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Association Between Human Blood Metabolome and the Risk of Psychiatric Disorders

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***Background and Hypothesis*: To identify promising drug targets for psychiatric disorders, we applied Mendelian randomization (MR) design to systematically screen blood metabolome for potential mediators of psychiatric disorders and further predict target-mediated side effects. *Study Design*: We selected 92 unique blood metabolites from 3 metabolome genome-wide association studies (GWASs) with totally 147 827 participants. Summary statistics for bipolar disorder (BIP), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), schizophrenia (SCZ), panic disorder (PD), autistic spectrum disorder (ASD), and anorexia nervosa (AN) originated from the Psychiatric Genomics Consortium, involving 1 143 340 participants. Mendelian randomization (MR) analyses were conducted to estimate associations of blood metabolites with psychiatric disorders. Phenome-wide MR analysis was further performed to predict side effects mediated by metabolite-targeted interventions. *Results*: Eight metabolites were identified associated with psychiatric disorders, including five established mediators: *N*-acetylornithine (BIP: OR, 0.72 [95% CI, 0.66–0.79]; SCZ: OR, 0.74 [0.64–0.84]), glycine (BIP: OR, 0.62 [0.50–0.77]), docosahexaenoic acid (MDD: OR, 0.96 [0.94–0.97]), 3-Hydroxybutyrate (MDD: OR, 1.14 [1.08–1.21]), butyrylcarnitine (SCZ: OR, 1.22 [1.12–1.32]); and three novel mediators: 1-arachidonoylglycerophosphocholine (1-arachidonoyl-GPC)(BIP: OR, 0.31 [0.23–0.41]), glycoproteins (BIP: OR, 0.94 [0.92–0.97]), sphingomyelins (AN: OR, 1.12 [1.06–1.19]). Phenome-wide MR analysis showed that all identified metabolites except for *N*-acetylornithine and 3-Hydroxybutyrate had additional effects on nonpsychiatric diseases, while glycine, 3-Hydroxybutyrate, *N*-acetylornithine, and butyrylcarnitine had no adverse side effects. *Conclusions*: This MR study identified five established and three novel mediators for psychiatric disorders. *N*-acetylornithine, glycine, 3-Hydroxybutyrate, and butyrylcarnitine might be promising targets against psychiatric disorders with no predicted adverse side effects.**

Key words: psychiatric disorders/metabolites/Mendelian randomization/biomarkers/antipsychotics.

Introduction

Psychiatric disorders are characterized by unhealthy and inflexible patterns of thoughts and behavior,[1] mainly including bipolar disorder (BIP), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD; a common anxiety disorder), major depressive disorder (MDD), schizophrenia (SCZ), panic disorder (PD; the most severe form of anxiety disorder), autistic spectrum disorder (ASD), and anorexia nervosa (AN).[2] In 2017, there were over 970 million patients with psychiatric disorders worldwide, and psychiatric disorders accounted for 14.39% of years lived with disability.[2] Although a number of antipsychotics have been discovered, a considerable proportion of patients still had a poor response to treatment[3] and experienced deleterious side effects.[4] Based on the high attrition rate of drug development, it is imperative to explore the potential mediators of psychiatric disorders before being tested in clinical trials.[5]

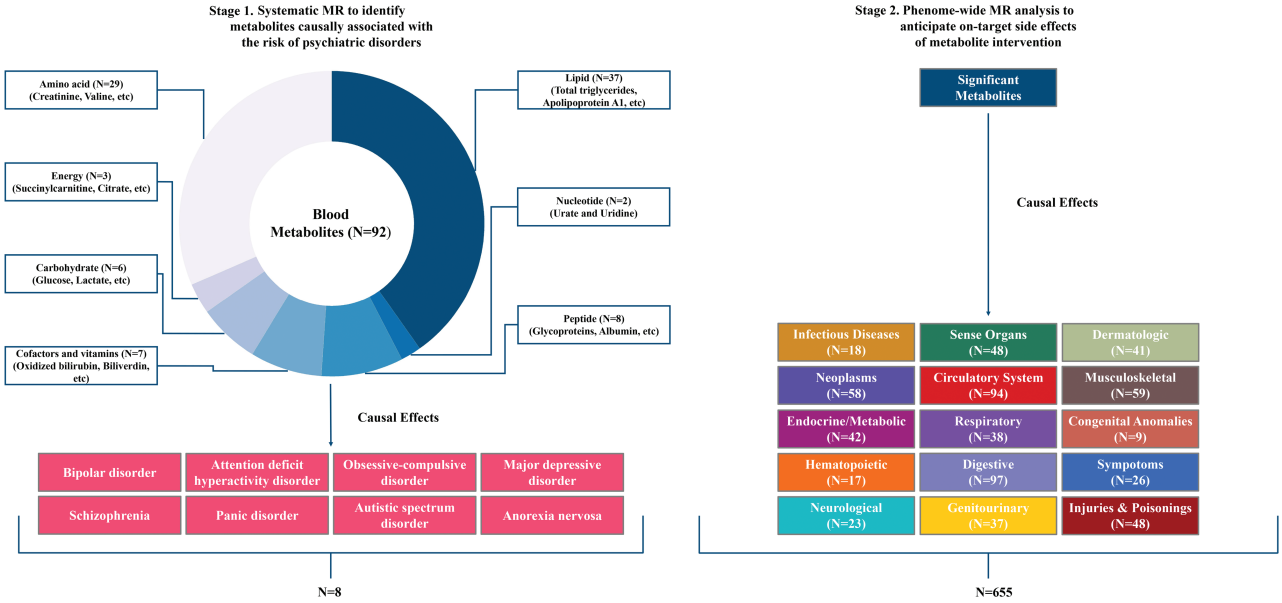

Figure 1. Study design and conceptual workflow. This schematic representation revealed a 2-stage design of our Mendelian randomization (MR) study. First, we estimated the effects of 92 blood metabolites on the risk of 8 psychiatric disorders. Second, we explored a broad spectrum of target-mediated side effects associated with metabolite intervention in 655 nonpsychiatric diseases, involving 15 different International Classification of Disease (ICD)-9 chapters. At each stage, the Bonferroni-corrected *P* value threshold was set accounting for the corresponding number of metabolites and diseases analyzed.

Recently, accumulating evidence suggested that metabolic abnormalities were implicated in the pathophysiology of psychiatric disorders.[6] Nelson et al. reported that genomics could help to elucidate the causal pathways linking risk factors and disease, and that drug with genetically supported targets would be twice as likely to reach market approval.[5] Recent advancements in mass spectrometry and high-throughput genotyping enabled genome-wide association studies (GWASs) to comprehensively reveal genetic determinants of metabolome.[7–9] Such developments offered an opportunity to accurately identify promising drug targets for psychiatric disorders by integrating genomic and metabolomics data through Mendelian randomization (MR) design.

MR is an emerging analytic approach using genetic variants associated with exposures as instrumental variables to estimate the potential causal effects of exposures on outcomes.[10] Notably, alleles are randomly allocated during gamete formation, so MR is considered as a "natural" RCT, which can minimize the confounding and reverse-causality biases.[11] In addition, genetic effects are lifelong, and datasets from psychiatric disorders GWASs with large sample sizes are available now.[12–19] Therefore, MR studies could simulate large-scale and long-term clinical trials for the primary and secondary prevention of psychiatric disorders, eliminating the expensive cost and time-consuming follow-up process. MR design has been widely applied to identify the potential mediators of BIP, ADHD, MDD, SCZ, and ASD from the blood metabolome in the previous studies, but the potential side effects associated with metabolite-targeted intervention remained unclear.[20] Of note, a phenome-wide MR (Phe-MR) analysis for drug-induced side effects could help to identify unexpected adverse effects and provide opportunities for drug repurposing prior to clinical testing.[21] In addition, although the MR evidence for the role of blood metabolites in the etiology of some psychiatric disorders (e.g., OCD, PD, and AN) is limited, GWAS data for these psychiatric disorders have been published.[14,17,19]

Herein, we conducted a two-stage MR study to identify promising drug targets for eight major psychiatric disorders, including BIP, ADHD, OCD, MDD, SCZ, PD, ASD, and AN. First, we systematically screened 92 circulating metabolites for the potential causal mediators of psychiatric disorders. Subsequently, we performed a Phe-MR analysis of 655 disease traits to predict on-target side effects of identified metabolites for a comprehensive appraisal of their clinical safety as intervention targets.

Methods

Study design

This two-stage MR study aimed to identify promising drug targets of psychiatric disorders from genetic perspective (figure 1). There were three core instrumental variable assumptions for MR study: (1) the genetic variants should be associated with the exposure; (2) the genetic variants should be independent of confounders;

and (3) the genetic variants should influence the outcome only through the exposure. The summary-level data of the blood metabolome, psychiatric disorders, and 655 nonpsychiatric diseases utilized in the present study were derived from the publicly available GWASs based on the cohorts of predominately European ancestry.[7–9,12–19,22] Details on the participant selection, genotyping and imputation steps of the population-based cohorts and the corresponding baseline characteristics have been reported previously.[7–9,12–19,22] This MR study followed the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR).

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol and data collection were approved by the ethics committee of the original GWASs, and written informed consent was obtained from each participant before data collection.

Data Source for Blood Metabolome

Summary-level data of the single nucleotide polymorphisms (SNPs) associated with the human metabolome originated from three large-scale GWASs with a combined total of 147 827 European participants (Table 1).[7–9] In brief, Shin et al.[7] analyzed 453 metabolic traits in 7824 participants with approximately 3 million SNPs from 2 cohorts; Kettunen et al.[8] analyzed 123 metabolic traits in 24 925 participants with approximately 12 million SNPs from 14 cohorts; and Borges et al.[9] analyzed 249 metabolic traits in 115 078 participants with approximately 12 million SNPs from UK Biobank (Table 1). Among these 825 metabolic traits, a total of 394 metabolic traits were excluded because they were overlapped metabolites, unknown metabolites, or non-metabolites (e.g., lipid concentrations in lipoproteins, relative proportion of lipids in lipoproteins, diameter for lipoproteins particles), and a total of 431 metabolites were retained.

Data Source for Psychiatric Disorders

We obtained the summary genetic statistics of psychiatric disorders from the Psychiatric Genomics Consortium (Table 1), which included 8 predominantly European ancestry-based GWAS meta-analyses (BIP [41 917 cases and 371 549 controls],[12] ADHD [20 183 cases and 35 191 controls],[13] OCD [2688 cases and 7037 controls],[14] MDD [170 756 cases and 329 443 controls],[15] SCZ [11 260 cases and 24 542 controls],[16] PD [2147 cases and 7760 controls],[17] ASD [18 381 cases and 27 969 controls],[18] and AN [16 992 cases and 55 525 controls][19]) (available from Psychiatric Genomics Consortium website: https://www.med.unc.edu/pgc). Diagnostic criteria for these psychiatric disorders have been previously described in detail.[12–19]

Genetic Instruments of Blood Metabolome

In this MR study, SNPs that were identified to be associated with blood metabolites at genome-wide significance level (P value $<5 \times 10^{-8}$) in the published GWASs and were not in linkage disequilibrium (LD) with other SNPs ($r^2 < 0.1$ within a clumping window of 500 kb) were used as genetic instruments for these metabolites. For SNPs exhibiting LD above a threshold of $r^2 = 0.1$, we only selected the SNP with the lowest P value for association with the metabolite. Subsequently, we removed the genetic variants which were not available in GWAS datasets of psychiatric disorders to ensure that the included genetic variants could link blood metabolites to psychiatric disorders, and calculated the phenotypic variance of each metabolite explained by the genetic instruments. The metabolites with variance explained by genetic instruments less than 0.5% were removed due to insufficient statistical power for a valid causal inference.[23] Furthermore, we excluded the metabolites associated with less than 3 SNPs to meet the minimum requirement of the number of SNP for some MR sensitivity analyses.[24]

Based on the above exclusion criteria, 339 of the 431 metabolites were further excluded. Finally, a total of 92 unique blood metabolites were retained for the present MR analyses (figure 1). An overview of the data concerning the SNPs used as genetic instruments in this MR study is listed in s-table S1, and further details are available in s-table S2. We calculated the F statistic to assess the strength of the genetic instruments for blood metabolites. An F statistic greater than 10 suggests a strong instrument.[25]

Statistical Analysis

In the main analysis, we adopted the inverse-variance weighted (IVW) MR method to estimate the associations between 92 blood metabolite and the risk of 8 psychiatric disorders, in which the SNP-psychiatric disorder estimate is regressed on the SNP-metabolite estimate and weighted by the inverse-variance of SNP-psychiatric disorder estimate, and the intercept is set to zero.[10] We performed Cochran's Q test to evaluate the heterogeneity among genetic variants used in the main analysis.[26] A fixed-effect IVW model was used under the hypothesis of homogeneity; otherwise, a random-effect IVW model was used.

Although the IVW method is a powerful option for causal inference, the main assumptions underlying IVW method are somewhat hard to meet in the presence of invalid instruments and pleiotropy. To assess the validity of the associations identified by the IVW method, we conducted a series of sensitivity analyses with different models. First, we adopted the penalized IVW method, which enabled us to penalize the SNPs with pleiotropy.[27] Second, the MR-Robust Adjusted Profile Scoring (MR-RAPS) method was undertaken, in which method the MR estimates were robust to violations of key MR

Table 1. Characteristics of GWASs on the Blood Metabolome and Psychiatric Disorders.

Phenotype	Cohort(s)	Sample size	Ethnicity
Metabolic trait ($N = 453$)	KORA; TwinsUK	7,824	German; British
Metabolic trait ($N = 123$)	EGCUT; ERF; FTC; FR97; COROGENE; GenMets; HBCS; KORA; LLS; NTR; NFBC 1966; PredictCVD; PROTE; YFS	24,925	Estonian; Dutch; Finnish; Finnish; Finnish; Finnish; Finnish; German; Dutch; Dutch; Finnish; Finnish; Estonian; Finnish
Metabolic trait ($N = 249$)	UK Biobank	115,078	British
BIP	BOMA-Australia; BOMA-Germany II; BOMA-Germany III; BOMA-Poland; BOMA-Spain; BOMA-Germany I; Trinity College Dublin; University of Edinburgh; FaST, TGEN1,2; French; BiGs: GAIN; BACCS; Nova Scotia, MGH i2b2 controls; ICCBD BDRN; Janssen, SAGE controls; Mayo Clinic; Pritzker Neuropsychiatric Disorders Research Consortium (U Michigan); Pfizer; BOMA-Romania; STEP2, MIGEN controls; STEP1; SWEBIC I Affy; SWEBIC I Illumina; TOP; TOP, additional samples on new platform; Dutch-UCLA; University College London; UMEA; ICCBD USC; WTCCC; Bulgarian trios; UK trios; Janssen; PsyCourse; BIGs/TGEN; Bipolar Depression Treatment Response Study; dutch[a]; gawli[a]; GUF-Bipolar; GPC; NeuRA-psych (including controls from The Australian Schizophrenia Research Bank); spsp3[a]; GEMS and EIMS; ukwa1[a]; usaw4[a]; usaw5[a]; iPSYCH; deCODE; Estonian Biobank; Nord-Trøndelag Health Study; UK Biobank; BOMA-Russia; ATLADIS; BIPGEN; BOMA-Romania II	413,466	Australian; German; German; Polish; Spanish; German; British; British; American; French; American; American; Canadian/American; British; American; American; American; American; Romanian; American; American; Swedish; Swedish; Norwegian; Norwegian; Dutch; British; Swedish; American; British; Bulgarian; British; East. European; German; American; German; Dutch; German; German; American; Australian; Spanish; Swedish; British; American; Canadian/American; Danish; Icelander; Estonian; Norwegian; British; Russian; Greek; Austrian; Romanian
ADHD	iPSYCH-ADHD, Denmark; Barcelona, Spain (from PGC); Beijing, China (from PGC); Bergen, Norway (from PGC); Cardiff, UK (from PGC); CHOP, USA (from PGC); Germany (from PGC); IMAGE-I (from PGC); IMAGE-II (from PGC); PUWMa (from PGC); Toronto, Canada (from PGC); Yale-Penn (from PGC)	55,374	Danish; Spanish; Han Chinese; Norwegian; British; American; German; European; European; Diverse (American); Canadian; American
OCD	IOCDFGC Ashkenazi Jewish; IOCDFGC Dutch; IOCDFGC European; IOCDFGC South African; IOCDFGC European Trios; OCGAS case/control; OCGAS Trios	9,725	European ancestry; European ancestry; European ancestry; European ancestry; European ancestry; European ancestry; European ancestry
MDD	UK Biobank; PGC_139k	500,199	British; European
SCZ	CLOZUK1; CardiffCOGS1; CLOZUK2; CardiffCOGS2; WTCCC2; Cardiff Controls; Generation Scotland; T1DGC; POBI; TWINSUK; QIMR; TEDS; GERAD	35,802	British; British; British; British; British; British; British; British; British; British; Australian; British; British
PD	Germany I; Germany II; Germany III; Sweden; Denmark; Estonia	9,907	German; German; German; Swedish; Danish; Estonian
ASD	iPSYCH-ASD	46,350	Danish

Table 1. Continued

Phenotype	Cohort(s)	Sample size	Ethnicity
AN	CHOP/PFCG; GCAN/WTCCC3; GCAN/WTCCC3/IARC/CNG; ANGI-DK; ANGI-ANZ/QSkin; ANGI-US/PFCG; ANGI-SE (Riksät/SCÄ/LifeGene/other); UK Biobank	72,517	American/Canadian, British, German, Italian; Finnish, French, German, Norwegian, Swedish, Southern Italian, Greek, Dutch, Spanish, British, American/Canadian; Polish, Czech; Danish; Australian, New Zealander; American; Swedish, Danish; British

Abbreviation: ADHD, attention deficit hyperactivity disorder; AN, anorexia nervosa; ANGI, Anorexia Nervosa Genetics Initiative; ASD, autistic spectrum disorder; ATLADIS, AThens Longitudinal Affective DIsorders Study; BACCS, Bipolar Association Case-Control Study; BDRN, Bipolar Disorder Research Network; BiGs, Bipolar Genome Study; BIP, bipolar disorder; BOMA, Bonn-Mannheim; CardiffCOGS, Cardiff Cognition in Schizophrenia; CHOP, Children's Hospital of Philadelphia; CLOZUK, United Kingdom Clozapine Clinic; CNG, Centre National de Génotypage; COROGENE, Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram; EGCUT, Estonian Genome Center of University of Tartu Cohort; EIMS, Epidemiological Investigation of Multiple Sclerosis; ERF, Erasmus Rucphen Family Study; FR97, a subsample of FINRISK 1997; FTC, Finnish Twin Cohort; GAIN, Genetic Association Information Network; GCAN, Genetic Consortium for Anorexia Nervosa; GEMS, Genes and Environment in Multiple Sclerosis; GenMets, Genetics of METabolic Syndrome; GERAD, Genetic and Environmental Risk for Alzheimer's Disease; GPC, Genomic Psychiatry Cohort; GUF, Goethe University Frankfurt; GWAS, genome-wide association study; HBCS, Helsinki Birth Cohort Study; IARC, International Agency for Research on Cancer; ICCBD, International Cohort Collection for Bipolar Disorder; IMAGE, International Multisite ADHD Genetics; IOCDFGC, International Obsessive Compulsive Disorder (OCD) Foundation Genetics Collaborative; iPSYCH, Integrative Psychiatric Research; KORA, Kooperative Health Research in the Region of Augsburg; LLS, Leiden Longevity Study; MDD, major depressive disorder; MGH, Massachusetts General Hospital; MIGEN, Myocardial Infarction Genetics Consortium; NFBC 1966, Northern Finland Birth Cohort 1966; NTR, Netherlands Twin Register; OCGAS, OCD Collaborative Genetics Association Study; PD, panic disorder; PFCG, Price Foundation Collaborative Group; PGC, Psychiatric Genomics Consortium; POBI, People of the British Isles; PredictCVD, FINRISK subsample of incident cardiovascular cases and controls; PROTE, EGCUT sub-cohort; PUWMa, Pfizer-funded study from University of Carlifornia, Los Angeles (UCLA), Washington University, and MGH; QIMR, Queensland Institute of Medical Research; QSkin, Sun and Health Study; Riksät, Swedish National Quality Register for Eating Disorders; SAGE, Study of ADHD, Genes and Environment; SCÄ, Stockholm Center for Eating Disorders; SCZ, schizophrenia; STEP, Systematic Treatment Enhancement Program for Bipolar Disorder; SWEBIC, Swedish Bipolar Collection; T1DGC, Type 1 Diabetes Genetics Consortium; TEDS, Twins Early Development Study; TGEN, Translational Genomics Research Institute; TOP, Thematically Organized Psychosis; WTCCC, Wellcome Trust Case-Control Consortium; YFS, The Cardiovascular Risk in Young Finns Study.

[a] Cohort whose sample name was not available was represented using the corresponding abbreviation in the original GWAS.

assumptions.[28] Third, we utilized the maximum likelihood method to provide reliable results in presence of measurement error in SNP-exposure association.[24] Fourth, we performed the MR-Egger regression to determine the potential pleiotropy through its intercept term.[24]

Phe-MR Analysis for Target-mediated Side Effects of Psychiatric Disorders-related Metabolites

We performed a Phe-MR analysis to explore the potential side effects of hypothetical interventions that reduced the risk of psychiatric disorders by targeting the identified metabolites. Summary statistics for 1403 disease traits were obtained from Zhou et al.' GWAS with 408 961 white British participants and 28 million SNPs in the UK Biobank cohort.[22] Disease traits were defined based on "PheCodes", which is a system organized International Classification of Disease (ICD) codes into phenotypic outcomes, enabling investigators to perform systematic genetic analysis of multiple disease traits.[22,23] To ensure the interpretability of the results, we only selected representative nonpsychiatric diseases to minimize the inherent redundancy between PheCodes. Moreover, sex-specific disease traits and disease traits with cases less than 500 had issues of data availability and statistical power, so we also excluded these disease traits. Finally, a total of 655 nonpsychiatric diseases were retained for the Phe-MR analysis (figure 1; s-table S3). According to the associations between metabolites and psychiatric disorders, Phe-MR findings are standardized to a change in metabolite level corresponding to a 10% reduction in the risk of psychiatric disorders, and the specific calculation formulas are available in Supplementary Methods. The standardized results in this manner enabled us to directly determine the direction of the side effects and compare their magnitude with the therapeutic effects of metabolite-targeted interventions in the prevention of psychiatric disorders.

All results for the outcomes are presented as odds ratios (ORs) and their 95% confidence intervals (CIs). In stage 1, an observed 2-sided $P < 6.79 \times 10^{-5}$ (Bonferroni-corrected significance threshold calculated as 0.05 divided by 736 [for 92 metabolites and 8 psychiatric disorders]) was considered as the statistically

significant evidence for a causal inference. A 2-sided $P < 0.05$ in the MR-Egger regression method was considered as the suggestively significant evidence for potentially directional pleiotropy. All analyses were performed in R (version 3.4.3; R Development Core Team) with the packages gtx, MendelianRandomization, TwoSampleMR, ggplot2, ggrepel, grid, gridExtra, gtable, qqman, RColorBrewer, and RGraphics.

Data Availability

All summary statistics used in this two-stage Mendelian randomization are available online from each genome-wide association study. Statistical code is available on the request by directly contacting the corresponding author (email: zbzhu@suda.edu.cn).

Results

Strength of the Genetic Instruments for Blood Metabolites

A total of 92 unique blood metabolites were analyzed in the present study (s-table S1), and a specific description of genetic instruments for each blood metabolite is presented in Tables S2. The observed phenotypic variance explained by the genetic instruments ranged from 0.54% for acetone to 45.18% for butyrylcarnitine. The *F* statistics for the genetic instruments of the blood metabolites ranged from 32 to 460, suggesting that there was no instrument bias in this study (s-table S1).

Screening the Blood Metabolome for Potential Causal Mediators of Psychiatric Disorders

In the main IVW MR analysis of 92 blood metabolites and 8 psychiatric disorders, genetically determined low 1-arachidonoylglycerophosphocholine (1-arachidonoyl-GPC), arachidonate, glycoproteins, *N*-acetylornithine, glycine, *N*-acetylglycine, and docosahexaenoic acid, and genetically determined high androsterone sulfate, epiandrosterone sulfate, 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins were significantly associated with increased risks of psychiatric disorders (figure 2 and s-table S4). Sensitivity analyses using the penalized IVW method, the MR-RAPS method, and the maximum likelihood method found the same associations identified in the main analysis, except for the attenuated associations of androsterone sulfate, epiandrosterone sulfate, arachidonate, and *N*-acetylglycine with BIP (s-table S5). The MR-Egger regression suggested that the genetic variants for these metabolites except for epiandrosterone sulfate had no directional pleiotropic effects on the risk of psychiatric disorders (all $P > 0.05$).

Overall, a total of 8 metabolites were identified as potential causal mediators for psychiatric disorders (table 2). Among these metabolites, per 1-SD increase in the genetically determined 1-arachidonoyl-GPC (BIP: OR = 0.31, 95% CI = 0.23–0.41, $P = 3.52 \times 10^{-16}$), glycoproteins (BIP: OR = 0.94, 95% CI = 0.92–0.97, $P = 3.10 \times 10^{-5}$), *N*-acetylornithine (BIP: OR = 0.72, 95% CI = 0.66–0.79, $P = 1.08 \times 10^{-13}$; SCZ: OR = 0.74, 95% CI = 0.64–0.84, $P = 5.14 \times 10^{-6}$), glycine (BIP: OR = 0.62, 95% CI =

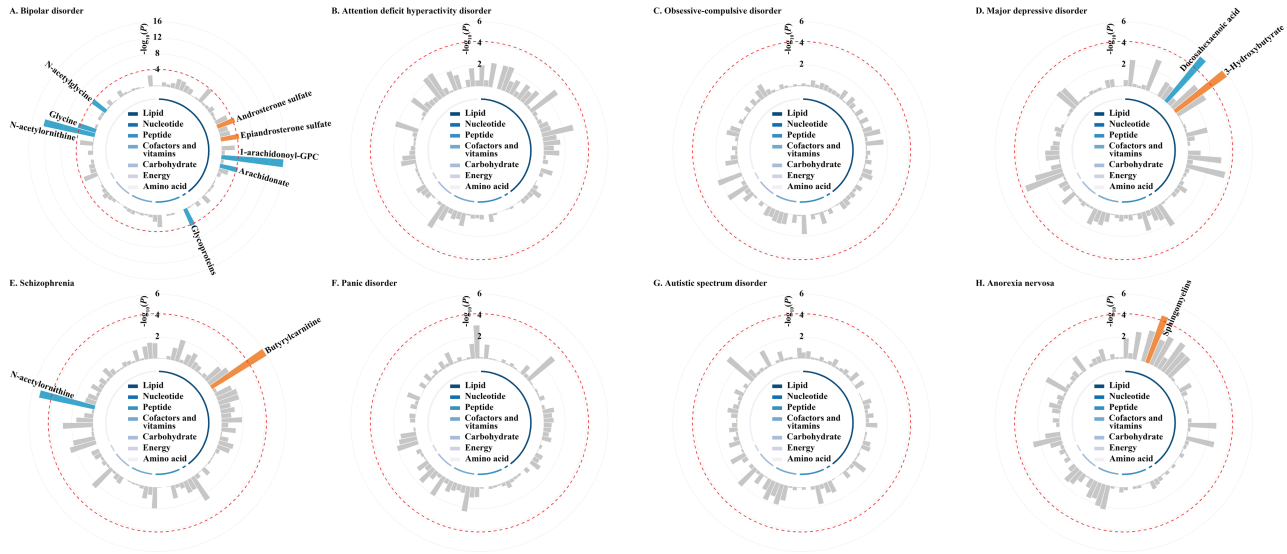

Figure 2. Circular Manhattan plot illustrating the inverse-variance weighted estimates of the associations between blood metabolites and the risk of psychiatric disorders in this Mendelian randomization study. The red dashed line represents the Bonferroni-corrected significance threshold ($P < 9.54 \times 10^{-6}$), with significant metabolites were annotated with labels. The orange bars represent significant harmful mediators of psychiatric disorders, while the blue bars represent significant protective mediators of psychiatric disorders. According to the super-pathway listed in s-table S1, we grouped and color-coded the 92 blood metabolites. The detailed results are available in s-table S4. Abbreviation: 1-arachidonoyl-GPC, 1-arachidonoylglycerophosphocholine.

Table 2. Significant Associations between Blood Metabolites and the Risk of Psychiatric Disorders in the MR Analysis.

		IVW		Penalized IVW		MR-RAPS		Maximum likelihood		MR-Egger Intercept
Metabolite	SNPs	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*P* value
Bipolar disorder										
1-Arachidonoyl-GPC	5	0.31 (0.23–0.41)	3.52×10^{-16}	0.31 (0.21–0.46)	6.76×10^{-9}	0.30 (0.23–0.41)	9.55×10^{-15}	0.30 (0.23–0.41)	9.53×10^{-15}	0.67
Glycoproteins	71	0.94 (0.92–0.97)	3.10×10^{-5}	0.94 (0.92–0.96)	2.55×10^{-6}	0.94 (0.92–0.96)	9.97×10^{-8}	0.94 (0.92–0.96)	1.66×10^{-7}	0.53
N-acetylornithine	9	0.72 (0.66–0.79)	1.08×10^{-13}	0.72 (0.66–0.79)	1.08×10^{-13}	0.72 (0.66–0.79)	2.16×10^{-13}	0.72 (0.66–0.78)	1.96×10^{-13}	0.15
Glycine	6	0.62 (0.50–0.77)	2.28×10^{-5}	0.62 (0.50–0.78)	2.87×10^{-5}	0.62 (0.50–0.78)	2.74×10^{-5}	0.62 (0.50–0.78)	2.59×10^{-5}	0.41
Major depressive disorder										
Docosahexaenoic acid	133	0.96 (0.94–0.97)	5.04×10^{-6}	0.96 (0.95–0.98)	4.13×10^{-5}	0.96 (0.94–0.97)	1.94×10^{-8}	0.96 (0.94–0.97)	2.57×10^{-8}	0.94
3-Hydroxybutyrate	25	1.14 (1.08–1.21)	1.50×10^{-6}	1.14 (1.08–1.21)	6.76×10^{-6}	1.15 (1.08–1.21)	1.74×10^{-6}	1.15 (1.09–1.21)	1.25×10^{-6}	0.55
Schizophrenia										
Butyrylcarnitine	17	1.22 (1.12–1.32)	1.10×10^{-6}	1.22 (1.12–1.32)	3.39×10^{-6}	1.22 (1.12–1.32)	1.18×10^{-6}	1.22 (1.13–1.32)	8.75×10^{-7}	0.15
N-acetylornithine	9	0.74 (0.64–0.84)	5.14×10^{-6}	0.74 (0.64–0.84)	5.14×10^{-6}	0.73 (0.67–0.80)	1.93×10^{-11}	0.73 (0.67–0.80)	2.49×10^{-11}	0.41
Anorexia nervosa										
Sphingomyelins	159	1.12 (1.06–1.19)	2.34×10^{-5}	1.13 (1.06–1.19)	4.37×10^{-5}	1.12 (1.07–1.19)	2.25×10^{-5}	1.12 (1.06–1.19)	2.45×10^{-5}	0.49

Odds ratios (ORs) with their 95% confidence intervals (CIs) represent the association estimates with the risk of psychiatric disorders of per 1-SD increase in 1-arachidonoylglycerophosphocholine (1-arachidonoyl-GPC), glycoproteins, *N*-acetylornithine, glycine, docosahexaenoic acid, 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins levels, respectively. An observed 2-sided $P < 6.79 \times 10^{-5}$ was considered as statistically significant. A 2-sided $P < .05$ was considered as suggestive evidence for directional pleiotropy in the MR-Egger regression.

Abbreviations: IVW, inverse-variance weighted; MR-RAPS, Mendelian randomization robust adjusted profile score.

0.50–0.77, $P = 2.28 \times 10^{-5}$), and docosahexaenoic acid (MDD: OR = 0.96, 95% CI = 0.94–0.97, $P = 5.04 \times 10^{-6}$) were associated with decreased risks of psychiatric disorders, while per 1-SD increase in genetically determined 3-Hydroxybutyrate (MDD: OR = 1.14, 95% CI = 1.08–1.21, $P = 1.50 \times 10^{-6}$), butyrylcarnitine (SCZ: OR = 1.22, 95% CI = 1.12–1.32, $P = 1.10 \times 10^{-6}$), and sphingomyelins (AN: OR = 1.12, 95% CI = 1.06–1.19, $P = 2.34 \times 10^{-5}$) were associated with increased risks of psychiatric disorders.

Phe-MR Analysis for the Associations between Identified Metabolites and 655 Nonpsychiatric Diseases

We further performed a Phe-MR analysis of 655 nonpsychiatric diseases to explore the potential side-effect profiles of targeting the identified metabolites. Notably, Phe-MR results were standardized to a 10% reduction in the risk of psychiatric disorders mediated by targeting a given metabolite, which can be interpreted as concomitant side effects expected to arise when each metabolite is targeted to prevent psychiatric disorders. Using the IVW method in the Phe-MR analysis, we found that 66 associations reached a Bonferroni-corrected significance threshold of $P = 9.54 \times 10^{-6}$ (0.05/5240 [8 metabolites*655 diseases]) (s-tables S6–S13; figure S1). Further sensitivity analyses robustly suggested 3 significant disease associations for 1-arachidonoyl-GPC, 10 significant disease associations for glycoproteins, 1 significant disease association for glycine, 18 significant disease associations for docosahexaenoic acid, 3 significant disease associations for butyrylcarnitine, and 22 significant disease associations for sphingomyelins, but none for N-acetylornithine and 3-Hydroxybutyrate (Table S14). In addition, the MR-Egger regression analysis found no directional pleiotropy for these significant associations, except for docosahexaenoic acid and sphingomyelins (s-table S14).

Overall, 6 out of 8 mediators of psychiatric disorders (1-arachidonoyl-GPC, glycoproteins, glycine, docosahexaenoic acid, butyrylcarnitine, and sphingomyelins) were identified to be associated with multiple diseases, involving 52 significant associations (table 3; figure 3). All side effects of interventions against glycine and butyrylcarnitine were protective, followed by a lower proportion against glycoproteins (80%), docosahexaenoic acid (47%), and sphingomyelins (44%), while the side effects of interventions against 1-arachidonoyl-GPC were all adverse (table S15). In terms of disease category, circulatory system was the most commonly affected system for the interventions against these metabolites (table S15). The most significant side effects of interventions against each metabolite was benign neoplasm of colon for 1-arachidonoyl-GPC (OR per 10% reduction in BIP risk = 1.10, 95% CI = 1.06–1.13, $P = 4.47 \times 10^{-10}$), cholelithiasis and cholecystitis for glycoproteins (OR per 10% reduction in BIP risk = 0.86, 95% CI = 0.82–0.90, $P = 5.38 \times 10^{-11}$), viral infection for glycine (OR per 10% reduction in BIP risk = 0.74, 95% CI = 0.65–0.84, $P = 2.23 \times 10^{-6}$), cholelithiasis for docosahexaenoic acid (OR per 10% reduction in MDD risk = 0.57, 95% CI = 0.50–0.66, $P = 2.57 \times 10^{-15}$), myocardial infarction for butyrylcarnitine (OR per 10% reduction in SCZ risk = 0.86, 95% CI = 0.82–0.91, $P = 6.42 \times 10^{-8}$), and disorders of lipid metabolism for sphingomyelins (OR per 10% reduction in AN risk = 0.57, 95% CI = 0.51–0.62, $P = 2.67 \times 10^{-30}$) (table 3).

Discussion

This is the first systematic MR study to screen human blood metabolome for the potential mediators of psychiatric disorders and comprehensively assess their potential on-target clinical side effects. Among the 92 blood metabolites, we identified 8 metabolites as potential causal mediators of psychiatric disorders, including 1-arachidonoyl-GPC, glycoproteins, N-acetylornithine, glycine, docosahexaenoic acid, 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins (figure 4). Specifically, 1-arachidonoyl-GPC, glycoproteins, *N*-acetylornithine, glycine, and docosahexaenoic acid had protective effects, while 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins had adverse effects on psychiatric disorders. We further performed a Phe-MR analysis to explore the on-target side effects associated with potential treatment of psychiatric disorders via interventions of the identified metabolites. In the Phe-MR analysis, we found that all identified metabolites except for *N*-acetylornithine and 3-Hydroxybutyrate could mediate a series of nonpsychiatric diseases, while glycine, 3-Hydroxybutyrate, *N*-acetylornithine, and butyrylcarnitine had no adverse side effects (figure 4).

Among the 8 mediators of psychiatric disorders, 5 metabolites have been identified in previous epidemiological studies. Glycine is a member of neurotransmitter, and glycine supplementation could improve brain morphology without neurotoxic effects.[29] In a previous clinical trial, high-dose adjuvant glycine was reported to be able to augment the efficacy of olanzapine and risperidone in the treatment of SCZ.[30] Our study further extended this information to BIP and suggested that glycine supplementation was associated with a decreased risk of BIP. In addition, our Phe-MR analysis also confirmed the previously reported antiviral activity of glycine.[31] Docosahexaenoic acid, an omega-3 polyunsaturated fatty acid, has been widely studied with respect to its role in the inhibition of neuroinflammation.[32] Some previous randomized clinical trials had demonstrated that docosahexaenoic acid had extensive health benefits, including the treatment of MDD.[33] However, in case of excessive supplementation, docosahexaenoic

Table 3. Significant Associations Between Identified Metabolites and the Risk of Multiple Nonpsychiatric Diseases in the Phe-MR Analysis.

PheCode	Outcome	SNPs	Disease chapter	IVW		Penalized IVW		MR-RAPS		Maximum likelihood		MR-Egger Intercept
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*P* value
1-Arachidonoyl-GPC supplementation												
208	Benign neoplasm of colon	5	Neoplasms	1.10 (1.06–1.13)	4.47×10^{-10}	1.10 (1.06–1.13)	4.47×10^{-10}	1.09 (1.06–1.13)	1.88×10^{-9}	1.09 (1.06–1.13)	1.45×10^{-9}	0.91
244.4	Hypothyroidism NOS	5	Endocrine/ metabolic	1.09 (1.05–1.13)	5.80×10^{-7}	1.09 (1.05–1.13)	6.34×10^{-6}	1.09 (1.05–1.13)	9.92×10^{-7}	1.09 (1.05–1.13)	9.29×10^{-7}	0.87
244	Hypothyroidism	5	Endocrine/ metabolic	1.09 (1.05–1.13)	6.80×10^{-7}	1.09 (1.05–1.13)	2.00×10^{-6}	1.09 (1.05–1.13)	1.18×10^{-6}	1.09 (1.05–1.13)	1.08×10^{-6}	0.90
Glycoproteins supplementation												
574	Cholelithiasis and cholecystitis	78	Digestive	0.86 (0.82–0.90)	5.38×10^{-11}	0.86 (0.83–0.90)	2.57×10^{-11}	0.86 (0.82–0.90)	5.33×10^{-11}	0.86 (0.82–0.90)	8.24×10^{-11}	0.30
574.1	Cholelithiasis	78	Digestive	0.85 (0.81–0.89)	8.55×10^{-11}	0.86 (0.82–0.90)	3.70×10^{-11}	0.85 (0.81–0.89)	8.52×10^{-11}	0.85 (0.81–0.89)	1.36×10^{-10}	0.52
454.11	Varicose veins of lower extremity, symptomtic	78	Circulatory system	1.92 (1.54–2.38)	4.20×10^{-9}	1.84 (1.50–2.26)	4.20×10^{-9}	1.90 (1.53–2.36)	5.41×10^{-9}	1.93 (1.55–2.40)	3.83×10^{-9}	0.21
426	Cardiac conduction disorders	78	Circulatory system	0.83 (0.77–0.89)	3.20×10^{-8}	0.84 (0.79–0.90)	3.71×10^{-7}	0.83 (0.78–0.89)	3.22×10^{-8}	0.83 (0.77–0.89)	4.75×10^{-8}	0.78
426.3	Bundle branch block	78	Circulatory system	0.79 (0.72–0.86)	7.24×10^{-7}	0.80 (0.73–0.88)	1.31×10^{-6}	0.79 (0.72–0.87)	6.97×10^{-7}	0.79 (0.72–0.87)	1.01×10^{-6}	0.88
577	Diseases of pancreas	78	Digestive	0.77 (0.69–0.85)	9.47×10^{-7}	0.78 (0.71–0.87)	2.34×10^{-6}	0.77 (0.69–0.85)	9.84×10^{-7}	0.77 (0.69–0.85)	1.14×10^{-6}	0.52
79	Viral infection	78	Infectious diseases	0.77 (0.70–0.86)	1.04×10^{-6}	0.79 (0.71–0.87)	1.04×10^{-6}	0.78 (0.70–0.86)	1.16×10^{-6}	0.77 (0.70–0.86)	1.20×10^{-6}	0.20
496	Chronic airway obstruction	78	Respiratory	1.14 (1.08–1.21)	2.10×10^{-6}	1.14 (1.08–1.20)	1.22×10^{-6}	1.14 (1.08–1.21)	2.08×10^{-6}	1.14 (1.08–1.21)	2.08×10^{-6}	0.54
414	Other forms of chronic heart disease	78	Circulatory system	0.73 (0.64–0.83)	2.66×10^{-6}	0.74 (0.65–0.84)	3.71×10^{-6}	0.73 (0.65–0.84)	2.69×10^{-6}	0.73 (0.64–0.84)	3.40×10^{-6}	0.37
727.5	Rupture of synovium	78	Musculoskeletal	0.60 (0.48–0.74)	5.59×10^{-6}	0.61 (0.50–0.76)	7.19×10^{-6}	0.60 (0.48–0.74)	5.35×10^{-6}	0.60 (0.48–0.75)	7.75×10^{-6}	0.32
Glycine supplementation												
79	Viral infection	9	Infectious diseases	0.74 (0.65–0.84)	2.23×10^{-6}	0.74 (0.65–0.84)	4.77×10^{-6}	0.74 (0.65–0.84)	2.77×10^{-6}	0.74 (0.65–0.84)	2.60×10^{-6}	0.20
Docosahexaenoic acid supplementation												
574.1	Cholelithiasis	152	Digestive	0.57 (0.50–0.66)	2.57×10^{-15}	0.52 (0.45–0.59)	1.49×10^{-21}	0.57 (0.51–0.63)	4.35×10^{-26}	0.57 (0.52–0.64)	3.78×10^{-25}	0.69
574	Cholelithiasis and cholecystitis	152	Digestive	0.61 (0.54–0.70)	6.61×10^{-13}	0.57 (0.51–0.64)	1.40×10^{-19}	0.61 (0.56–0.67)	2.28×10^{-23}	0.62 (0.56–0.68)	1.76×10^{-22}	0.25
743	Osteoporosis, osteopenia and pathological fracture	152	Musculoskeletal	1.44 (1.26–1.66)	1.61×10^{-7}	1.57 (1.31–1.87)	7.86×10^{-7}	1.44 (1.26–1.65)	1.55×10^{-7}	1.45 (1.26–1.66)	1.50×10^{-7}	0.63
172	Skin cancer	152	Neoplasms	1.37 (1.22–1.54)	2.33×10^{-7}	1.49 (1.29–1.71)	4.84×10^{-8}	1.37 (1.23–1.52)	2.98×10^{-9}	1.37 (1.24–1.52)	3.27×10^{-9}	0.08
195.1	Malignant neoplasm, other	152	Neoplasms	1.27 (1.16–1.40)	5.54×10^{-7}	1.34 (1.19–1.51)	9.39×10^{-7}	1.27 (1.16–1.40)	5.57×10^{-7}	1.27 (1.16–1.40)	5.09×10^{-7}	0.05
195	Cancer, suspected or other	152	Neoplasms	1.25 (1.14–1.38)	1.45×10^{-6}	1.32 (1.17–1.48)	3.63×10^{-6}	1.25 (1.14–1.38)	1.44×10^{-6}	1.26 (1.15–1.38)	1.34×10^{-6}	0.10

Table 3. Continued

PheCode	Outcome	SNPs	Disease chapter	IVW		Penalized IVW		MR-RAPS		Maximum likelihood		MR-Egger Intercept
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*P* value
743.2	Pathologic fracture	152	Musculoskeletal	6.84 (4.07–11.47)	3.43×10^{-13}	9.90 (5.25–18.66)	1.34×10^{-12}	6.79 (4.05–11.38)	3.95×10^{-13}	6.88 (4.09–11.56)	3.35×10^{-13}	0.63
145	Cancer of mouth	152	Neoplasms	3.23 (2.03–5.12)	6.79×10^{-7}	4.34 (2.47–7.64)	3.57×10^{-7}	3.21 (2.03–5.10)	7.05×10^{-7}	3.23 (2.03–5.13)	6.98×10^{-7}	0.43
594.2	Calculus of lower urinary tract	152	Genitourinary	0.37 (0.25-0.57)	5.16×10^{-6}	0.30 (0.18–0.50)	3.83×10^{-6}	0.38 (0.25–0.57)	5.27×10^{-6}	0.37 (0.24–0.57)	4.35×10^{-6}	0.45
574.2	Calculus of bile duct	152	Digestive	0.56 (0.45–0.71)	1.12×10^{-6}	0.50 (0.37–0.66)	1.76×10^{-6}	0.57 (0.45–0.71)	1.13×10^{-6}	0.57 (0.45–0.71)	1.36×10^{-6}	0.21
611	Abnormal findings on mammogram or breast exam	152	Genitourinary	2.31 (1.64–3.27)	2.00×10^{-6}	2.96 (2.02–4.35)	2.85×10^{-8}	2.31 (1.72–3.11)	2.88×10^{-8}	2.32 (1.72–3.13)	3.10×10^{-8}	0.74
380	Disorders of external ear	152	sense Organs	0.48 (0.35–0.65)	2.34×10^{-6}	0.40 (0.28–0.59)	2.34×10^{-6}	0.48 (0.35–0.65)	2.42×10^{-6}	0.48 (0.35–0.65)	2.61×10^{-6}	0.63
384	Other disorders of tympanic membrane	152	Sense organs	0.38 (0.28–0.53)	3.45×10^{-9}	0.31 (0.21–0.46)	1.18×10^{-8}	0.38 (0.28–0.53)	3.46×10^{-9}	0.38 (0.28–0.53)	3.60×10^{-9}	0.82
384.4	Perforation of tympanic membrane	152	Sense organs	0.38 (0.27–0.55)	2.14×10^{-7}	0.30 (0.19–0.47)	1.30×10^{-7}	0.38 (0.27–0.55)	2.22×10^{-7}	0.38 (0.26–0.55)	1.90×10^{-7}	0.75
598	Abnormal findings on examination of urine	152	Genitourinary	0.63 (0.52–0.77)	5.33×10^{-6}	0.56 (0.44–0.71)	2.90×10^{-6}	0.63 (0.52–0.77)	5.43×10^{-6}	0.63 (0.52–0.77)	6.01×10^{-6}	0.72
803.2	Fracture of radius and ulna	152	Injuries & Poisonings	1.46 (1.24–1.73)	6.27×10^{-6}	1.63 (1.33–1.99)	2.36×10^{-6}	1.46 (1.24–1.72)	6.33×10^{-6}	1.46 (1.24–1.73)	6.24×10^{-6}	0.67
743.11	Osteoporosis NOS	152	Musculoskeletal	1.45 (1.23–1.70)	6.44×10^{-6}	1.62 (1.32–1.97)	2.27×10^{-6}	1.45 (1.23–1.70)	6.32×10^{-6}	1.45 (1.23–1.70)	6.27×10^{-6}	0.95
Butyrylcarnitine inhibition												
411.2	Myocardial infarction	25	Circulatory system	0.86 (0.82–0.91)	6.42×10^{-8}	0.86 (0.81–0.92)	1.06×10^{-6}	0.86 (0.82–0.91)	5.75×10^{-8}	0.86 (0.82–0.91)	3.79×10^{-8}	0.30
352	Disorders of other cranial nerves	25	Neurological	0.69 (0.59–0.80)	8.97×10^{-7}	0.69 (0.59–0.80)	8.97×10^{-7}	0.69 (0.59–0.80)	9.76×10^{-7}	0.69 (0.60–0.80)	8.80×10^{-7}	0.86
721.1	Spondylosis without myelopathy	25	Musculoskeletal	0.83 (0.77–0.90)	6.13×10^{-6}	0.83 (0.77–0.90)	6.13×10^{-6}	0.83 (0.77–0.90)	6.44×10^{-6}	0.83 (0.77–0.90)	4.37×10^{-6}	0.88
Sphingomyelins inhibition												
272	Disorders of lipid metabolism	185	Endocrine/metabolic	0.57 (0.51–0.62)	2.67×10^{-30}	0.65 (0.62–0.69)	1.53×10^{-71}	0.53 (0.52–0.55)	1.00×10^{-99}	0.55 (0.53–0.57)	1.00×10^{-99}	0.21
272.11	Hypercholesterolemia	185	Endocrine/metabolic	0.57 (0.51–0.62)	3.01×10^{-30}	0.67 (0.64–0.71)	6.04×10^{-58}	0.53 (0.52–0.55)	1.00×10^{-99}	0.54 (0.52–0.56)	1.00×10^{-99}	0.25
272.1	Hyperlipidemia	185	Endocrine/metabolic	0.57 (0.52–0.63)	4.27×10^{-30}	0.66 (0.63–0.69)	4.62×10^{-69}	0.53 (0.52–0.55)	1.00×10^{-99}	0.54 (0.53–0.56)	1.00×10^{-99}	0.21
411.4	Coronary atherosclerosis	185	Circulatory system	0.73 (0.67–0.80)	1.33×10^{-11}	0.75 (0.71–0.79)	2.75×10^{-27}	0.72 (0.69–0.75)	5.56×10^{-73}	0.72 (0.70–0.75)	1.40×10^{-63}	0.08
411	Ischemic Heart Disease	185	Circulatory system	0.79 (0.74–0.85)	2.46×10^{-10}	0.79 (0.75–0.82)	1.31×10^{-30}	0.79 (0.76–0.81)	1.97×10^{-59}	0.79 (0.77–0.81)	8.80×10^{-52}	0.06

Table 3. Continued

PheCode	Outcome	SNPs	Disease chapter	IVW		Penalized IVW		MR-RAPS		Maximum likelihood		MR-Egger Intercept
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*P* value
411.2	Myocardial infarction	185	Circulatory system	0.75 (0.68–0.82)	1.30×10^{-9}	0.75 (0.71–0.79)	4.28×10^{-24}	0.74 (0.71–0.78)	2.60×10^{-37}	0.75 (0.71–0.78)	3.64×10^{-34}	0.20
785	Abdominal pain	185	Symptoms	1.06 (1.04–1.09)	1.14×10^{-6}	1.06 (1.03–1.08)	3.50×10^{-6}	1.06 (1.04–1.09)	1.23×10^{-6}	1.06 (1.04–1.09)	1.34×10^{-6}	0.77
550.2	Diaphragmatic hernia	185	Digestive	1.09 (1.05–1.13)	4.84×10^{-6}	1.08 (1.05–1.12)	1.41×10^{-6}	1.09 (1.06–1.12)	2.46×10^{-8}	1.09 (1.06–1.12)	4.28×10^{-8}	0.57
599.4	Urinary incontinence	185	Genitourinary	1.13 (1.07–1.19)	4.96×10^{-6}	1.12 (1.07–1.18)	7.90×10^{-6}	1.13 (1.07–1.19)	4.86×10^{-6}	1.13 (1.07–1.19)	5.20×10^{-6}	0.70
740.1	Osteoarthritis; localized	185	Musculoskeletal	1.12 (1.06–1.17)	6.32×10^{-6}	1.10 (1.05–1.14)	5.73×10^{-6}	1.12 (1.08–1.16)	2.90×10^{-9}	1.12 (1.08–1.16)	6.50×10^{-9}	0.21
1011	Complications of surgical and medical procedures	185	Injuries & poisonings	1.12 (1.07–1.18)	7.34×10^{-6}	1.12 (1.07–1.17)	4.21×10^{-6}	1.12 (1.07–1.18)	7.41×10^{-6}	1.12 (1.07–1.18)	7.16×10^{-6}	0.99
701.2	Scar conditions and fibrosis of skin	185	Dermatologic	0.75 (0.68–0.83)	6.77×10^{-9}	0.76 (0.69–0.84)	1.34×10^{-8}	0.75 (0.68–0.83)	7.19×10^{-9}	0.75 (0.68–0.83)	7.42×10^{-9}	0.26
381.1	Otitis media	185	Sense organs	1.33 (1.19–1.48)	4.42×10^{-7}	1.31 (1.18–1.46)	7.41×10^{-7}	1.33 (1.19–1.48)	4.46×10^{-7}	1.33 (1.19–1.49)	4.49×10^{-7}	0.24
381	Otitis media and Eustachian tube disorders	185	Sense organs	1.29 (1.17–1.42)	5.12×10^{-7}	1.28 (1.16–1.41)	5.12×10^{-7}	1.29 (1.17–1.42)	5.35×10^{-7}	1.29 (1.17–1.43)	4.93×10^{-7}	0.09
574.3	Cholecystitis without cholelithiasis	185	Digestive	1.40 (1.23–1.60)	5.36×10^{-7}	1.36 (1.24–1.49)	2.05×10^{-11}	1.40 (1.28–1.54)	1.26×10^{-13}	1.40 (1.28–1.53)	4.88×10^{-13}	0.98
411.1	Unstable angina (intermediate coronary syndrome)	185	Circulatory system	0.77 (0.70–0.85)	1.65×10^{-7}	0.77 (0.71–0.84)	7.48×10^{-10}	0.77 (0.72–0.82)	3.11×10^{-15}	0.77 (0.72–0.82)	1.18×10^{-14}	0.34
722.9	Other and unspecified disc disorder	185	Musculoskeletal	1.20 (1.12–1.29)	6.34×10^{-7}	1.18 (1.10–1.27)	2.43×10^{-6}	1.20 (1.12–1.29)	6.27×10^{-7}	1.20 (1.12–1.29)	6.33×10^{-7}	0.75
858	Complication of internal orthopedic device	185	Injuries & poisonings	1.25 (1.14-1.37)	2.38×10^{-6}	1.24 (1.13–1.35)	2.22×10^{-6}	1.25 (1.15–1.36)	1.82×10^{-7}	1.25 (1.15–1.36)	2.08×10^{-7}	0.38

Odds ratios (ORs) with their 95% confidence intervals (CIs) represent the effect estimates on the risk of multiple non-psychiatric diseases of per 10% reduction in risk for psychiatric disorders by targeting 1-arachidonoylglycerophosphocholine (1-arachidonoyl-GPC), glycoproteins, glycine, docosahexaenoic acid, butyrylcarnitine, and sphingomyelins, respectively. An observed 2-sided $P < 9.54 \times 10^{-6}$ was considered as statistically significant. A 2-sided $P<0.05$ was considered as suggestive evidence for directional pleiotropy in the MR-Egger regression.
Abbreviations: IVW, inverse-variance weighted; MR-RAPS, Mendelian randomization robust adjusted profile score; Phe-MR, phenome-wide Mendelian randomization.

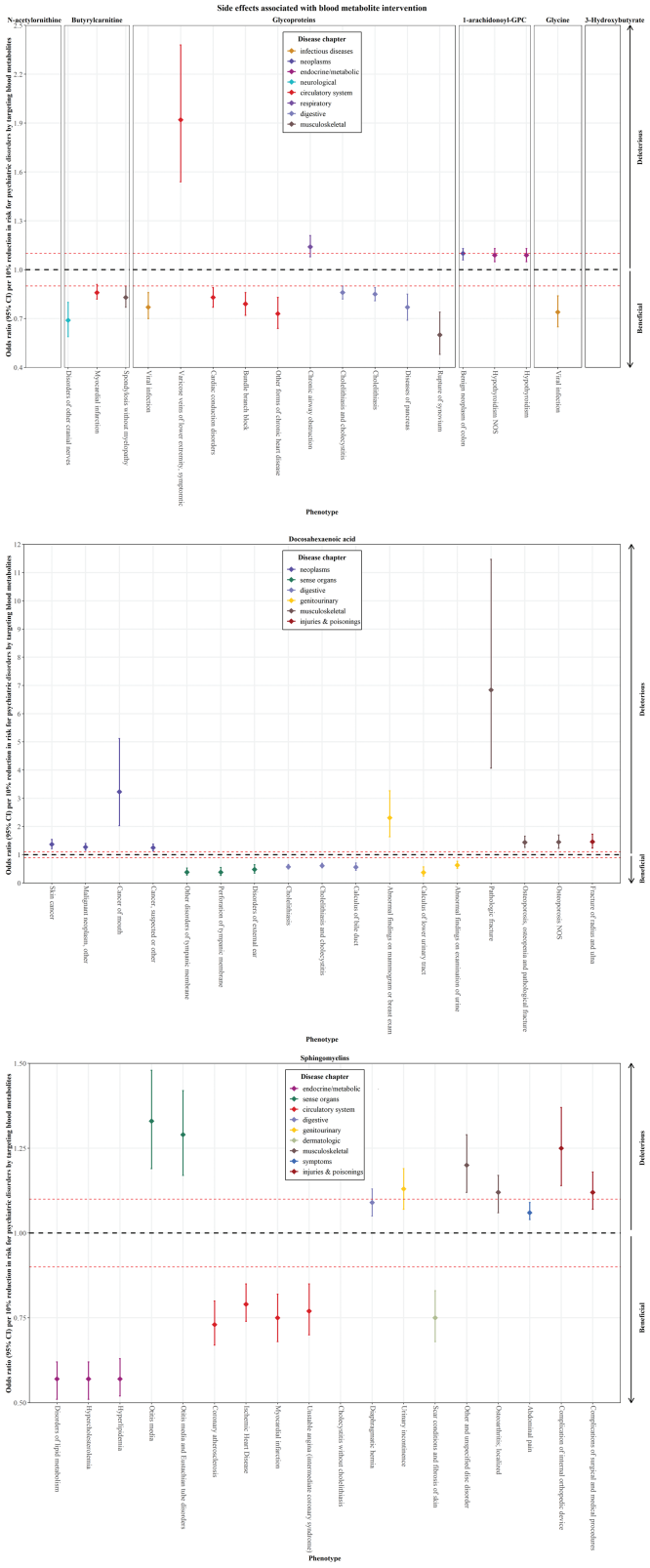

Figure 3. Potential on-target side effects of identified metabolites using phenome–wide Mendelian randomization analysis. Odds ratios (ORs) with the 95% confidence intervals (CIs) represent the effects on the risk of multiple non-psychiatric diseases of per 10% reduction in risk for psychiatric disorders associated with intervention targeting 1-arachidonoylglycerophosphocholine (1-arachidonoyl-GPC), glycoproteins, *N*-acetylornithine, glycine, docosahexaenoic acid, 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins, respectively. Associations above the horizontal black midline represent deleterious side effects, while these below the horizontal black midline represent beneficial side effects. The horizontal red line (OR = 1.10) represents the point at which decreased risk of psychiatric disorders is counterbalanced by an equal increase in decrease risk.

acid may adversely impact multiple diseases via its oxidation products, such as 4-hydroxy-2-hexenal.[34] In the present systematic MR study, we confirmed these associations of docosahexaenoic acid with the risk of MDD and some non-psychiatric diseases from genetic perspective. 3-Hydroxybutyrate is a ketone body managing emotional system in the brain via energy metabolism.[35] Recently, a multicenter pilot analysis of plasma metabolome suggested that 3-Hydroxybutyrate levels were positively associated with the severity of depression and suicidal ideation.[35] Similarly, we found that genetically determined high 3-Hydroxybutyrate levels were associated with an increased risk of MDD, and lowering 3-Hydroxybutyrate for treating MDD had no side effects on the other nonpsychiatric diseases. Butyrylcarnitine belongs to acylcarnitines, which is a family of prooxidative compounds generated with incomplete fatty acid β-oxidation.[36] In a recent mass spectrometry analysis of plasma acylcarnitine profiles, butyrylcarnitine level was found higher in patients with SCZ than that in healthy individuals.[37] By combining genetics and metabolomics, our findings supported a positive association between butyrylcarnitine and the risk of SCZ from the perspective of causality. Further Phe-MR analysis also suggested a protective effect of lowering butyrylcarnitine levels on the risk of 3 nonpsychiatric diseases. *N*-Acetylornithineis is an important intermediate in arginine metabolism,[38] and a previous MR study had showed beneficial effects of *N*-acetylornithine on both BIP and SCZ.[20] Using stricter criteria for genetic instruments selection in the present study, we further confirmed the inverse associations of *N*-acetylornithine levels with the risk of BIP and SCZ. These shared associations might be attributed to the common genetic etiology between BIP and SCZ.[39] In addition, our Phe-MR analysis also found no side effects of *N*-acetylornithine supplementation for treating BIP and SCZ. Taken together, glycine, 3-Hydroxybutyrate, and *N*-acetylornithine can serve as promising drug targets for psychiatric disorders without predicted adverse side effects.

In the present study, we also identified 3 novel mediators for psychiatric disorders, including 1-arachidonoyl-GPC, glycoproteins, and sphingomyelins. Although the biological role of these metabolites in central nervous system was not well defined, inflammation might be the potential pathophysiological mechanism underlying the associations between these metabolites and psychiatric

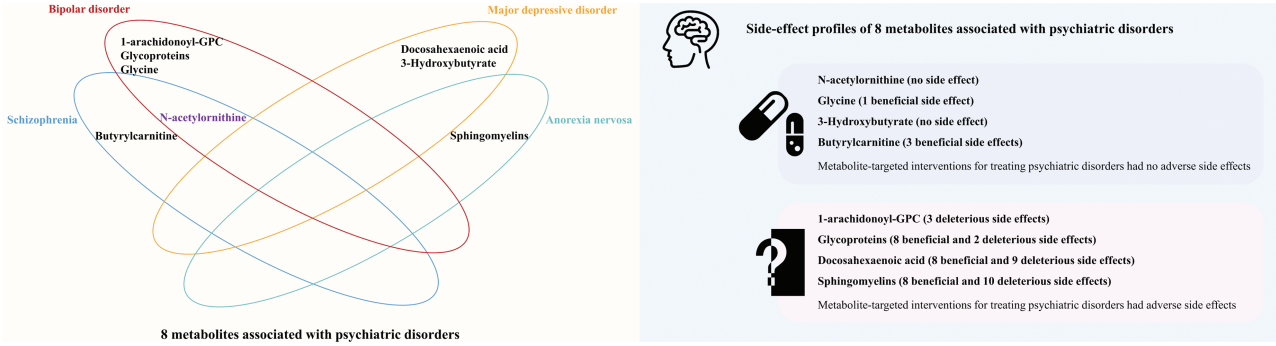

Figure 4. Blood metabolites associated with risk of psychiatric disorders and a comprehensive assessment of their potential on-target clinical side effects. Abbreviation: 1-arachidonoyl-GPC, 1-arachidonoylglycerophosphocholine.

disorders.[40] 1-arachidonoyl-GPC is an important lysophosphatidylcholine, which can suppress CXCR3-mediated T cell migration to inflamed microenvironments.[41,42] In the present study, genetically determined higher 1-arachidonoyl-GPC levels were associated with a lower risk of BIP. However, based on the Phe-MR analysis of 655 diseases, 1-arachidonoyl-GPC supplementation appeared to be deleterious for thyroid gland and colon neoplasms. Glycoproteins are molecules that comprise protein and carbohydrate chains, and play a critical role in relieving inflammation.[43] For example, as major glycoproteins, progranulin[44] and fetuin-A[45] were implicated in neuroprotection by inhibiting proinflammatory cytokine production. In this MR study, we revealed a beneficial role of glycoproteins in the etiology of BIP. Moreover, our Phe-MR analysis indicated that glycoproteins supplementation had additional benefits on multiple systems, but it could also lead to increased risks of varicose veins of lower extremity and chronic airway obstruction. Sphingomyelins are dominant sphingolipids in cell membranes, acting as both constructive components and signal carriers in physiological processes. Accumulating experimental evidence had suggested the integral role of sphingomyelins cycle in the proinflammatory process (e.g., Nuclear factor kappa B signaling pathway),[46] and downregulation of sphingomyelin synthases was able to reduce microglial inflammation in mice.[47] In our MR and Phe-MR analyses, higher sphingomyelins levels were shown to be significantly associated with an increased risk of AN, while lowering sphingomyelins for treating AN had a series of adverse side effects. Therefore, interventions targeting 1-arachidonoyl-GPC, glycoproteins and sphingomyelin for preventing and treating psychiatric disorders should be applied with a comprehensive consideration of the therapeutic effects and target-mediated side effects.

Our study has important public health and clinical implications. Psychiatric disorders are a major global public health challenge today, while the high-risk criteria appears to be insufficient to predict the onset of first-episode psychiatric disorders.[48] Therefore, it is of public health importance to identify novel biomarkers for better monitoring high-risk individuals and improving the early prevention of psychiatric disorders. From the findings of our study, 1-arachidonoyl-GPC, glycoproteins, *N*-acetylornithine, glycine, docosahexaenoic acid, 3-Hydroxybutyrate, butyrylcarnitine, and sphingomyelins are potential predictive biomarkers for psychiatric disorders. Moreover, the misdiagnosis rate of psychiatric disorders is approximately 40%,[49] so further studies are warranted to assess the clinical value of these biomarkers in differential diagnosis of psychiatric disorders.

On the other hand, the current available treatment approach for psychiatric disorders mainly includes psychotherapy and pharmacotherapy.[1] As the most commonly used antipsychotics, atypical (second generation) antipsychotics still cause a series of adverse side effects, such as diabetes, hyperlipidemia, and myocarditis.[4] In addition, preliminary tests are recommended in clinical practice before taking certain antipsychotic drugs to ascertain the appropriate dose due to the interindividual heterogeneity of the antipsychotic response.[3] Given the limited therapeutic options currently available for psychiatric disorders, it is of clinical interest for psychiatrists to develop novel intervention strategies in the management of psychiatric disorders by targeting *N*-acetylornithine, glycine, 3-Hydroxybutyrate, and butyrylcarnitine. Further clinical trials are warranted to verify our findings and assess the effective dose of each promising drug target for psychiatric disorders.

The present study has several strengths. Firstly, based on genomics and metabolomics data, this systematic MR study provided new insight into the potential causal mediators of BIP, ADHD, OCD, MDD, SCZ, PD, ASD, and AN. Secondly, based on the multi-cohort setting of the original GWASs, we could make a valid causal inference among large-scale populations with a high statistical power. Finally, we conducted the Phe-MR analysis to comprehensively assess side-effect profiles of interventions against our identified metabolites, which could further help inform drug target prioritization in the drug

development and clinical trials. However, our study also has certain limitations. First, this MR study was based on the summary-level data on the blood metabolome, while psychiatric disorders were mainly caused by brain lesions. Further studies are warranted to analyze metabolite changes in cerebrospinal fluid to identify additional promising biomarkers and drug targets for psychiatric disorders. Second, the present study was conducted in individuals of predominantly European descent, which minimized the population stratification bias but restricted the interethnic extrapolation of our findings. Further studies conducted in non-European individuals are needed to confirm our findings. Third, patients in PheCode system were diagnosed in hospital, so the disease traits with low rates of hospital admission may be poorly represented. Finally, there might be an overlap between participants in the GWASs, which may lead to weak instrument bias. Although the *F* statistics suggested that there was no instrument bias in this MR study, further MR studies based on the independent cohorts without participant overlap are needed to better understand the role of blood metabolites in the etiology of psychiatric disorders.

In this systematic MR analysis, 8 mediators were identified for psychiatric disorders, including 5 established metabolites (N-acetylornithine, glycine, docosahexaenoic acid, 3-Hydroxybutyrate, and butyrylcarnitine) and 3 novel metabolites (1-arachidonoyl-GPC, glycoproteins, and sphingomyelins). Side-effect profiles were characterized to help inform drug target prioritization. *N*-acetylornithine, glycine, 3-Hydroxybutyrate, and butyrylcarnitine might be promising targets against psychiatric disorders with no predicted adverse side effects.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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Author contributions

The study was conceived and designed by YJ, LH and ZZ. YJ, LH and ZZ coordinated the study. YJ, LH, LS, DG, MS, KZ, PY, YW, FL, OS and ZZ contributed to data collection. YJ and LH performed the statistical analysis and prepared the first draft of manuscript. ZZ revised the paper and helped to write the final draft of manuscript. ZZ is guarantor.

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Ethical approval

This study is based on publicly available summarized data. The protocol and data collection were approved by the ethics committee of each genome-wide association study.

Consent to participate

Written informed consent was obtained from each participant of previously published GWASs before data collection.

Conflicts of interest

The authors report no conflicts of interest.

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