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Blood metabolites, neurocognition and psychiatric disorders: a Mendelian randomization analysis to investigate causal pathways

Jing Guo[1,4], Ping Yang[2,4], Jia-Hao Wang[1], Shi-Hao Tang[1], Ji-Zhou Han[1], Shi Yao[3], Ke Yu[1], Cong-Cong Liu[1], Shan-Shan Dong[1], Kun Zhang[1], Yuan-Yuan Duan[1], Tie-Lin Yang[1] and Yan Guo[1]✉

BACKGROUND: Neurocognitive dysfunction is observationally associated with the risk of psychiatric disorders. Blood metabolites, which are readily accessible, may become highly promising biomarkers for brain disorders. However, the causal role of blood metabolites in neurocognitive function, and the biological pathways underlying their association with psychiatric disorders remain unclear.

METHODS: To explore their putative causalities, we conducted bidirectional two-sample Mendelian randomization (MR) using genetic variants associated with 317 human blood metabolites ($n_{max} = 215{,}551$), g-Factor (an integrated index of multiple neurocognitive tests with $n_{max} = 332{,}050$), and 10 different psychiatric disorders ($n = 9{,}725$ to 807,553) from the large-scale genome-wide association studies of European ancestry. Mediation analysis was used to assess the potential causal pathway among the candidate metabolite, neurocognitive trait and corresponding psychiatric disorder.

RESULTS: MR evidence indicated that genetically predicted acetylornithine was positively associated with g-Factor (0.035 standard deviation units increase in g-Factor per one standard deviation increase in acetylornithine level; 95% confidence interval, 0.021 to 0.049; $P = 1.15 \times 10^{-6}$). Genetically predicted butyrylcarnitine was negatively associated with g-Factor (0.028 standard deviation units decrease in g-Factor per one standard deviation increase in genetically proxied butyrylcarnitine; 95% confidence interval, −0.041 to −0.015; $P = 1.31 \times 10^{-5}$). There was no evidence of associations between genetically proxied g-Factor and metabolites. Furthermore, the mediation analysis via two-step MR revealed that the causal pathway from acetylornithine to bipolar disorder was partly mediated by g-Factor, with a mediated proportion of 37.1%. Besides, g-Factor mediated the causal pathway from butyrylcarnitine to schizophrenia, with a mediated proportion of 37.5%. Other neurocognitive traits from different sources provided consistent findings.

CONCLUSION: Our results provide genetic evidence that acetylornithine protects against bipolar disorder through neurocognitive abilities, while butyrylcarnitine has an adverse effect on schizophrenia through neurocognition. These findings may provide insight into interventions at the metabolic level for risk of neurocognitive and related disorders.

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INTRODUCTION

Although neurocognitive abilities are considered indispensable in the assessment of psychiatric disorders [1, 2], the pathogenesis underlying this relationship has not been well established. Observational clinical evidence, for example, has suggested that neurocognitive impairment occurs prior to the onset of schizophrenia and exacerbate following the episode [3, 4]. Neurocognitive deficits may be inherent to psychiatric disorders, independent of other psychotic symptom domains [5]. Medical guidelines have recommended cognitive remediation as a therapeutic strategy for psychiatric patients [6]. The effectiveness of antipsychotics to improve neurocognition in patients with psychiatric disorders is controversial. There are studies showing that taking antipsychotics such as clozapine, olanzapine, and aripiprazole significantly improves cognitive performance in psychotic patients [7, 8], but not all antipsychotics have a uniform positive cognitive profile [9, 10]. This inconsistency in neurocognition is likely due to the varying degrees of metabolic discrepancies induced by antipsychotics [11]. For instance, antipsychotic medications have been associated with disrupted lipid metabolism [12, 13], with concentrations of these lipid metabolites shown to correlate with cognitive functions such as verbal memory and processing speed [14]. The use of anticholinergic medication may adversely affect cognitive performance in patients with schizophrenia [15]. Antipsychotic medications can have a

[1]Key Laboratory of Biomedical Information Engineering of Ministry of Education, Biomedical Informatics & Genomics Center, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, Shaanxi 710049, P. R. China. [2]Hunan Brain Hospital, Clinical Medical School of Hunan University of Chinese Medicine, Changsha, Hunan 410007, P. R. China. [3]Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524000, China. [4]These authors contributed equally: Jing Guo, Ping Yang. ✉email: guoyan253@xjtu.edu.cn

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negative impact on cognitive processes by increasing the occupancy of dopamine D2 receptors [16]. It implies that the metabolites could serve as potentially modifiable therapeutic targets whose regulation may yield better clinical effects.

Metabolites are promising biomarkers reflecting biological and physiological processes [17]. Several studies have shown that metabolic abnormalities may worsen cognitive impairments in both the general population and individuals with psychiatric disorders [18–24]. For example, in untargeted metabolomics research with elderly subjects, β-cryptoxanthin plasma levels were associated with improved cognitive function, while N-acetylisoleucine and tyramine O-sulfate concentrations were linked to poorer cognitive function [19]. Metabolic syndrome, characterized by abnormal serum glucose and dyslipidemia, negatively impacts memory and executive function [21]. Docosahexaenoic acid plays a vital role in brain development and cognitive function from pregnancy to childhood [25]. Elevated kynurenine levels in brain parenchyma caused by peripheral inflammation are associated with depression and schizophrenia risk [26]. Sarcosine supplementation to antipsychotics can improves cognitive symptoms in patients with schizophrenia [27]. High triglyceride levels in female patients with major depressive disorder may lead to decreased neurocognitive functions in terms of memory, language, and attention [28, 29]. Some randomized controlled trials (RCTs) support the impact of N-acetylcysteine [30], vitamin D3 [31], folic acid [32, 33], choline and betaine [34] on cognitive function in individuals with psychiatric disorders. However, the causal relationships between metabolites and neurocognitive function remain unclear, and the pathways involved in such effects during pathology require further investigation.

Mendelian Randomization (MR) is an alternative method that using genetic variants robustly associated with the exposure as instrumental variables to uncover the potential causal effect of an exposure on an outcome [35]. While RCTs are still the gold standard for causal inference when properly designed, MR methods can use observational data to provide causal estimates given certain assumptions are met. Additionally, MR methods offer advantages in terms of sample size, study duration, and economic costs. With the accessibility of data from large-scale genome-wide association studies (GWASs), it provides an opportunity to explore causal associations between human blood metabolites, neurocognitive traits, and psychiatric disorders using two-sample MR studies [36].

In this study, we collected human blood metabolites with the benefits of small-molecule permeability, heritability and detectability. Given the high correlation among diverse neurocognitive domains, a general cognitive factor score (g-Factor), also known as a general intelligence, can be obtained statistically by modeling multiple neurocognitive specific tests [37]. Using bidirectional two-sample MR analysis, we evaluated which of the 317 human blood metabolites had a putative causal relationship with g-Factor. Furthermore, we performed mediation analysis to investigate the causal pathways mediated by g-Factor from risk metabolite to 10 different psychiatric disorders, such as schizophrenia, bipolar disorder, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), autism spectrum disorder (ASD), posttraumatic stress disorder (PTSD), anxiety, obsessive–compulsive disorder (OCD) and Tourette syndrome. We also used cognitive traits from other sources to validate the putative causal pathways. Our findings may provide new insights into the prediction or improvement of neurocognitive decline in psychiatric disorders through the regulation of endogenous metabolites.

MATERIALS AND METHODS

GWAS data sources

Blood metabolites. Given that the study was based on summary-level data, we selected the human blood metabolites from the publicly available GWAS summary statistics [38–40]. Among these, the GWAS results with the largest sample size to date, including 174 metabolites and ranging from 8,569 to 86,507 individuals, were published by Lotta et al. [38]. In addition, Klarin et al. [40] provided data on four lipid cholesterol classes, derived from more than 200,000 participants in the US Million Veteran Program (MVP) database. For lipid metabolism, we supplemented the study with five selected data points from Kettunen et al. [39], with sample sizes ranging from 13,476 to 24,871. To enrich the dataset, we included 134 metabolites from the smaller-scaled metabolic data published by Shin et al. [41], with sample sizes ranging from 1,163 to 7,822. In total, 317 metabolites were collected in the study, which can be classified into six super-pathway-based categories: amino acids (67), lipids (208), carbohydrates (14), cofactors and vitamins (11), energy metabolites (6), and nucleotides (11). Samples for all metabolic data were exclusively of European ancestry, and detailed information can be found in Supplementary Table 1.

Neurocognitive traits. The most recent publicly available GWAS summary statistics for neurocognitive traits and psychiatric disorders were obtained from individuals of European ancestry (Supplementary Table 2). A total of six neurocognitive traits were analyzed in this study. The data set included the following traits: g-Factor ($n = 332{,}050$) [42], intelligence ($n = 269{,}867$) [43], cognitive performance ($n = 257{,}828$) [44], general cognitive function ($n = 282{,}014$) [45], reaction time ($n = 330{,}069$) [45], and verbal numerical reasoning ($n = 168{,}033$) [45]. Among these traits, the g-Factor was the most discriminating. It represents a unified phenotype resulting from the integration of multiple neurocognitive tests [37] and is characterized by the largest sample size. Consequently, we selected g-Factor as the representative neurocognitive trait for our study, while utilizing the other neurocognitive traits from different sample sources to validate our findings. It is crucial to highlight that no instances of overlapping samples were observed between any metabolite and neurocognitive trait in our analysis.

Psychiatric disorders. We considered ten of the most prevalent psychiatric disorders known to impact cognitive function. These disorders include schizophrenia [46] ($n = 130{,}644$), bipolar disorder [47] ($n = 413{,}466$), anorexia nervosa [48] ($n = 72{,}517$), ADHD [49] ($n = 53{,}293$), MDD [50] ($n = 807{,}553$), ASD [51] ($n = 46{,}350$), PTSD [52] ($n = 146{,}660$), anxiety [53] ($n = 17{,}310$), OCD [54] ($n = 9{,}725$) and Tourette syndrome [55] ($n = 14{,}307$). To ensure that no overlap existed between the neurocognitive traits and psychiatric disorders within our sample participants, we employed external GWAS statistics for bipolar disorder [47] ($n = 353{,}899$), anorexia nervosa [48] ($n = 68{,}684$), and MDD [56] ($n = 142{,}646$) that did not include individuals from UK Biobank. Detailed information and the specific release link are provided in Supplementary Table 2.

Overall study design

The overall study workflow is depicted in Fig. 1. Prior to conducting MR analysis, we first utilized genetic correlation analysis to identify blood metabolites that are genetically associated with g-Factor. Subsequently, we performed bidirectional two-sample MR analyses between these blood metabolites and g-Factor to estimate potential causal relationships. Concurrently, we conducted genetic correlation and MR analyses between g-Factor and psychiatric disorders to gather genetic evidence of neurocognitive associations with these psychiatric disorders. In the final stage, we employed mediation analysis to explore potential causal pathways connecting the identified metabolites, g-Factor, and psychiatric disorders. To validate the putative causal pathways, we also incorporated other neurocognitive traits, including intelligence, cognitive performance, general cognitive function, reaction time, and verbal numerical reasoning. The additional traits were employed to further substantiate the observed associations and provide further corroboration for the putative causal relationships.

Genetic correlation

The LD-score regression software (https://github.com/bulik/ldsc) was employed to calculate the genetic correlation with the default parameters [57]. The reference variants were used from the HapMap3 dataset, excluding the major histocompatibility complex regions (https://ibg.colorado.edu/cdrom2021/Day06-nivard/GenomicSEM_practical/eur_w_ld_chr/w_hm3.snplist). Precalculated LD scores were used the 1 KG European reference panel (https://ibg.colorado.edu/cdrom2021/Day06-nivard/GenomicSEM_practical/eur_w_ld_chr/).

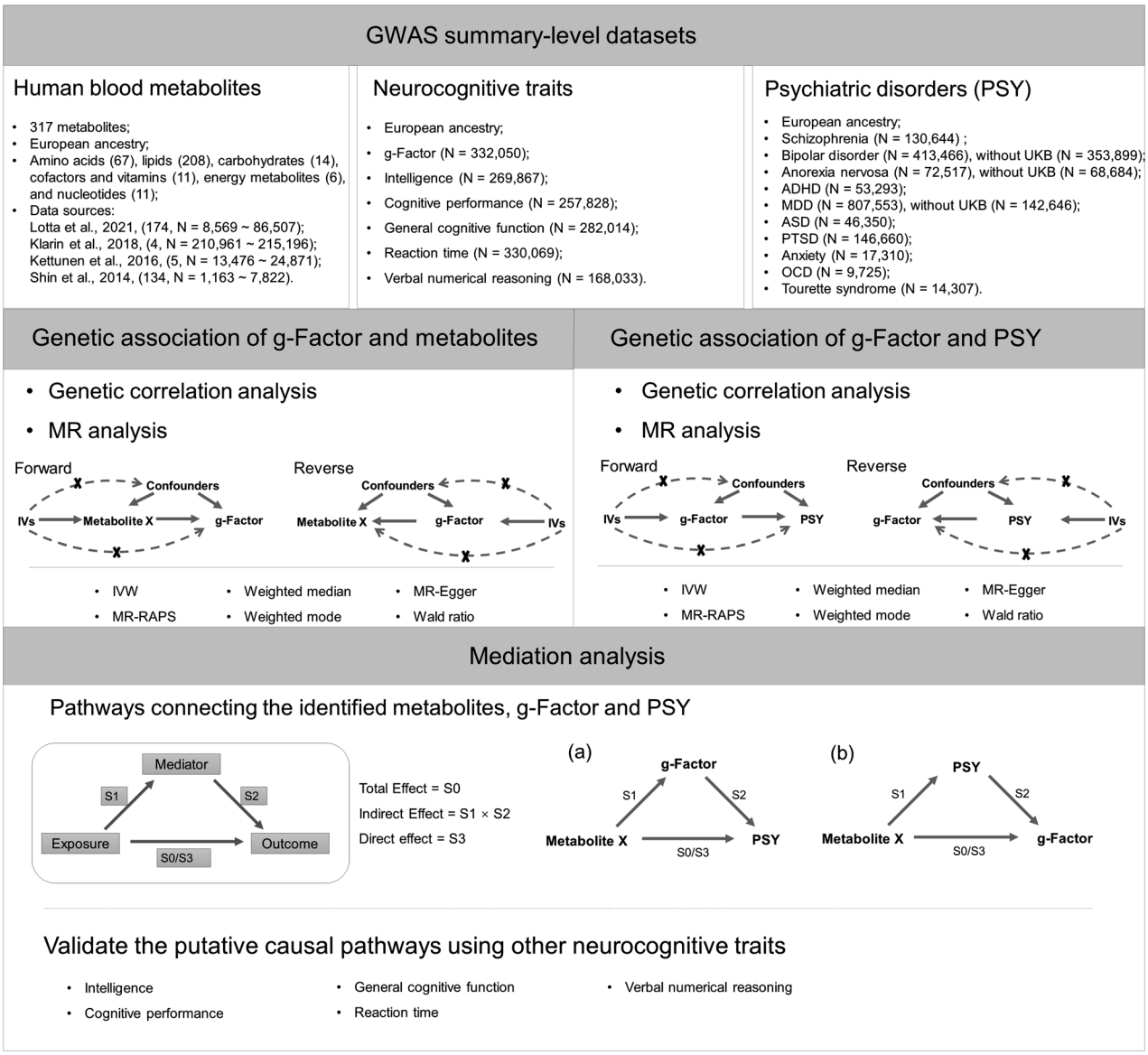

Fig. 1 Workflow of overall study design.

Two sample MR analysis

Selection of instrument variants (IVs). The MR analysis was performed in accordance with the previously described procedure [58], and in strict adherence to the STROBE-MR checklist [59]. In brief, SNPs with MAF > 0.01 and *P* value $< 5 \times 10^{-8}$ were selected from the GWAS datasets. The palindromic SNPs were removed according to the default parameters of the "harmonise_data" function in TwoSampleMR R package (version 0.4.26, https://mrcieu.github.io/TwoSampleMR/) [60]. SNPs in the long-range LD regions (https://genome.sph.umich.edu/wiki/Regions_of_high_linkage_disequilibrium_(LD)#cite_note-3) were removed [61]. We then used 315,147 European UK Biobank data as LD reference genome to clump conditionally independent SNPs using PLINK software [62] ($r^2 = 0.001$, window size = 1 Mb and *p*-value $= 5 \times 10^{-8}$). After obtaining SNPs independently associated with exposure, the selection of IVs is also subject to the following conditions: (i) no correlation with the outcome except through the exposure; (ii) if the SNPs are not present in the outcome, highly correlated proxy SNPs ($r^2 > 0.8$) can be selected to replace; and (iii) removing SNPs associated with confounders.

Removing confounders. We considered alcohol consumption and smoking as confounders affecting the relationship between blood metabolites [63, 64], neurocognition [65, 66], and psychiatric disorders [67, 68]. We removed instrumental SNPs associated with alcohol- and smoking- related traits ($P < 5 \times 10^{-8}$) by using the NHGRI GWAS catalog database [69] (v1.0.2-associations_e104, release in 22 October 2021; https://www.ebi.ac.uk/gwas/docs/file-downloads).

Heterogeneity, F-statistics and statistical power for IVs. We performed heterogeneity test for IVs using RadialMR R package ("ivw_radial" and "egger_radial" functions with default parameters, https://github.com/WSpiller/RadialMR/) [70], setting *P* values < 0.05 to filter out the outliers. We used the F-statistics to assess the strength of the IVs. The specific formula is $F = (R^2 \times (N\text{-}K\text{-}1)) / ((1 - R^2) \times K)$, R^2 denoted the explained variance of IVs on exposure ($R^2 = \beta^2 / (\beta^2 + SE^2 \times N)$), N denoted the sample size of exposure, K denoted the number of IVs, β^2 and SE^2denoted the genetic effect size and standard error from GWAS data of exposure. A threshold of $F > 10$ is usually used to indicate strong IVs. In addition, we estimated the statistical power of the IVs based on the sample size for each MR test according to the method proposed by Burgess [71]. We calculated the estimated effect size for each MR test with the 80% power at a significance level of 0.05.

Two-sample MR models. The primary method used to estimate causality was inverse variance weighted regression (IVW) [72]. To complement the IVW results, we used five additional MR models. These included MR-robust adjusted profile score (MR-RAPS) [73], weighted median [74], weighted

mode [75], MR-Egger regression [76], and Wald ratio [77]. The Wald ratio is particularly applicable when there is only one genetic variant in the instrumental variable. To implement these methods, all of the above approaches can be invoked using the corresponding functions available in the TwoSampleMR R package ("mr_ivw", "mr_raps", "mr_weighted_median", "mr_weighted_mode", "mr_egger_regression", and "mr_wald_ratio" with default parameters).

Sensitivity analyses

The objective of these analyses was to address potential concerns, such as outlier IVs, pleiotropy, and to assess the robustness of the causal hypothesis under different scenarios. Leave-one-out (LOO) analysis was used to ascertain the potential for an outlying IV. In the event that an outlier was identified, it was removed, and the subsequent IVs selection and MR tests were repeated accordingly. MR-PRESSO [78] (Mendelian randomization pleiotropy residual sum and outlier) global test was used to identify any horizontal pleiotropy in the MR test. We performed MR-Egger regression to assess whether the Egger intercept was close to zero, which would indicate the absence of potential pleiotropy [76].

Since the metabolites we analyzed for MR were genetically correlated with cognitive function, this could bias the causal results. A latent causal variable (LCV) model [79, 80] and causal analysis using summary effect estimates (CAUSE) method [81] were constructed between each significantly correlated causal pair to estimate partial genetic causality. The LCV differs from other MR methods in that it does not offer a direct test for causal effects. In contrast, LCV assesses the proportion of each trait that is influenced by a shared factor, quantified as the posterior mean genetic causality proportion (GCP), with $|GCP| > 0.6$ considered as strong evidence of partial genetic causality. LCV model scripts are at https://github.com/lukejoconnor/LCV. The CAUSE method is employed to calculate the posterior probabilities of the causal effect, shared effect, and the proportion of variants that show correlated horizontal pleiotropy, known as the q value. The causal effect reflects how the variants influence the outcome through the exposure, whereas the shared effect indicates the presence of correlated horizontal pleiotropy. In the CAUSE method, we set all the parameters at their default values (https://jean997.github.io/cause/ldl_cad.html).

To address pleiotropy among metabolites, which poses a challenge for MR selection, we examined other metabolites associated with their IVs for the putative causal metabolites. We annotated the relevant genes of genetic instruments using annovar software (http://www.openbioinformatics.org/annovar/annovar_download.html) and expression quantitative trait loci (eQTL) data from whole blood samples in GTExV8 (http://www.gtexportal.org). This investigation aimed to identify IVs that are directly and unambiguously linked to the metabolites through molecules such as transporters or metabolizing enzyme. The MR effect size of each single SNP in the IVs was estimated using the function ("mr_singlesnp") in the TwoSampleMR R package.

Mediation analysis

The principle of mediation analysis is to calculate the product of two-step MR coefficients [82]. The procedure is as follows:

i. Estimate the causal effect (β_{S1}) of the exposure on the mediator.
ii. Estimate the causal effect (β_{S2}) of the mediator on the outcome.
iii. Multiply these two estimates together to calculate the mediation effect ($\beta_M = \beta_{S1} \times \beta_{S2}$), also known as the indirect effect.

The standard error for the mediation effect is calculated using the following formula:

$$SE_M = |\beta_{S1} \times \beta_{S2}| \sqrt{\left(\frac{SE_{S1}}{\beta_{S1}}\right)^2 + \left(\frac{SE_{S2}}{\beta_{S2}}\right)^2}$$

where SE_{S1}, SE_{S2}, β_{S1}, β_{S1} represent the standard errors and coefficients, respectively. The P value is then calculated from the standard normal distribution for a two-tailed test. The total effect refers to the effect of the exposure on the outcome directly through the MR analysis. The mediated proportion indicates the ratio of the indirect effect to the total effect. It is important to note that both the indirect effect and the total effect should be in the same direction. The MR Steiger test is employed to ascertain the absence of an inverse relationship between exposure and outcome, thereby ensuring the validity of the causal pathway hypothesis [82, 83]. This test employs the "directionality_test" function within the TwoSampleMR R package.

Statistical analysis

In our genetic correlation analysis, we used a threshold of nominal p-values < 0.05 for metabolic-cognitive and cognitive-psychiatric pairs to assess potential causality. For specific MR analysis, we conducted Bonferroni correction to adjust for multiple tests. Consequently, to establish causal relationships between metabolites and the g-Factor, we set a significant p-value threshold at 7.89×10^{-5} (0.05/317/2), where 317 represents the number of metabolites and 2 denotes forward and reverse MR tests. To determine causal relationships between the g-Factor and psychiatric disorders, the threshold was 2.50×10^{-3} (0.05/10/2), with 10 representing the number of psychiatric disorders and 2 indicating bidirectional MR tests.

Upon analysis, we found causal relationships between two metabolites and three diseases and g-Factor. For mediation analysis, we used a significance threshold of 8.33×10^{-3} (0.05/2/3). In tests for pleiotropy, such as MR-PRESSO, MR-Egger regression, CAUSE, LCV and additional MR models, a p-value < 0.05 indicated moderate support. All statistical tests, except for CAUSE, used two-tailed p-values; CAUSE used a one-tailed p-value to test whether the sharing model fit the data.

RESULTS

Genetic correlations between g-Factor, blood metabolites and psychiatric disorders

Before making any causal inferences, we used LD-score regression to examine whether there was a potential common genetic basis between g-Factor and 317 blood metabolites. We assessed their genetic correlations and identified 18 metabolites that showed nominal and weaker correlations with g-Factor ($|r_g| \leq 0.23$, $P < 0.05$) (Fig. 2A and Supplementary Table 3). Moreover, genetic correlation analyses between g-Factor and 10 psychiatric disorders revealed that seven of these disorders have potential genetic associations with g-Factor (Fig. 2B). These included robust negative correlations with schizophrenia ($r_g = -0.35$, $P = 7.30 \times 10^{-70}$), PTSD ($r_g = -0.44$, $P = 3.40 \times 10^{-31}$), and bipolar disorder ($r_g = -0.22$, $P = 3.67 \times 10^{-25}$). MR analyses were then performed using these18 metabolites and seven disorders.

Causal inferences between blood metabolites and g-Factor

In a bidirectional two-sample MR analysis, we defined the causal effect of metabolite on g-Factor as a forward direction and vice versa. The SNPs associated with confounders such as alcohol consumption were excluded from the genetic instruments, as detailed in Supplementary Table 4. For each of the MR tests with F-statistic values exceeding 10, the minimum effect size with sufficient statistical power exceeding 80% was calculated (Supplementary Tables 5, 6).

In the forward MR results, two blood metabolites, acetylornithine and butyrylcarnitine, were identified as statistically significant putative causal factors for g-Factor (Fig. 3 and Supplementary Table 7). A 1-standard deviation (SD) increase in acetylornithine was found to be significantly associated with a 0.035 SD increase in g-Factor ($\beta = 0.035$, 95% CI 0.021 to 0.049, $P = 1.15 \times 10^{-6}$), suggesting a protective effect of acetylornithine on neurocognition. Conversely, a 1-SD increase in butyrylcarnitine was significantly associated with a 0.028 SD decrease in g-Factor ($\beta = -0.028$, 95% CI −0.041 to −0.015, $P = 1.31 \times 10^{-5}$), indicating a detrimental effect of butyrylcarnitine on neurocognition. Scatter plots illustrating the genetic associations between acetylornithine and g-Factor, and butyrylcarnitine and g-Factor are presented in Supplementary Fig. 1. In the reverse direction, the analysis did not provide evidence to suggest that g-Factor has a causal effect on any of the metabolites (Supplementary Table 8).

The sensitivity analyses demonstrated the reliability of these two putative causalities. Estimates from MR-RAPS (acetylornithine $\beta = 0.035$, 95% CI 0.020 to 0.049, $P = 2.43 \times 10^{-6}$; butyrylcarnitine $\beta = -0.028$, 95% CI −0.044 to −0.014, $P = 2.13 \times 10^{-4}$), weighted median (acetylornithine $\beta = 0.031$, 95% CI 0.017 to 0.046, $P = 2.88 \times 10^{-5}$; butyrylcarnitine $\beta = -0.030$, 95% CI −0.045 to −0.016, $P = 4.40 \times 10^{-5}$), and weighted mode (acetylornithine

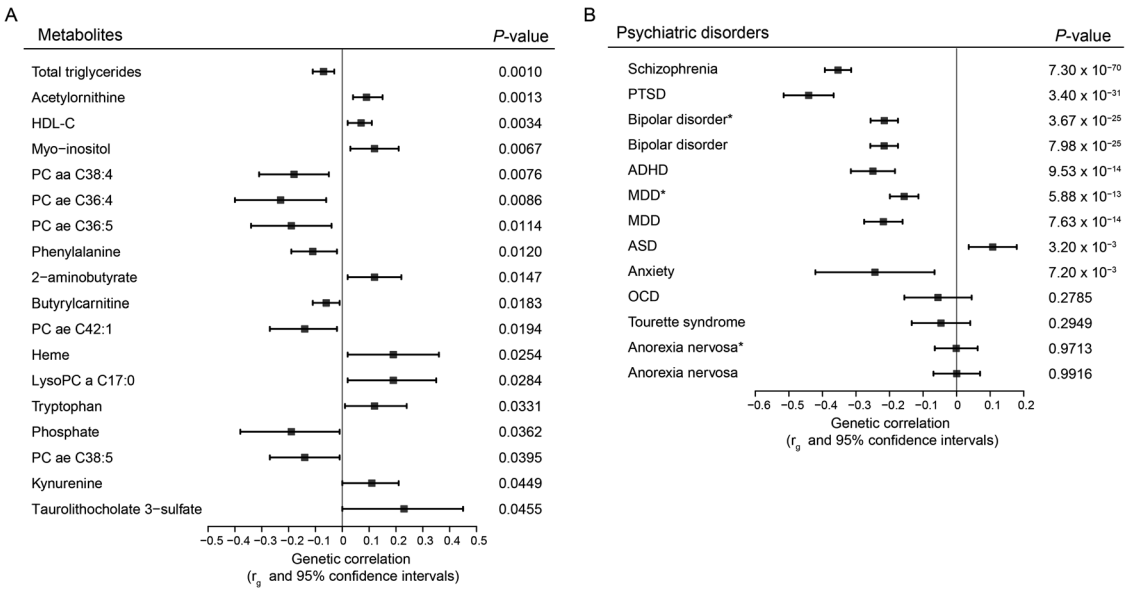

Fig. 2 The results of genetic correlation analyses. A Genetic correlations between g-Factor and metabolites. **B** Genetic correlations between g-Factor and psychiatric disorders. Genetic correlation is estimated by LD score regression. The statistical tests were two-sided. *P*-value < 0.05 was considered significant. The asterisk represents that GWAS summary-level data contains samples from UK Biobank.

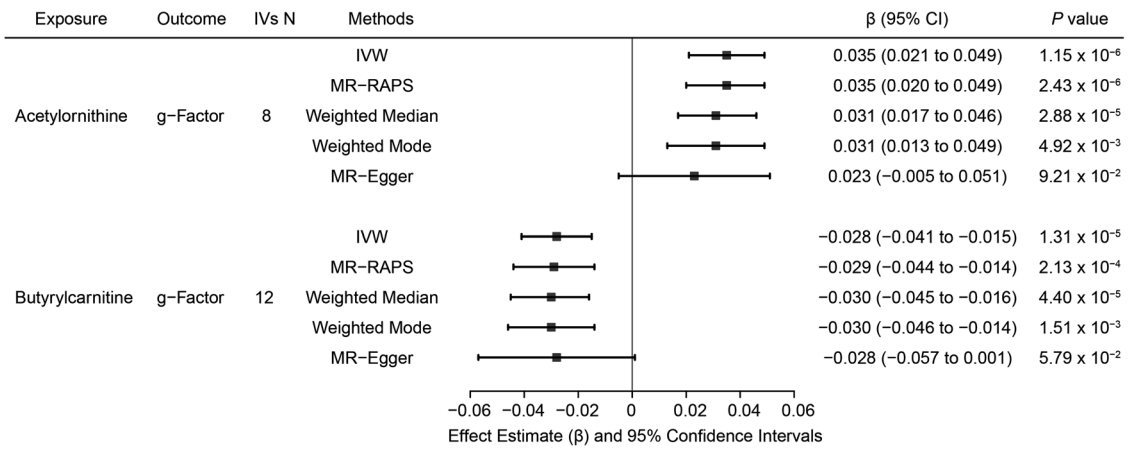

Fig. 3 MR estimates between genetically predicted blood metabolites and g-Factor. The forest plot shows significant associations. The effect estimates (β) indicate change in mean g-Factor per unit change in g-Factor, and the error bars indicate 95% confidence interval. All statistical tests were two-sided. A *P*-value < 7.89×10^{-5} after Bonferroni correction was considered significant.

$\beta = 0.031$, 95% CI 0.013 to 0.049, $P = 4.92 \times 10^{-3}$; butyrylcarnitine $\beta = -0.030$, 95% CI −0.046 to −0.014, $P = 1.51 \times 10^{-3}$) methods were generally consistent with those of the IVW method in terms of the effect size and direction (Fig. 3). Confidence intervals obtained from MR-Egger were wider than those obtained from IVW, probably due to the lower power of the MR-Egger. Leave-one-out analyses showed that the estimates from IVW remained similar after excluding each SNP from the instrumental variables, suggesting that no single SNP drove the causal estimates (Supplementary Fig. 2). MR-PRESSO (acetylornithine $P = 0.558$; butyrylcarnitine $P = 0.338$) and MR-Egger intercept analyses (acetylornithine $P = 0.242$; butyrylcarnitine $P = 0.998$) provided no evidence of pleiotropy (Supplementary Table 9).

Given that the risk causal metabolites were genetically correlated with g-Factor, this could potentially bias the causal results. To address this, we conducted an LCV model, which revealed that acetylornithine → g-Factor (GCP = 0.50) and butyrylcarnitine → g-Factor (GCP = 0.62) exhibited a tendency towards strong evidence of partial genetic causality (Supplementary Table 10). The CAUSE method did not reject the sharing model for acetylornithine → g-Factor ($ELPD_{Sharing\ vs\ Causal} = -2.2$, $P = 0.098$), estimating that 5% of acetylornithine variants act through a shared factor (Supplementary Table 10). Additionally, we found latent causal evidence supporting butyrylcarnitine → g-Factor using the CAUSE method ($ELPD_{Sharing\ vs\ Causal} = -4.1$, $P = 0.035$) (Supplementary Table 10).

In addition, we considered pleiotropy among metabolites, which poses a challenge for MR selection. For butyrylcarnitine, three IVs (rs1171617, rs662138, rs77010315) were associated with 17 other metabolites, including various carnitine derivatives, total cholesterol, and low-density lipoprotein cholesterol (Supplementary Table 11). However, no associations were found between the IVs of acetylornithine and any other metabolite. We identified the relevant genes of genetic instruments through annotation of their physical locations and eQTL signals in blood tissues (Supplementary Table 12), some of which genes are involved in functions such as transporters and metabolizing enzymes. Next, we estimated the MR effect size of each individual SNP in the IVs (Supplementary Fig. 3). The results suggest that specific IVs may play crucial roles in causal relationships. Specifically, rs17349049 is an important IV

for the acetylornithine → g-Factor relationship, but the MR estimate remained unchanged after its removal (β = 0.059, 95% CI 0.022 to 0.096, $P = 1.93 \times 10^{-3}$). Additionally, rs71454652 and rs1151874 appeared to be crucial for the butyrylcarnitine → g-Factor relationship; their removing resulted in a non-significant MR estimate (β = −0.018, 95% CI −0.041 to 0.005, $P = 0.125$). These SNPs are located within genes involved in biological functions such as microtubule organization, ribonuclease activity, and calcium-mediated cellular signal transduction.

Causal inferences between g-Factor and psychiatric disorders

Furthermore, we conducted bidirectional two-sample MR analyses between the g-Factor and the seven psychiatric disorders previously identified. We have defined the MR analysis from g-Factor to disorder in a forward direction and vice versa as a reverse inference. Detailed information on confounding SNPs, F-statistic values and statistical power of each MR test, can be found in Supplementary Tables 4, 13 and 14.

With regard to the forward MR results, three putative causal relationships were identified between g-Factor and schizophrenia (IVW OR = 0.38, 95% CI 0.30 to 0.48, $P = 1.72 \times 10^{-15}$), PTSD (IVW OR = 0.38, 95% CI 0.25 to 0.57, $P = 3.38 \times 10^{-6}$), and bipolar disorder (IVW OR = 0.51, 95% CI 0.41 to 0.64, $P = 3.80 \times 10^{-9}$) (Table 1). Specifically, a 1-SD increase in the g-Factor was associated with a 62% lower risk of schizophrenia, a 62% lower risk of PTSD, and a 49% lower risk of bipolar disorder. In the reverse MR analyses, a higher risk of schizophrenia was associated with a decreased g-Factor (IVW β = −0.062, 95% CI −0.071 to −0.052, $P = 3.78 \times 10^{-38}$) (Table 1).

A series of sensitivity analyses were conducted, including MR-RAPS, weighted median, weighted mode, and MR-Egger methods. These yielded patterns of similar estimates in size, although the confidence intervals were wider than those of the IVW (Table 1). The scatter plots (Supplementary Fig. 4) and leave-one-out plots (Supplementary Fig. 5) provided further evidence of unbiased estimates. The MR-PRESSO and MR-Egger intercept analyses were conducted to examine the presence of pleiotropy, but no evidence of pleiotropy was detected (Supplementary Table 15).

Mediation analysis between metabolites, g-Factor and psychiatric disorders

Metabolites like acetylornithine and butyrylcarnitine, as well as psychiatric disorders such as schizophrenia, PTSD and bipolar disorder, have been found to be genetically related to g-Factor in the study. The next step involves examining whether the relationship between these metabolites and disorders is mediated through g-Factor. Mediation analyses were conducted to investigate potential pathways linking the identified metabolites to the g-Factor, and psychiatric disorders.

MR analyses provided moderate support for the causal relationships between acetylornithine and bipolar disorder, as well as between butyrylcarnitine and schizophrenia using the IVW method (Supplementary Fig. 6). Specifically, a 1-SD increment in acetylornithine was associated with a 6% lower odds of bipolar disorder risk (IVW OR = 0.94, 95% CI 0.90 to 0.98, $P = 8.09 \times 10^{-3}$), while a 1-SD increase in the butyrylcarnitine was associated with a 9% higher odds of schizophrenia risk (IVW OR = 1.09, 95% CI 1.04 to 1.14, $P = 2.05 \times 10^{-4}$). The effect estimates showed consistent direction and magnitude across the MR-RAPS, weighted median, and weighted mode methods. Notably, when the weighted median method was used instead of the IVW method, the results indicated a positive association between acetylornithine levels and schizophrenia risk (OR = 0.94, 95% CI 0.90 to 0.98, $P = 5.09 \times 10^{-3}$) (Supplementary Fig. 6).

Our results are consistent with those of a previous MR study [84], which also reported negative associations between *N*-acetylornithine and bipolar disorder (IVW OR = 0.72, 95% CI 0.66 to 0.79, $P = 1.08 \times 10^{-13}$) as well as schizophrenia (IVW OR = 0.74, 95% CI 0.64 to 0.84, $P = 5.14 \times 10^{-6}$), and a positive association between butyrylcarnitine and schizophrenia (IVW OR = 1.22, 95% CI 1.12 to 1.32, $P = 1.10 \times 10^{-6}$). The confidence intervals of our MR estimates differed from theirs, which may be due to the use of different GWAS data and more stringent criteria for IVs selection. To ensure the reliability of the estimates, sensitivity analyses were conducted, including scatter plots (Supplementary Fig. 7), leave-one-out plots (Supplementary Fig. 8), MR-PRESSO (Supplementary Table 16), and MR-Egger intercept (Supplementary Table 16). These results revealed that the estimates were free from bias. A summary of the IVs for acetylornithine and butyrylcarnitine in relation to schizophrenia, PTSD, and bipolar disorder is presented in Supplementary Table 17.

Furthermore, mediation analysis was conducted to investigate the causal pathways from acetylornithine to bipolar disorder and from butyrylcarnitine to schizophrenia via the g-Factor. Two potential regulatory networks were identified (Fig. 4): a pathway from acetylornithine on bipolar disorder, mediated by g-Factor with a mediated effect of −0.023 (95% CI −0.036 to −0.011, $P = 1.76 \times 10^{-4}$) and accounting for a mediated proportion of 37.3% (Fig. 4A); and a pathway from butyrylcarnitine to schizophrenia, also mediated by the g-Factor with a mediation effect of 0.027 (95% CI 0.013 to 0.042, $P = 1.32 \times 10^{-4}$), representing approximately 32.8% of the total effect (Fig. 4B). The Steiger test [82, 83] was performed to confirm the absence of evidence for reverse causality from acetylornithine or butyrylcarnitine to bipolar disorder, schizophrenia, and g-Factor (Supplementary Table 18).

Additionally, considering the reverse causal direction from schizophrenia to the g-Factor, we found support for the causal pathway from butyrylcarnitine to the g-Factor via schizophrenia (Supplementary Fig. 9). The mediation effect of butyrylcarnitine on the g-Factor, estimated at −0.005 (95% CI −0.008 to −0.002, $P = 3.60 \times 10^{-4}$), accounted for approximately 18.4% of the total effect. This suggests that butyrylcarnitine may serve as a promising risk factor, either directly or indirectly, influencing both schizophrenia and g-Factor. Specifically, it implies that during the early stages of schizophrenia, butyrylcarnitine affects schizophrenia through cognitive modulation. However, as schizophrenia progresses, butyrylcarnitine exacerbates its effects on neurocognition.

Validating the causal pathways by other relevant neurocognitive traits

To validate the causal pathways, we examined the findings using summary statistics from other sources of neurocognitive data (Supplementary Table 2). The results showed that the causal pathway from acetylornithine to bipolar disorder was mediated through three neurocognitive traits (cognitive performance, general cognitive function, and verbal numerical reasoning) with varying mediated proportions (5.9%, 7.9% and 21.1%, respectively) (Supplementary Table 19). Similarly, the causal pathway from butyrylcarnitine to schizophrenia was found to be mediated through four neurocognitive traits (intelligence, cognitive function, general cognitive function, and verbal numerical reasoning) with varying mediated proportions (7.9%, 6.9%, 13.7% and 11.0%, respectively) (Supplementary Table 19). The MR Steiger test did not provide evidence of reverse causality from these two metabolites on neurocognitive traits (Supplementary Table 20).

DISCUSSION

In this study, we aimed to investigate the relationships between blood metabolites and neurocognitive traits by using genetic variants as unconfounded proxies. Given the observed genetic associations between neurocognitive traits and psychiatric disorders, we conducted mediation analyses to uncover the causal pathways from blood metabolites to these disorders through

Table 1. Bidirectional MR results between g-Factor and psychiatric disorders.

Psychiatric disorders	MR Method	MR of g-Factor on psychiatric disorders			MR of psychiatric disorders on g-Factor		
		Number of SNPs	OR (95% CI)[a]	*P* value	Number of SNPs	β (95% CI)[b]	*P* value
Schizophrenia							
	IVW	14	0.38 (0.30 to 0.48)	1.72×10^{-15}	116	−0.062 (−0.071 to −0.052)	3.78×10^{-38}
	MR-RAPS		0.37 (0.29 to 0.49)	3.43×10^{-13}		−0.064 (−0.074 to −0.054)	2.56×10^{-33}
	Weighted Median		0.41 (0.30 to 0.58)	1.78×10^{-7}		−0.057 (−0.071 to −0.042)	6.65×10^{-15}
	Weighted Mode		0.43 (0.25 to 0.75)	5.38×10^{-3}		−0.021 (−0.066 to 0.024)	0.358
	MR-Egger		0.39 (0.06 to 2.40)	0.283		−0.046 (−0.090 to −0.002)	0.041
PTSD							
	IVW	17	0.38 (0.25 to 0.57)	3.38×10^{-6}	3	−0.049 (−0.081 to −0.017)	2.56×10^{-3}
	MR-RAPS		0.35 (0.22 to 0.54)	2.62×10^{-6}		−0.050 (−0.085 to −0.015)	4.79×10^{-3}
	Weighted Median		0.34 (0.19 to 0.61)	3.10×10^{-4}		−0.054 (−0.092 to −0.015)	6.11×10^{-3}
	Weighted Mode		0.31 (0.09 to 1.06)	0.599		−0.065 (−0.182 to 0.052)	0.139
	MR-Egger		1.76 (0.08 to 39.89)	0.705		−0.067 (−3.061 to 2.927)	0.823
Bipolar disorder							
	IVW	19	0.51 (0.41 to 0.64)	3.80×10^{-9}	26	−0.021 (−0.041 to −0.001)	0.037
	MR-RAPS		0.50 (0.40 to 0.64)	2.34×10^{-8}		−0.019 (−0.040 to 0.001)	0.060
	Weighted Median		0.53 (0.38 to 0.72)	6.90×10^{-5}		−0.003 (−0.031 to 0.024)	0.801
	Weighted Mode		0.49 (0.25 to 0.93)	3.20×10^{-2}		0.019 (−0.036 to 0.073)	0.491
	MR-Egger		2.24 (0.26 to 19.08)	0.436		−0.012 (−0.117 to 0.094)	0.821
ADHD							
	IVW	23	0.66 (0.49 to 0.90)	7.63×10^{-3}	9	−0.034 (−0.060 to −0.007)	0.012
	MR-RAPS		0.65 (0.47 to 0.90)	0.106		−0.036 (−0.064 to −0.007)	0.014
	Weighted Median		0.69 (0.45 to 1.06)	0.090		−0.040 (−0.074 to −0.006)	0.021
	Weighted Mode		0.70 (0.28 to 1.72)	0.420		−0.064 (−0.140 to 0.011)	0.086
	MR-Egger		0.18 (0.02 to 1.79)	0.137		−0.121 (−0.252 to 0.010)	0.066
MDD							
	IVW	20	0.93 (0.74 to 1.18)	0.574	2	−0.111 (−0.245 to 0.023)	0.106
	MR-RAPS		0.94 (0.73 to 1.23)	0.672		−0.113 (−0.223 to −0.003)	0.044
	Weighted Median		0.88 (0.65 to 1.20)	0.427			
	Weighted Mode		0.71 (0.35 to 1.47)	0.339			
	MR-Egger		1.32 (0.05 to 34.99)	0.861			
ASD							
	IVW	22	1.03 (0.73 to 1.45)	0.871	1		
	MR-RAPS		1.02 (0.70 to 1.49)	0.903		0.010 (−0.061 to 0.080)	0.789
	Weighted Median		0.98 (0.63 to 1.53)	0.936			
	Weighted Mode		0.84 (0.31 to 2.29)	0.715			
	MR-Egger		0.29 (0.03 to 3.06)	0.283			
	Ward ratio					0.010 (−0.061 to 0.080)	0.789

Table 1. continued

Psychiatric disorders	MR Method	MR of g-Factor on psychiatric disorders			MR of psychiatric disorders on g-Factor		
		Number of SNPs	OR (95% CI)[a]	*P* value	Number of SNPs	β (95% CI)[b]	*P* value
Anxiety							
	IVW	22	0.90 (0.47 to 1.71)	0.751	1		
	MR-RAPS		0.91 (0.46 to 1.80)	0.797		−0.009 (−0.047 to 0.030)	0.657
	Weighted Median		0.98 (0.39 to 2.41)	0.959			
	Weighted Mode		0.46 (0.06 to 3.54)	0.434			
	MR-Egger		0.06 (0.00 to 7.19)	0.238			
	Ward ratio					−0.009 (−0.046 to 0.029)	0.648

PTSD post-traumatic stress disorder, *ADHD* attention deficit hyperactivity disorder, *MDD* major depressive disorder, *ASD* autism spectrum disorder.
[a]Indicates the odds for disorder per one SD increase in mean g-Factor change.
[b]Indicates the change in mean g-Factor per disorder versus control status. All statistical tests were two-sided.

cognition. Our findings suggested that acetylornithine has a protective effect on the g-Factor, a measure of general cognitive ability. We observed that the g-Factor partially mediates the association between acetylornithine and bipolar disorder. Similarly, we identified a deleterious causal effect of butyrylcarnitine on the g-Factor, with the g-Factor acting as a partial mediator in the association between butyrylcarnitine and schizophrenia. These results were robust across a variety of sensitivity analyses designed to address potential horizontal pleiotropy. To further validate the reliability of our findings, we corroborated them with cognitive phenotypes derived from independent sources, which consistently supported our conclusions.

Acetylornithine, a member of the class of biogenic amines, is an intermediate product in the biosynthesis of arginine from glutamate. The acetylornithine pathway may facilitate the polyamine-mediated stress response, which regulates intracellular polyamine homeostasis and metabolic processes in organisms [85, 86]. The cognitive protective effect of acetylornithine is supported by evidence. Prior study has shown that individuals with Alzheimer's disease exhibit higher serum acetylornithine levels compared to those with mild cognitive impairment [87]. Acetylornithine has also been demonstrated to exhibit high stability over a 10-year period, as evidenced by a study assessing metabolite stability in humans [88]. It can be obtained through dietary sources such as fruits and legumes [89–92], making it a potential target for healthcare interventions. This allows for the provision of appropriate dietary advice to patients.

Conversely, butyrylcarnitine, a plasma metabolite belonging to the acylcarnitine class, has been associated with detrimental effects on neurocognition. Abnormalities in acylcarnitine metabolism have been linked to impaired fatty acid oxidation and mitochondrial dysfunction, which can affect the brain's energy supply [93, 94]. Elevated plasma concentrations of butyrylcarnitine have been observed in individuals with developmental and cognitive impairment [95]. A study has suggested that individuals with schizophrenia exhibit elevated levels of butyrylcarnitine when compared to healthy individuals [96]. Elevated butyrylcarnitine level have been demonstrated to regulate accelerated neuronal differentiation in aged subjects [97]. Butyric acid, a precursor to butyrylcarnitine, is derived primarily from microbial fermentation of dietary fiber in the intestine [98]. Consequently, butyrylcarnitine is intimately linked with dietary intake and can facilitate the transfer of metabolites from food to the brain via the circulatory system.

It has been shown that there is a significant genetic overlap between cognitive traits and psychiatric disorders [99–101]. For instance, while the majority of schizophrenia risk variants are associated with poorer cognitive performance, bipolar disorder risk variants are associated with either poorer or better cognitive performance [102]. Moreover, gene set enrichment analyses revealed shared loci for biological processes related to neural development, synaptic integrity, and neurotransmission between schizophrenia and intelligence [103]. Therefore, the relationship between psychiatric disorders and neurocognition is complex and multifaceted. The findings of this study suggest that butyrylcarnitine may increase the risk of schizophrenia by impairing neurocognitive function. This impairment may, in turn, exacerbate neurocognitive impairment and contribute to the onset of schizophrenia. Clinical studies have consistently shown that neurocognitive deficits precede the onset of schizophrenia [3] and persist even after the onset of the disorder [4]. Recent MR studies have also supported our findings, indicating bidirectional genetic associations between schizophrenia and neurocognition [43, 104], as well as associations of the metabolites acetylornithine and butyrylcarnitine with schizophrenia and bipolar disorder [84, 105]. Nevertheless, no study to date has investigated the interrelationship between metabolites, cognition, and psychiatric disorders.

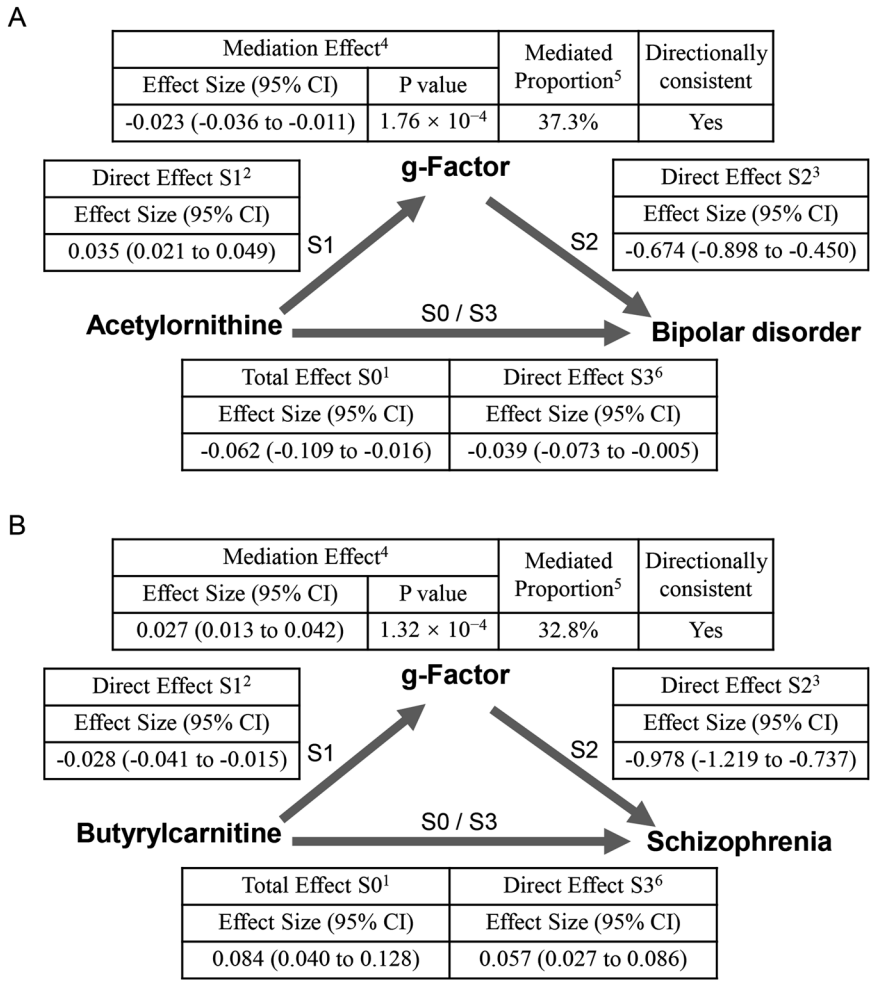

Fig. 4 Mediation estimates between metabolites, g-Factor and psychiatric disorders. A Pathway from acetylornithine to bipolar disorder via the mediator of g-Factor. **B** Pathway from butyrylcarnitine to schizopherenia via the mediator of g-Factor. The indirect effect was calculated by mediation analysis via two-step MR framework. Inverse-variance weighted method was used as the MR test. All statistical tests were two-sided from normal distribution. A *P*-value < 8.33×10^{-3} was considered significant after correction. Abbreviation: g-Factor, general cognitive factor score; CI, confidence intervals. [1]Total effect S0 indicates the causal effect of the exposure on the outcome. [2] Direct effect S1 indicates the causal effect of the exposure on the mediator. [3] Direct effect S2 indicates the causal effect of the mediator on the outcome. [4]Mediation effect indicates the indirect effect of exposure on outcome through the mediator. Indirect effect and total effect should be in the consistent direction. [5]Mediated proportion indicates the ratio of indirect effect to the total effect of the exposure on the outcome. [6]Direct effect S3 indicates the total effect minus the indirect effect of the exposure on the outcome.

The studies of plasma pharmacometabolomics have revealed that the concentration of acetylornithine undergoes significant alterations following the administration of psychiatric or neurodegenerative drugs [106, 107]. To date, no studies have been conducted to elucidate the functional role of acetylornithine in the central nervous system. Acetylornithine generates the metabolites ornithine and citrulline via deacetylase and carbamoyltransferase, which ultimately participate in the metabolic pathway of arginine synthesis. Arginine is also known to influence nitric oxide synthesis in the brain, as well as vasodilatation, neuronal conduction, and brain cell protection [108–110]. These effects have been suggested to impact brain cognitive function and psychiatric symptoms. Since the pathway of acetylornithine to arginine synthesis is not unidirectional, our findings may imply that acetylornithine may also play an important role in brain cognition and its associated psychiatric symptoms. A deficiency of short-chain acyl-CoA dehydrogenase, resulting from variations in genes encoding ACAD family members, may be responsible for the elevation of butyrylcarnitine in the blood [111]. Butyrylcarnitine belongs to the acylcarnitine family, which is involved in fatty acid metabolism, particularly mitochondrial fatty acid beta-oxidation [112]. Such abnormalities may be indicative of mitochondrial dysfunction, which affects the energy supply to the brain and consequently triggers disorders in brain function [113]. Impaired fatty acid and glucose oxidation due to mitochondrial dysfunction is strongly associated with cognitive dysfunction and the development of psychiatric disorders [114, 115]. At present, there is a paucity of mechanistic studies on butyrylcarnitine, whereas there is considerable evidence supporting the neuroprotective effects of acetylcarnitine on cognitive impairment [116].

Our findings highlight the impact of blood metabolism levels on cognitive performance, particularly in relation to the risk of mental illness. However, it is essential to acknowledge several limitations in the study. Firstly, while we ensured the independence of IVs in terms of physical location, we cannot exclude the possibility of bio-functional interactions among genetic instruments. Secondly, the GWAS data used for the majority of metabolites were summary-level statistics derived from various meta-analyses, which may potentially introduce implications pertaining to population stratification. Thirdly, it should be noted that environmental and social factors, including assortative mating, lifestyle, and economic status, can introduce biases in MR estimates

[117, 118]. Fourthly, caution should be exercised in applying MR estimates to clinical interventions and health care decisions because MR primarily examines the long-term effects of lifetime exposures rather than short-term interventions [119]. Lastly, the use of a binary outcome in the mediation approach is a potential source of bias [82]. Since both schizophrenia and bipolar disorder are relatively rate (< 10%) [120], this is likely to be less of an issue, as the odds ratio will approximate the risk ratio somewhat sufficiently. If the outcome is common, then the product method used in the study is invalid for the direct and indirect effects. One way to address this issue is to estimate the direct and indirect effects using log-binomial models [82].

CONCLUSIONS

In conclusion, this study used large-scale GWAS data, MR, and mediation analysis to uncover causal pathways between blood metabolites, neurocognitive traits, and psychiatric disorders. The results suggested a protective role of acetylornithine and a detrimental role of butyrylcarnitine on neurocognition, linking acetylornithine to bipolar disorder and butyrylcarnitine to schizophrenia. These findings offer insights into the pathophysiology of these disorders and highlight potential metabolic targets for prevention and treatment. Further research is needed to explore these metabolic factors in schizophrenia and bipolar disorder.

DATA AVAILABILITY

All GWAS summary statistics used in our study are publicly available online. Detailed information and specific release links are provided in Supplementary Table 1 and 2. Briefly, summary-level data for metabolites GWAS were obtained from the following sources: https://omicscience.org/apps/crossplatform/, http://metabolomics.helmholtz-muenchen.de/gwas, https://gwas.mrcieu.ac.uk, and NCBI dbGaP (phs001672.v4.p1). The g-Factor GWAS summary data were downloaded from https://datashare.ed.ac.uk/handle/10283/3756, and other cognitive traits were sourced from http://www.thessgac.org, https://ctg.cncr.nl, and http://www.psy.ed.ac.uk/ccace/downloads/. Data for nine psychiatric disorders were downloaded from https://pgc.unc.edu/for-researchers/download-results/, with PTSD data available from NCBI dbGaP (phs001672.v1.p1).

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AUTHOR CONTRIBUTIONS

YG and JG designed this project. JG, PY, J-HW, S-HT, KY, and C-CL conducted the computational work. JG wrote the manuscript. YG revised the manuscript. JG, J-ZH and SY summarized the tables and figures. SY, S-SD, KZ, Y-YD and T-LY summarized the public data and offered some advices. YG and T-LY supported and supervised this project.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics committee of Xi'an Jiaotong University (Shaanxi, China). All datasets were publicly available, and ethical approval and informed consent were acquired for all original studies.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Yan Guo.

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