$ and $P_{FDR}<0.2$, (2) Consistency in the direction of the MR analysis results (β values) from the three methods, and (3) MR-Egger with $P>0.05$ to eliminate pleiotropy of each IV. Finally, the effect of individual SNPs on the results was analyzed using the leave-one-out method of analysis.

Results

Information on instrumental variables (SNP)

After screening 1400 metabolites or ratio of all SNPs, a total of 34,843 SNPs were found to meet the IV selection criteria (Supplementary Table 2) with $R^2=0.001$ and distance (kb=10000), F>10. These SNPs were then merged with the GWAS data of SCZ, resulting in a final inclusion of 30,184 SNPs for subsequent analysis (Supplementary Table 3).

MR analyses results

We selected the IVW, MR-Egger, Simple mode, Weighted median, and Weighted mode methods for two-sample MR analysis and visualized the results. Results with $p>0.05$ for all five methods were excluded. The final results are shown in Fig. 2 (complete results can be found in Supplementary Table 4).

To obtain more accurate and effective results, we subsequently performed FDR correction. Data meeting the following three criteria were retained, with the IVW

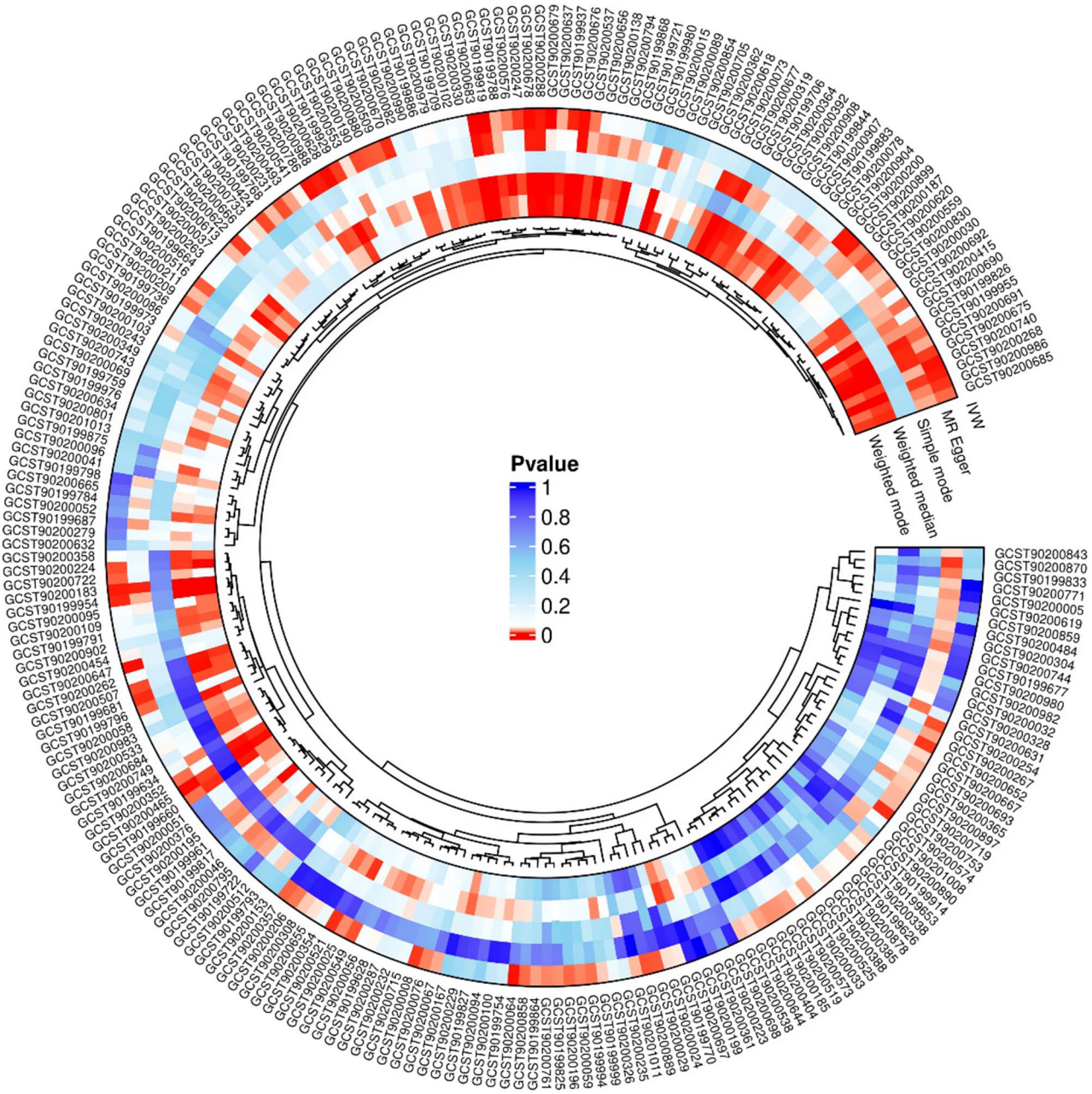

Fig. 2 Causal relationship results of blood metabolites and metabolic ratios with SCZ

method as the main analytical method: (1) IVW $P<0.05$, FDR < 0.2 is considered suggestive of a causal relationship, while FDR < 0.05 is considered to indicate a significant causal relationship, (2) Consistency in OR values across all methods (either all greater than 1 or all less than 1, Figs. 3), (3) Elimination of heterogeneity in each IV with MR-Egger $P>0.05$.

The final 2 metabolites were found to be significantly associated with SCZ in a causal relationship. And 16 metabolites and ratios were found to be suggestively associated with SCZ in a causal relationship.

Among these 18 metabolites and ratios, the levels of 5 metabolites and 2 metabolite ratios were found to be associated with a decreased risk of schizophrenia (SCZ) per 1-SD increase in the genetically determined Alliin (OR = 0.915, 95%CI = 0.879–0.953, $P=1.93\times10^{-5}$, FDR = 0.013), 2-aminooctanoate (OR = 0.904, 95%CI = 0.847–0.964, $P=0.002$, FDR = 0.160), N-lactoylvaline (OR = 0.853, 95%CI = 0.775–0.938, $P=0.001$,FDR = 0.122), X − 21,310 (OR = 0.917, 95%CI = 0.866–0.971, $P=0.003$,FDR = 0.195), X − 26,111 (OR = 0.932, 95%CI = 0.890–0.976, $P=0.003$,FDR = 0.189),

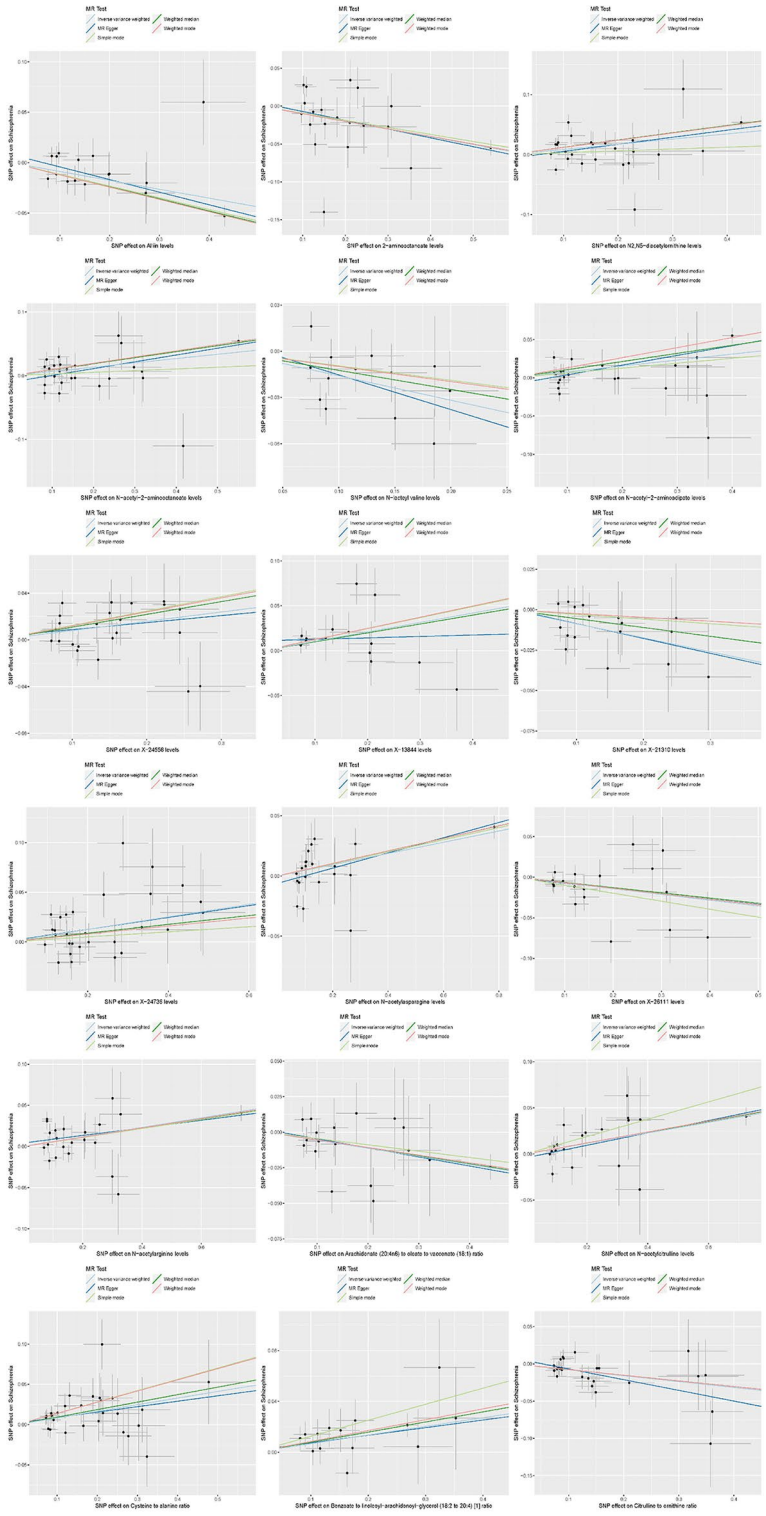

Fig. 3 Scatter plot of the genetic correlation between metabolites, metabolic ratios, and SCZ using different MR methods

Arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio (OR = 0.945, 95%CI = 0.914–0.977, $P = 8.2 \times 10^{-4}$, FDR = 0.104), and Citrulline to ornithine ratio (OR = 0.924, 95%CI = 0.881–0.969, $P = 0.001$, FDR = 0.122).

On the other hand, the levels of 9 metabolites and 2 metabolite ratios were found to be associated with an increased risk of SCZ per 1-SD increase in the genetically determined N-actylcitrulline (OR = 1.058,

95%CI=1.034–1.083, $P=1.4\times10^{-6}$, FDR=0.002), N2, N5-diacetylornithine (OR=1.090, 95%CI=1.031–1.153, $P=0.003$, FDR=0.185), N−acetyl−2–aminooctanoate (OR=1.069, 95%CI=(1.027–1.114, $P=0.001$, FDR=0.127), N−acetyl−2–aminoadipate (OR=1.081, 95%CI=1.030–1.133, $P=0.001$, FDR=0.128), X−13844 (OR=1.110, 95%CI=1.036–1.190, $P=0.003$, FDR=0.196), X−24556 (OR=1.083, 95%CI=1.036–1.132, $P=4.5\times10^{-4}$, FDR=0.098), X−24736 (OR=1.065, 95%CI=1.028–1.104, $P=5.6\times10^{-4}$, FDR=0.098), N−acetylasparagine (OR=1.048, 95%CI=1.021–1.075, $P=4.5\times10^{-4}$, FDR=0.098), N−acetylarginine (OR=1.060, 95%CI=1.028–1.092, $P=1.8\times10^{-4}$, FDR=0.083), Cysteine to alanine ratio (OR=1.086, 95%CI=1.036–1.138, $P=6.5\times10^{-4}$, FDR=0.101), and Benzoate to linoleoyl−arachidonoyl−glycerol (18:2 to 20:4) ratio (OR=1.070, 95%CI=1.025–1.117, $P=0.002$, FDR=0.158). (Fig. 4 for details, full table available in Supplementary Table 5).

We plotted scatter plots and funnel plots to illustrate the MR estimates of SCZ at different metabolite levels or ratios and analyzed the effect of individual SNPs on the results using leave-one-out sensitivity analysis, whereas the funnel plots showed minimal heterogeneity (Supplementary Fig. S1), and the results of the leave-one-out method indicated that there were no individual SNPs that significantly affected the results (Supplementary Fig. S2). In conclusion, our results are stable, reliable, and accurate.

Reverse analysis

A reverse Mendelian randomization analysis was conducted on the two metabolites that demonstrated significant causal associations with schizophrenia. In this analysis, 154 instrumental variables (IVs) (Supplementary Table 6) strongly associated with schizophrenia were identified based on previously established threshold criteria. The findings indicated no evidence of reverse causality between the two metabolites and schizophrenia (Fig. 5).

Discussion

SCZ is considered a severe mental disorder and has received widespread attention. Diagnosing SCZ has long relied on subjective scales, with the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM-5) being a common reference. However, unfortunately, a definitive biochemical marker for diagnosing SCZ has yet to be found. In recent years, a significant amount of research has been conducted by numerous researchers in an effort to identify such a marker. For example, Rodrigues et al. [31] conducted a retrospective study indicating that the current biomarkers for SCZ primarily fall into five main categories: (1) Neuroimaging biomarkers, (2) Genetic biomarkers, (3) Epigenetic biomarkers, (4) Protein biomarkers, and (5) Metabolic biomarkers. While these studies are abundant, the majority of them are observational. With the development of MR methods, a new approach has been provided for studying the causal relationships between SCZ and various exposure factors. There are already some MR studies for SCZ, and they have achieved promising results [12, 32, 33]. Currently, most of the research on the relationship between metabolite levels and schizophrenia is observational. For example, Koike et al. [34] observed a significant increase in free bile acids in the plasma of SCZ patients, and Liu et al. [35] identified 182 metabolites with significant differences in levels between SCZ patients and healthy controls using metabolomics methods. The finding of Jia et al. [13] found two metabolites that were causally related to SCZ. Yang et al. [14] further investigated the relationship between 486 metabolites and psychiatric disorders using MR methods, and found 22 metabolites that appeared to have a potential causal relationship with SCZ. However, a recent study by Lu et al. [36] revealed causal relationships between metabolite abundance and psychiatric disorders. Notably, the findings of both studies showed no overlap with the results of the present study. The GWAS data used by Yang et al. were derived from an earlier metabolite GWAS study that included only 486 metabolites, fewer than those examined in the current study. While Lu et al. used the same schizophrenia GWAS data as the present study, their MR analysis covered only around 600 metabolites. Building on these previous studies, the current research expands the scope by analyzing a larger set of 1091 metabolites and, for the first time, performing MR analysis on 309 metabolic ratios in relation to schizophrenia. These findings contribute further evidence for future research in this field.

Our study is based on two large-scale GWAS summary datasets, and we conducted rigorous two-sample MR analyses to assess blood metabolites and metabolic ratios. Our research suggests that there is a causal relationship of 14 metabolite levels and 4 metabolic ratios with schizophrenia. This includes 9 known metabolites and 5 unknown metabolites. Alliin is a non-protein amino acid and an important precursor for the synthesis of Allicin, a sulfur-containing compound derived from garlic. Numerous studies have demonstrated that Allicin is a neuroprotective agent [37, 38]. Neuroinflammation can be suppressed by inhibiting brain inflammation factors and the activation of microglial cells [39]. The vulnerability-stress-inflammation model for schizophrenia currently suggests that neuroinflammation is one of the potential causes of schizophrenia [40]. Numerous studies have indicated that inhibiting neuroinflammation and microglial cell activation can reverse symptoms of

exposure	nsnp	method	pval	OR(95% CI)
Alliin levels	16	MR Egger	**0.003**	0.882 (0.825 to 0.943)
	16	Weighted median	**<0.001**	0.887 (0.846 to 0.929)
	16	Inverse variance weighted	**<0.001**	0.915 (0.879 to 0.953)
	16	Simple mode	0.095	0.890 (0.783 to 1.012)
	16	Weighted mode	**<0.001**	0.885 (0.846 to 0.926)
2−aminooctanoate levels	20	MR Egger	**0.049**	0.890 (0.799 to 0.992)
	20	Weighted median	**<0.001**	0.904 (0.870 to 0.938)
	20	Inverse variance weighted	**0.002**	0.904 (0.847 to 0.964)
	20	Simple mode	0.106	0.911 (0.817 to 1.015)
	20	Weighted mode	**<0.001**	0.905 (0.872 to 0.939)
N2,N5−diacetylornithine levels	25	MR Egger	**0.030**	1.125 (1.018 to 1.242)
	25	Weighted median	**<0.001**	1.129 (1.077 to 1.184)
	25	Inverse variance weighted	**0.003**	1.090 (1.031 to 1.153)
	25	Simple mode	0.624	1.031 (0.913 to 1.166)
	25	Weighted mode	**<0.001**	1.127 (1.079 to 1.177)
N−acetyl−2−aminooctanoate levels	26	MR Egger	**0.002**	1.112 (1.047 to 1.181)
	26	Weighted median	**<0.001**	1.099 (1.060 to 1.138)
	26	Inverse variance weighted	**0.001**	1.069 (1.027 to 1.114)
	26	Simple mode	0.729	1.027 (0.885 to 1.192)
	26	Weighted mode	**<0.001**	1.102 (1.063 to 1.143)
N−lactoyl valine levels	13	MR Egger	0.205	0.798 (0.575 to 1.108)
	13	Weighted median	**0.024**	0.883 (0.793 to 0.984)
	13	Inverse variance weighted	**0.001**	0.853 (0.775 to 0.938)
	13	Simple mode	0.330	0.910 (0.758 to 1.092)
	13	Weighted mode	0.272	0.906 (0.766 to 1.072)
N−acetyl−2−aminoadipate levels	22	MR Egger	**0.005**	1.135 (1.049 to 1.228)
	22	Weighted median	**<0.001**	1.112 (1.056 to 1.172)
	22	Inverse variance weighted	**0.001**	1.081 (1.030 to 1.133)
	22	Simple mode	0.372	1.066 (0.930 to 1.222)
	22	Weighted mode	**<0.001**	1.141 (1.089 to 1.195)
X−13844 levels	15	MR Egger	0.840	1.016 (0.872 to 1.184)
	15	Weighted median	**0.030**	1.104 (1.010 to 1.207)
	15	Inverse variance weighted	**0.003**	1.110 (1.036 to 1.190)
	15	Simple mode	0.165	1.130 (0.959 to 1.332)
	15	Weighted mode	0.139	1.132 (0.970 to 1.323)
X−21310 levels	17	MR Egger	0.269	0.912 (0.779 to 1.067)
	17	Weighted median	0.186	0.947 (0.873 to 1.027)
	17	Inverse variance weighted	**0.003**	0.917 (0.866 to 0.971)
	17	Simple mode	0.703	0.972 (0.840 to 1.124)
	17	Weighted mode	0.743	0.977 (0.850 to 1.122)
X−24556 levels	24	MR Egger	0.301	1.062 (0.950 to 1.187)
	24	Weighted median	**<0.001**	1.115 (1.050 to 1.184)
	24	Inverse variance weighted	**<0.001**	1.083 (1.036 to 1.132)
	24	Simple mode	0.067	1.131 (0.998 to 1.282)
	24	Weighted mode	**0.004**	1.127 (1.047 to 1.213)
X−24736 levels	29	MR Egger	0.179	1.062 (0.975 to 1.156)
	29	Weighted median	0.062	1.045 (0.998 to 1.095)
	29	Inverse variance weighted	**<0.001**	1.065 (1.028 to 1.104)
	29	Simple mode	0.606	1.026 (0.932 to 1.129)
	29	Weighted mode	0.125	1.041 (0.990 to 1.094)
X−26111 levels	19	MR Egger	0.199	0.937 (0.851 to 1.031)
	19	Weighted median	0.050	0.938 (0.880 to 1.000)
	19	Inverse variance weighted	**0.003**	0.932 (0.890 to 0.976)
	19	Simple mode	0.106	0.906 (0.809 to 1.015)
	19	Weighted mode	0.070	0.934 (0.872 to 1.001)
N−acetylasparagine levels	21	MR Egger	**0.002**	1.065 (1.030 to 1.102)
	21	Weighted median	**<0.001**	1.053 (1.029 to 1.078)
	21	Inverse variance weighted	**<0.001**	1.048 (1.021 to 1.075)
	21	Simple mode	0.202	1.051 (0.976 to 1.133)
	21	Weighted mode	**<0.001**	1.053 (1.030 to 1.077)
N−acetylarginine levels	22	MR Egger	**0.044**	1.047 (1.004 to 1.092)
	22	Weighted median	**<0.001**	1.058 (1.032 to 1.084)
	22	Inverse variance weighted	**<0.001**	1.060 (1.028 to 1.092)
	22	Simple mode	0.256	1.056 (0.964 to 1.157)
	22	Weighted mode	**<0.001**	1.058 (1.031 to 1.086)
N−acetylcitrulline levels	19	MR Egger	**<0.001**	1.070 (1.036 to 1.104)
	19	Weighted median	**<0.001**	1.060 (1.033 to 1.088)
	19	Inverse variance weighted	**<0.001**	1.058 (1.034 to 1.083)
	19	Simple mode	**0.047**	1.098 (1.007 to 1.198)
	19	Weighted mode	**<0.001**	1.061 (1.034 to 1.089)
Arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio	18	MR Egger	**0.030**	0.938 (0.890 to 0.989)
	18	Weighted median	**0.005**	0.946 (0.910 to 0.984)
	18	Inverse variance weighted	**<0.001**	0.945 (0.914 to 0.977)
	18	Simple mode	0.391	0.957 (0.867 to 1.056)
	18	Weighted mode	**0.019**	0.948 (0.910 to 0.987)
Cysteine to alanine ratio	27	MR Egger	0.216	1.070 (0.964 to 1.187)
	27	Weighted median	**0.005**	1.097 (1.028 to 1.171)
	27	Inverse variance weighted	**<0.001**	1.086 (1.036 to 1.138)
	27	Simple mode	0.051	1.151 (1.006 to 1.316)
	27	Weighted mode	0.050	1.149 (1.007 to 1.311)
Citrulline to ornithine ratio	25	MR Egger	**0.027**	0.866 (0.769 to 0.976)
	25	Weighted median	**0.023**	0.927 (0.868 to 0.990)
	25	Inverse variance weighted	**0.001**	0.924 (0.881 to 0.969)
	25	Simple mode	0.272	0.927 (0.811 to 1.058)
	25	Weighted mode	0.262	0.927 (0.814 to 1.055)
Benzoate to linoleoyl−arachidonoyl−glycerol (18:2 to 20:4) [1] ratio	14	MR Egger	0.278	1.062 (0.958 to 1.177)
	14	Weighted median	**0.009**	1.083 (1.020 to 1.149)
	14	Inverse variance weighted	**0.002**	1.070 (1.025 to 1.117)
	14	Simple mode	**0.034**	1.134 (1.022 to 1.259)
	14	Weighted mode	**0.027**	1.089 (1.018 to 1.165)

Fig. 4 Results of Mendelian randomization analysis of the causal association between metabolites and metabolic ratios with SCZ using 5 methods

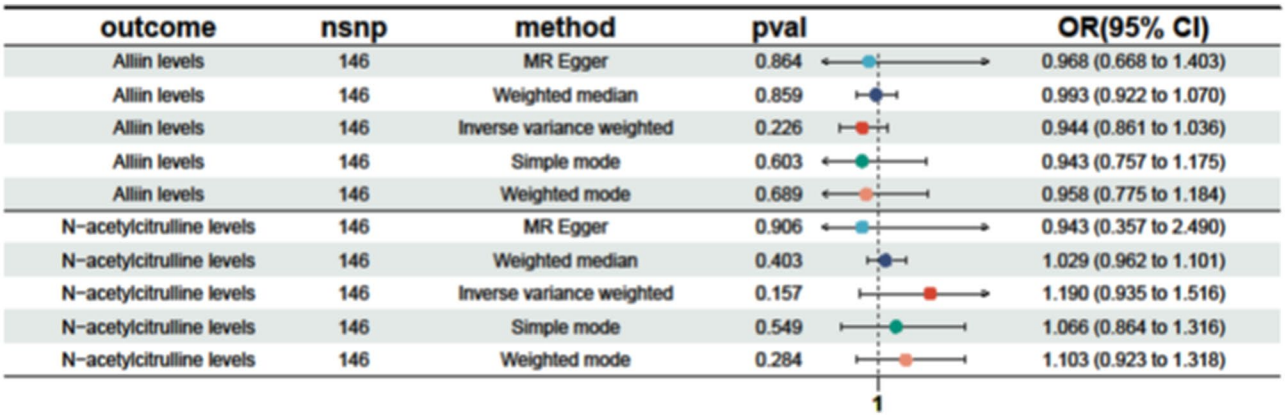

Fig. 5 Results of reverse Mendelian randomization analysis

schizophrenia [41]. Therefore, Alliin may be associated with the inflammatory pathways of schizophrenia.

2-aminooctanoate is an alpha-amino acid. In a metabolomics study on depression, it was found to be negatively correlated with depression [42]. N-lactoyl valine is a N-acyl-amino acid and is widely used in diabetes research [43]. Interestingly, in a metabolomics study on diabetes and cognitive impairment, N-lactoyl valine was found to be associated with the cognitive impairment that accompanies diabetes [44]. As is well known, cognitive impairment has long been considered a key symptom of schizophrenia, which is consistent with our findings. N-acetylarginine is believed to be associated with oxidative stress in the brain [45, 46]. Research has shown that the cognitive impairment in schizophrenia is associated with increased oxidative stress. Levels of thio-barbituric acid reactive substances, a measure of oxidative stress, are elevated in the bodies of schizophrenia patients, and this elevation is significantly correlated with poor performance on working memory tests [47]. According to previous MR results, N-acetylarginine is negatively correlated with schizophrenia, which may differ from our findings [13]. This difference may be related to the criteria for IV selection and the FDR correction standards. N2, N5-Diacetylornithine is a metabolic by-product of the urea cycle, and there is currently limited research on its role. A related study shows its association with heart function [48]. Similarly, there are few reports on the roles of N-acetyl-2-aminooctanoate, N-acetyl-2-aminoadipate, N-acetylasparagine, and N-acetylcitrulline in psychiatric disorders.

As mentioned above, there is still no stable, reliable, and objective standard for the diagnosis of schizophrenia. In recent years, thanks to the development of metabolomics, an increasing number of studies have demonstrated the association between human metabolic compounds and schizophrenia [49–51]. Unfortunately, to date, we have yet to find a reliable physiological marker to serve as a diagnostic standard.

However, the emergence of MR has provided us with a new approach. Our study explores the causal relationship between metabolites, metabolic ratios, and schizophrenia from the perspective of genetic polymorphism. Compared to descriptive studies, our research results are more reliable. Our study is based on genetic exploration of the entire metabolome and its causal relationship with schizophrenia. To our knowledge, this is currently the study with the largest number of metabolites included in the research on the causal relationship of schizophrenia. After FDR correction, our study excluded pleiotropy and heterogeneity. Therefore, compared to observational studies, we have eliminated confounding factors, making our research results more reliable.

Our study has several limitations. Firstly, the population in this study consisted only of individuals of European. The results obtained may not be applicable to populations of Asian or African. Secondly, our study only explores the causal relationship between the metabolome and schizophrenia, without further investigation into the underlying mechanisms. Additionally, because schizophrenia is a mental illness significantly associated with brain function, it may have minimal impact on plasma. Therefore, in future studies, it would be important to collect more cerebrospinal fluid or brain tissue samples from individuals with schizophrenia to obtain more data from within the brain. Lastly, the results of MR depend on sample size and enlarging the sample size would make the results more stable and reliable.

Overall, our study is the most comprehensive MR study to date, incorporating a total of 1091 metabolites and 309 metabolic ratios, investigating their impact on schizophrenia, ultimately identifying 14 metabolites and 4 metabolic ratios with a causal link to schizophrenia. Our study analyzes from the perspective of genetic genes and metabolomics, providing strong evidence for the search

for diagnostic biomarkers for schizophrenia and offering preliminary evidence for further research on metabolomics and schizophrenia. In consequence, our results are stable and reliable.

Conclusion

Our study has identified the relationship between blood metabolites and metabolic ratios based on genetic polymorphisms with SCZ. Our research provides a potential discovery for diagnostic biomarkers of SCZ. Subsequently, further research is needed to assess the universality of the results and to explore the underlying mechanisms between metabolites and SCZ.

Abbreviations

SCZ	Schizophrenia
MR	Mendelian randomization
GWAS	genome-wide association study
PGC	Psychiatric Genomics Consortium
CLDS	Canadian Longitudinal Study
IV	Instrumental Variable
IVW	Inverse variance weighted

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12991-024-00521-1.

Supplementary Material 1: Supplementary Fig. S1: Funnel plot for metabolites

Supplementary Material 2: Supplementary Fig. S2: Leave-one-out analysis of SNPs

Supplementary Material 3: Supplementary Table 1: Metabolite GWAS data Details

Supplementary Material 4: Supplementary Table 2: Detailed information on all metabolite SNPs

Supplementary Material 5: Supplementary Table 3: Detailed information on all metabolite SNPs finally used after screening

Supplementary Material 6: Supplementary Table 4: Complete results of MR

Supplementary Material 7: Supplementary Table 5: MR results after screening

Supplementary Material 8: Supplementary Table 6: Detailed information on all SCZ SNPs finally used after screening

Author contributions

Yu Huang and Hanxuan Wang provided the concept and designed the study and conducted the analyses and wrote the manuscript. Jiayu Zheng participated in data collection and the analysis of the data. NaZhou revised and proof-read the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

The datasets generated and analysed during the current study are available in the GWAS Catalog (accession numbers from GCST90199621 to GCST90201020) and EU Open GWAS project at https://gwas.mrcieu.ac.uk/ (ID: ieu-b-5102).

Declarations

Competing interests

The authors declare no competing interests.

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