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Mediation-adjusted multivariable Mendelian randomisation study identified novel metabolites related to mental health

Dennis Freuer , Christa Meisinger

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Epidemiology, Medical Faculty, University of Augsburg, Augsburg, Germany

Correspondence to
Dr Dennis Freuer, Epidemiology, Medical Faculty, University of Augsburg, Augsburg, 86156, Germany; dennis.freuer@med.uni-augsburg.de

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ABSTRACT

Background From the pathway perspective, metabolites have the potential to improve knowledge about the aetiology of psychiatric diseases. Previous studies suggested a link between specific blood metabolites and mental disorders, but some Mendelian randomisation (MR) studies in particular are insufficient for various reasons.

Objective This study focused on bias assessment due to interdependencies between metabolites and psychiatric mediation effects.

Methods In a multistep framework containing network and multivariable MR, direct effects of 21 mutually adjusted metabolites on 8 psychiatric disorders were estimated based on summary statistics of genome-wide association studies from multiple resources. Robust inverse-variance weighted models were used in primary analyses. Several sensitivity analyses were performed to assess different patterns of pleiotropy and weak instrument bias. Estimates for the same phenotypes from different resources were pooled using fixed effect meta-analysis models.

Findings After adjusting for mediation effects, genetically predicted metabolite levels of six metabolites of lipid, amino acid and cofactors pathways were directly associated with overall six mental disorders (attention-deficit/hyperactivity disorder, bipolar disorder, anorexia nervosa, depression, post-traumatic stress disorder and schizophrenia). Point estimates ranged from −0.45 (95% CI −0.67; −0.24, p=1.0×10^{4}) to 1.78 (95% CI 0.85; 2.71, p=0.006). No associations were found with anxiety and suicide attempt.

Conclusions This study provides insights into new metabolic pathways that seems to be causally related to certain mental disorders.

Clinical implications Further studies are needed to investigate whether the identified associations are effects of the metabolites itself or the biochemical pathway regulating the metabolites.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic alterations are thought to be involved in the pathophysiology of psychiatric disorders.

⇒ However, recent studies investigating the causal effects appear to be biased for several reasons.

WHAT THIS STUDY ADDS

⇒ This study demonstrates the need for consideration of interdependencies between both metabolites and psychiatric disorders and triangulates the existing evidence by estimating causal lifetime effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides insights into the paths between mutually adjusted metabolite levels and mental health, taking into account psychiatric mediation effects.

⇒ It opens the door for further research to answer the question of whether metabolites themselves or the underlying biochemical pathways are responsible for the identified relationships.

BACKGROUND

Worldwide, around 970 million people live with a mental disease, and about 50% of people will develop a mental disorder at some point in their lives.[1] Furthermore, mental disorders account for a high percentage of the total global burden of disease in adults.[2] Although various theories have been put forward, the exact pathophysiology of most psychiatric diseases remains unclear. Subsequently, inaccurate diagnostic criteria and an incomplete understanding of the underlying pathophysiology pose a major challenge in the treatment of psychiatric disorders.[3] In addition, psychiatric disorders such as depression are often accompanied by other psychiatric diseases at the same time or during the course of the illness.[4] A recent Mendelian randomisation (MR) study from our research group could, for example, show that attention-deficit/hyperactivity disorder (ADHD) serves as an early indicator of other mental disorders due to shared psychopathologies or is an independent risk factor for several other common psychiatric disorders.[5] Thus, a better understanding of psychiatric diseases in terms of underlying pathogenesis could lead to more advanced and targeted treatment options.

Metabolomics have the potential to improve knowledge of the aetiology of psychiatric disorders by identifying new pathways to diseases and to identify potential biomarkers.[6] The blood metabolome, which is influenced by a variety of endogenous and exogenous factors, provides a snapshot of human physiology and reflects aspects of human health and diseases.[7] Observational studies and systematic

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reviews suggested that metabolic abnormalities are involved in the pathophysiology of psychiatric disorders.[6] More recently, some MR studies were conducted to identify metabolites, which could play an aetiological role in psychiatric diseases.[8 9] However, most of these studies focused on single psychiatric diseases[8] or used MR approaches[9] that are not able to satisfy appropriately the non-negligible MR assumption of horizontal pleiotropy. A key point is that many of the genetic instruments are associated with more than one metabolite. Ignoring such associations by performing univariable MR analyses leads to biased estimates (often overestimation).

Objective

The present study demonstrates the need for consideration of these associations and estimates lifetime effects while accounting for dependencies between all metabolites and considering potential mediation effects using the multivariable MR approach, including a recently proposed method to address weak instrument bias.

METHODS

Study design: stepwise MR

MR is an instrumental variable framework for assessing causal effects of modifiable risk factors on health outcomes. By using genetic variants as instruments randomly allocated at the conception according to Mendel's laws (segregation and independent assortment) and thus independent of any confounding factors of an exposure-outcome association, MR is a natural equivalent to an randomized controlled trial (RCT). One of the key challenges of MR is horizontal pleiotropy. Briefly, an instrument is not allowed to affect an outcome through any other path than through the exposure of interest. However, it is hardly possible to find genetic variants that are uniquely associated with a specific metabolite but not with other metabolites (online supplemental figure 1). As a consequence, the resulting estimate comprises a direct and an indirect effect, that is, an effect that can be directly attributed to a particular metabolite and an effect of at least one other metabolite (another path). We particularly aimed to assess the direct effects. Thus, to get unbiased estimates, horizontal pleiotropy must be considered. Multivariable MR (MVMR) is an extension to the standard MR and is able to estimate direct effects of each metabolite on the respective psychiatric outcome. We performed two-sample MVMR analyses with all available metabolites in one model per outcome to account for mutually interdependencies between them (online supplemental figure 2). In order to obtain an unbiased test of a causal relationship, three core assumptions defining an instrument have to be met in the multivariable setting. A genetic variant must be

1. Associated with at least one of the exposures (relevance assumption).
2. Independent of all confounding factors of the exposure-outcome associations (independence assumption).
3. Independent of the outcome given a set of exposures (ie, not affect the outcome directly, exclusion restriction assumption).

It is known that some psychiatric disorders do not occur independently of each other and may therefore lie on a pathway between metabolites and another psychiatric disease. Thus, a three-step procedure was performed to identify and assess potential mediation mechanisms. If a metabolite was found to be associated with at least two psychiatric disorders in the first step, a network MR was used in a second step to identify paths between the affected outcomes. In this context, univariable MR was applied to determine any association between all possible combinations of outcomes related to a specific metabolite. The third step consisted of another multivariable MR that included the potential mediators as additional covariates to obtain unbiased direct effects adjusted for the mediation component.

Data collection

Basically, data sources were selected with regard to the two-sample setting in order to avoid sample overlaps between exposure and outcome datasets. Where possible, datasets were restricted to genetic variants with a minor allele frequency of more than 0.01 and an imputation information score of at least 0.8.

For metabolites, summary data were derived from a genome-wide association study (GWAS) by Shin *et al*.[10] This GWAS investigated associations of 453 different metabolites in human blood and comprised up to 7824 participants from two distinct European population studies (KORA and TwinsUK).[11] The cohort composition was described in online supplemental table 1.

Data for the following eight psychiatric disorders were taken from multiple sources: ADHD, anxiety, bipolar disorder, anorexia nervosa, depression, post-traumatic stress disorder (PTSD), schizophrenia and at least one suicide attempt. We included these psychiatric disorders to build on our earlier study in which we identified common psychopathologies between some of them.[5] All phenotypes were selected with regard to data quality and appropriateness to the study design and research question. The iPSYCH project and the Psychiatric Genomics Consortium (PGC) provide summary level data based on clearly defined psychiatric phenotypes diagnosed by psychiatrists (ICD10 (international classification of diseases 10th revision) and DSM (diagnostic and statistical manual of mental disorders)). Basically, the data from iPSYCH project and the PGC are of high quality, as cases were identified using register data (Danish Psychiatric Central Research Register that is linked with the Danish National Patient Register), thus minimising selection bias. Further information on the cohort compositions and ICD classifications of the included GWASs can be found in online supplemental table 1. Replication datasets came from the FinnGen database including self-reported cases from the ninth wave in the Finnish cohort.[12] However, no comparable dataset for bipolar disorders could found in the FinnGen database. In addition, as the GWAS meta-analysis for depression already included the FinnGen cohort, the corresponding replication dataset was not included in our analyses. Dataset characteristics of the psychiatric phenotypes used can be found in table 1.

Instrument selection

With the view on the relevance assumption, single nucleotide polymorphisms (SNPs) associated with a specific metabolite were selected as instruments for the analyses based on the strict genome-wide significance threshold of $p=5\times10^{-8}$. Dependent SNPs in LD (linkage disequilibrium) in a window of 10 000 kb were pruned using a clumping threshold of $r^2=0.001$ within the PLINK clumping procedure. Regarding numerical behaviour, only metabolites associated with more than three genetic variants were considered as exposures. Palindromic SNPs with intermediate allele frequencies were removed as part of the multivariable harmonisation process. Steiger filtering was applied including the MR-Steiger directionality test for all individual SNPs in each exposure-outcome association to investigate the correct causal direction by statistically comparing the explained variances of the SNP-exposure and SNP-outcome associations. As a result, 138 SNPs associated with a total of 21 metabolites were selected

Table 1 Dataset characteristics of psychiatric disorders used as outcomes in the two-sample multivariable Mendelian randomisation analyses

Outcome	Cases (PGC/iPSYCH)	Controls (PGC/iPSYCH)	Cases (FinnGen)	Controls (FinnGen)
ADHD	38691	275986	2340	37117
Anxiety	7016	10294	24662	337577
Bipolar disorder	41917	371549		
Anorexia nervosa	16992	55525	1897	366876
Depression	294322	741438		
PTSD	23185	151309	2282	337577
Schizophrenia	53386	77258	6515	364160
Suicide attempt	6024	44240	263	377014

References to original genome-wide association studies provided by the PGC and iPSYCH consortia can be found in online supplemental table 7.
ADHD, attention-deficit/hyperactivity disorder; PGC, Psychiatric Genomics Consortium; PTSD, post-traumatic stress disorder.

as instruments for the MVMR analyses (online supplemental tables 2 and 3).

Statistical analyses

Multivariable MR

Genetic correlations between metabolites were taken directly from the original study[10] and were used for calculating both the conditional F-statistics and conditional Q-statistics to quantify the instrument strength and instrument validity (due to the exclusion restriction assumption), respectively.

To account for pleiotropic pathways of the non-strictly independent exposures, all 21 metabolites were mutually adjusted, by using them simultaneously in the MVMR. The robust inverse-variance weighted (IVW) multiplicative random effects model was used as the principal regression method, which has the highest statistical power in case of either no pleiotropy or balanced pleiotropy (ie, average pleiotropic effect of 0) and allow also a small number of invalid instruments.[13] To assess the plausibility of the non-testable assumptions (independence and exclusion restriction), several pleiotropy robust methods were performed as a part of sensitivity analyses.

Multivariable MR-Egger with random effects accounts for directional pleiotropy if it is uncorrelated with the magnitude of the SNP-exposure association (InSIDE assumption).[14] If up to 50% of genetic instruments are invalid, the weighted median approach provides a consistent estimate.[13] The multivariable Lasso procedure identifies potential outliers using penalisation and applies the multivariable IVW method to the set of valid genetic instruments.[13] Since most of the calculated conditional F-statistics were below the widely proposed threshold of 10 (see the Findings section), indicating SNPs weakly associated with a particular metabolite conditional on all other metabolites, we finally performed the recently proposed multivariable adjusted debiased IVW (adIVW) model.[15] This regression method adjusts for many weak instruments and can handle exposures with different degrees of instrument strength. Furthermore, it provides an own strength parameter λ_{min} as the minimum eigenvalue of the sample IV strength matrix. Directional pleiotropy and substantial heterogeneity were assessed by applying the multivariable MR-Egger intercept test and testing the conditional Q-statistics on an α level of 0.05, respectively.

Network MR and mediation analysis

To identify potential mediators, between-outcome associations related to a particular metabolite were investigated using univariable MR. The framework included an iterative version of an IVW regression with modified second-order weights to emphasise and eliminate outliers. The implementation, that is, instrument selection and sensitivity analyses (involving MR-Egger, weighted median, weighted mode and MR-RAPS as many weak instrument analysis), was conducted analogously to the multivariable case. Evidence for directional pleiotropy and heterogeneity was assessed by testing the MR-Egger intercept and Cochran's and Ruecker's Q-statistics, respectively.

To obtain the final direct effects, psychiatric disorders, which were categorised as potential mediators based on $\alpha=0.05$, were used subsequently as additional covariates in a multivariable MR.

Finally, based on the PGC/iPSYCH and FinnGen cohorts, pooled meta-analysis estimates were calculated using IVW fixed effect models. The inflation of the type I error due to multiple testing was considered by the FDR adjustment of reported p values in main analyses and Bonferroni adjustment in mediation analyses. Estimates represent the direct lifetime effects of genetically predicted metabolite levels on a particular psychiatric disorder on the log-OR scale.

Data processing and statistical analyses were conducted in R (V.4.3.2). The packages TwoSampleMR (V.0.5.6), MendelianRandomization (V.0.9.0), MVMR (V.0.4), mr.divw (V.0.1.0) and meta (V.7.0.0) were used for MR and meta-analyses. For data processing, the packages data.table (V.1.15.0) and dplyr (V.1.1.4) were used. Figures were created with ggplot2 (V.3.5.0).

Reporting follows the STROBE-MR Statement (Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization).

Findings

Regarding the MR-Steiger directionality test, all 138 SNPs in all models fulfilled the assumption of a valid causal direction. Under consideration of the correlation structure between metabolites, the conditional F-statistics ranged from 1.8 to 18.0, with a mean F-statistic of 4.6 (online supplemental figure 3). The model-specific strength parameters λ_{min} ranged between 2.1 and 6.7 (online supplemental figure 3). In the following, meta-analysis estimates (reported on the log-OR scale) represent the lifetime effects of different metabolite levels on the risk of psychiatric disorders.

Multivariable MR

The strongest positive association in terms of point estimate was found for genetically predicted tryptophan levels and the genetic liability to schizophrenia ($\beta=1.78$; 95% CI 0.85; 2.71; $P_{FDR}=0.006$) (figure 1). However, there was a numerical issue that caused the robust IVW estimate for the FinnGen cohort not to be calculated (online supplemental figure 4). The estimates in the FinnGen cohort generally had wide CIs compared with the estimates in the PGC cohort (online supplemental figure 4). Although directional pleiotropy was detected in both the main and the replication analyses (online supplemental table 4), the pooled MR-Egger estimate confirmed the strong association (online supplemental figure 4). The same states for meta-estimates of both the MR-Lasso method after removing 11 outlier-SNPs due to notable heterogeneity in the PGC cohort and the adIVW method with regard to the low exposure-specific conditional F-statistic as well as outcome-specific λ_{min} of about 4 representing the presence of weak instruments (online

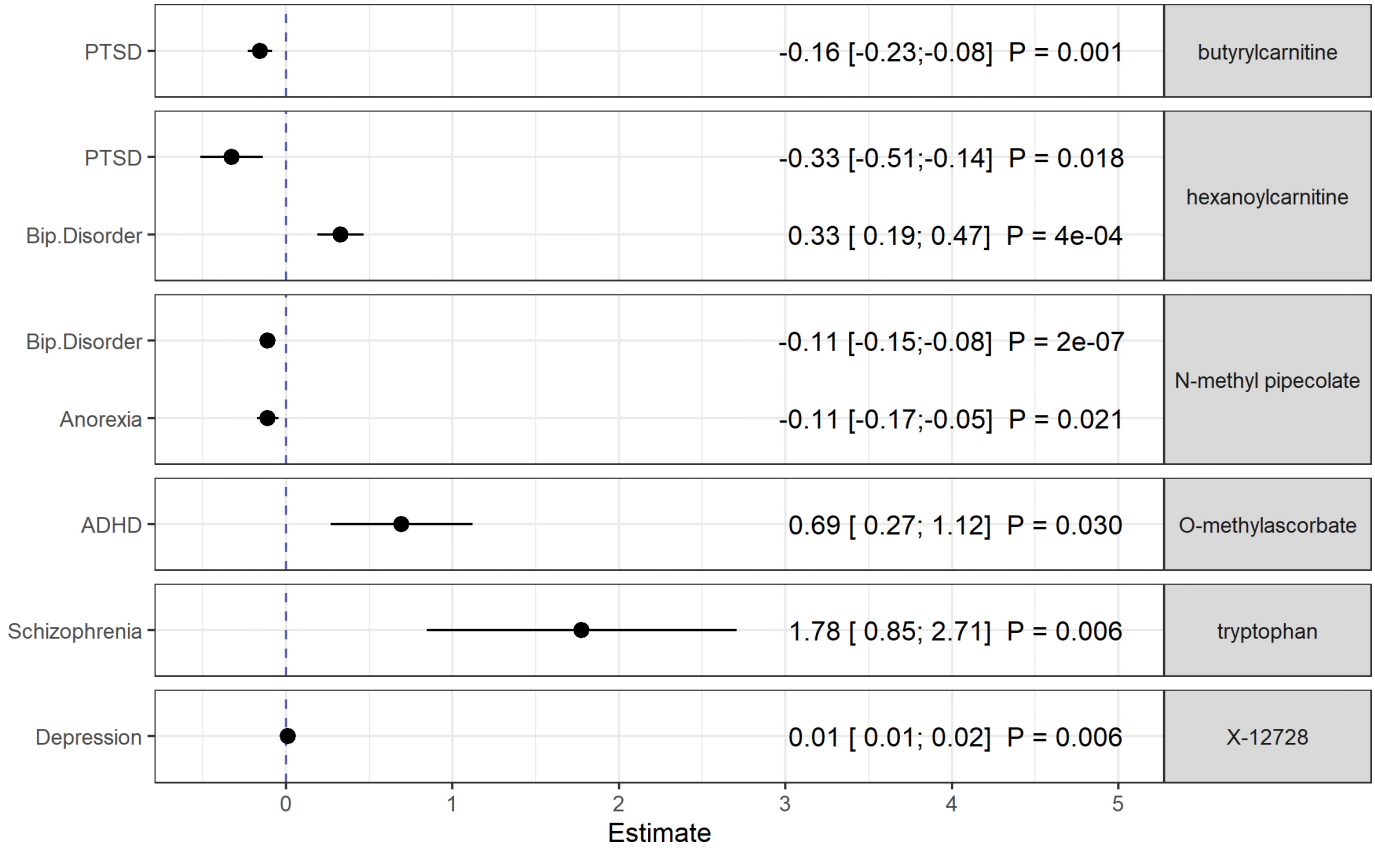

Figure 1 Effect estimates and 95% CIs on the log-OR scale derived from meta-analyses based on multivariable Mendelian randomisation analyses considering 21 mutually adjusted metabolites in two cohorts. Only notable associations between genetically predicted metabolite levels and the genetic liability to psychiatric disorders are shown. P values were FDR (false discovery rate) adjusted. ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder.

supplemental figure 5). Therefore, considering different pleiotropy patterns, all robust methods supported the evidence of a positive relationship.

A similar situation was observed for the positive association between genetically predicted X-12728 levels and the occurrence of depression (β 0.01; 95% CI 0.01; 0.02; P_{FDR}=0.006), where despite detected heterogeneity (P_Q 0.004), all pooled pleiotropy-robust estimates confirmed the relationship (figure 1, online supplemental figure 4, online supplemental table 4).

Analogously, the associations of genetically predicted levels of hexanoylcarnitine and *N*-methyl pipecolate with genetic susceptibility to bipolar disorder (β=0.33; 95% CI 0.19; 0.47; $P_{FDR}=4\times10^{-4}$; F-statistic=5.8; λ_{min}=6.6 and β=−0.11; 95% CI −0.15; −0.08; $P_{FDR}=2\times10^{-7}$; F-statistic=17.8, respectively) (without detected heterogeneity) were consistently confirmed assuming the different pleiotropy scenarios. The remaining associations presented in figure 1 were supported by consistent but less strong estimates from sensitivity analyses (without indication of substantial heterogeneity). No further associations could be detected (online supplemental figure 5 and 6).

Mediation analyses

With regard to the results from multivariable analyses (shown in figure 1), associations between the outcomes bipolar disorder, PTSD and anorexia nervosa had to be assessed. Network MR revealed bipolar disorder as a potential mediator on a path between hexanoylcarnitine and PTSD as well as *N*-methyl pipecolate and anorexia nervosa, respectively, as it was positively associated with both outcomes (figure 2, online supplemental figure 7). For these associations, all pleiotropy-robust approaches led to consistent estimates, without evidence for considerable heterogeneity (online supplemental figure 7, online supplemental table 5).

Adding bipolar disorder as an additional parameter to the multivariable models and combining the effect estimates in subsequent meta-analyses resulted in a slightly decreased negative direct effect for *N*-methyl pipecolate and anorexia nervosa (β=−0.10; 95% CI −0.16; −0.03; $P_{Bonferroni}$=0.014) and an even stronger negative association between hexanoylcarnitine and PTSD (β=−0.45; 95% CI −0.67; −0.24; $P_{Bonferroni}=1\times10^{-4}$) (figure 3). No substantial heterogeneity could be observed in any of the multivariable models (online supplemental table 6).

DISCUSSION

The present stepwise two-sample MR study identified six circulating blood metabolites associated with psychiatric disorders. We found evidence for an association between genetically predicted tryptophan levels and schizophrenia, and for an association between butyrylcarnitine as well as hexanoylcarnitine and PTSD. Hexanoylcarnitine and *N*-methyl pipecolate were related to bipolar disorder; *N*-methyl pipecolate was also associated with anorexia. Furthermore, we identified a relationship between O-methyl-ascorbate with ADHD, and between the unknown metabolite X-12728 and depression.

The essential amino acid tryptophan plays an important role in protein biosynthesis in humans.[16] Tryptophan cannot be synthesised endogenously by the human body and must therefore be obtained from external sources. Around 90% of the tryptophan

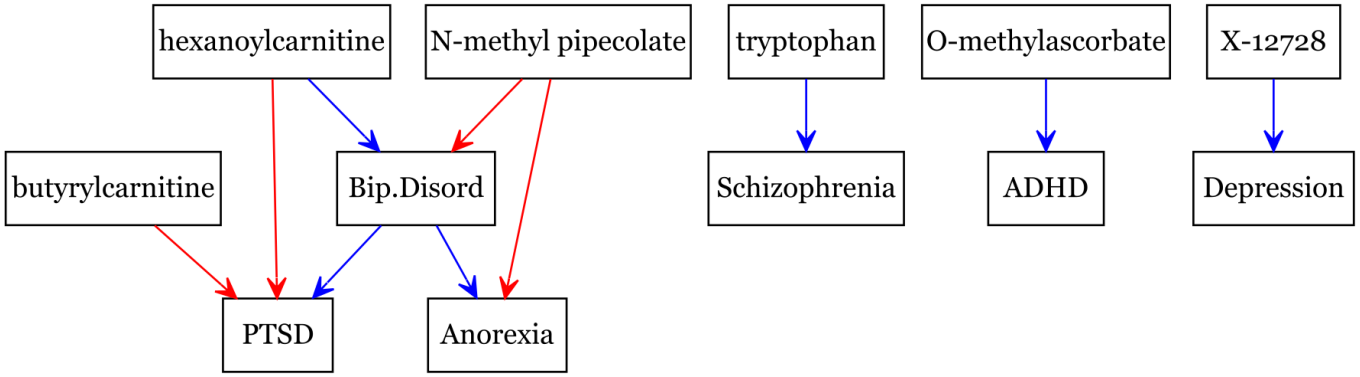

Figure 2 Graphical summary of study findings from network and multivariable Mendelian randomisation analyses. Blue arrows denote positive associations and red arrows denote negative associations. ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder.

circulates bound to albumin in the blood, while the remaining 10% is present in free form in the plasma.[16] Only tryptophan in its free form is available for tissue uptake and can cross the blood-brain barrier. Once in the central nervous system, tryptophan acts as a precursor for several metabolic pathways, such as the synthesis of the neurotransmitter serotonin.[16] However, the majority of free tryptophan is degraded along the kynurenine pathway, producing a number of metabolites that are involved in various metabolic functions in the body. Tryptophan is the biochemical precursor of nicotinamide adenine dinucleotide, which acts as a hydrogen cache for mitochondria and thus represents an important cofactor in cellular energy metabolism.[17]

Studies have shown that imbalances in tryptophan metabolism lead to neurodegenerative diseases[18] and there is evidence that plasma tryptophan and its degradation products play a role in the development of schizophrenia.[19] Prior research found that dysregulation of neuroprotective kynurenic acid in the central nervous system is associated with schizophrenia.[20] In contrast with the recently published MR studies,[9 21] the present study found a positive association between the genetically predicted blood metabolite tryptophan and schizophrenia, confirming previous results of a systematic review that tryptophan metabolism plays an important role in neuropsychiatric disorders, among other things.[16]

We identified an inverse relationship between the metabolites butyrylcarnitine and hexanoylcarnitine and PTSD. Both metabolites belong to the acylcarnitines, which are the product of the conjugation of carnitine with acyl-coenzyme A, which enables the transport of fatty acids across mitochondrial membranes. Medium- and long-chain fatty acids are mainly involved in cell metabolism, but the role of medium-chain fatty acids in gluconeogenesis and lipogenesis or in mitochondrial function and metabolism is still unclear.[22] Disturbances in fatty acid oxidation can lead to mitochondrial dysfunction and consequently have an impact on the energy supply to the brain.[23] It is therefore possible that acylcarnitines are involved in metabolic regulatory pathways that affect cognitive status and promote neurological disorders. PTSD animal models resulted in mitochondrial dysfunction, which includes dysregulation of β-oxidation of fatty acids in addition to dysregulation of a number of other metabolic pathways.[24]

For bipolar disorders, we also identified a positive relationship with blood hexanoylcarnitine. Furthermore, *N*-methyl pipecolate, which belongs to the xenobiotic pathway and the bacterial/fungal subpathway,[25] was inversely associated with the disease. In addition, *N*-methyl pipecolate was also inversely related to anorexia. So far, *N*-methyl pipecolate has not been previously examined very extensively. One very recent metabolome-wide

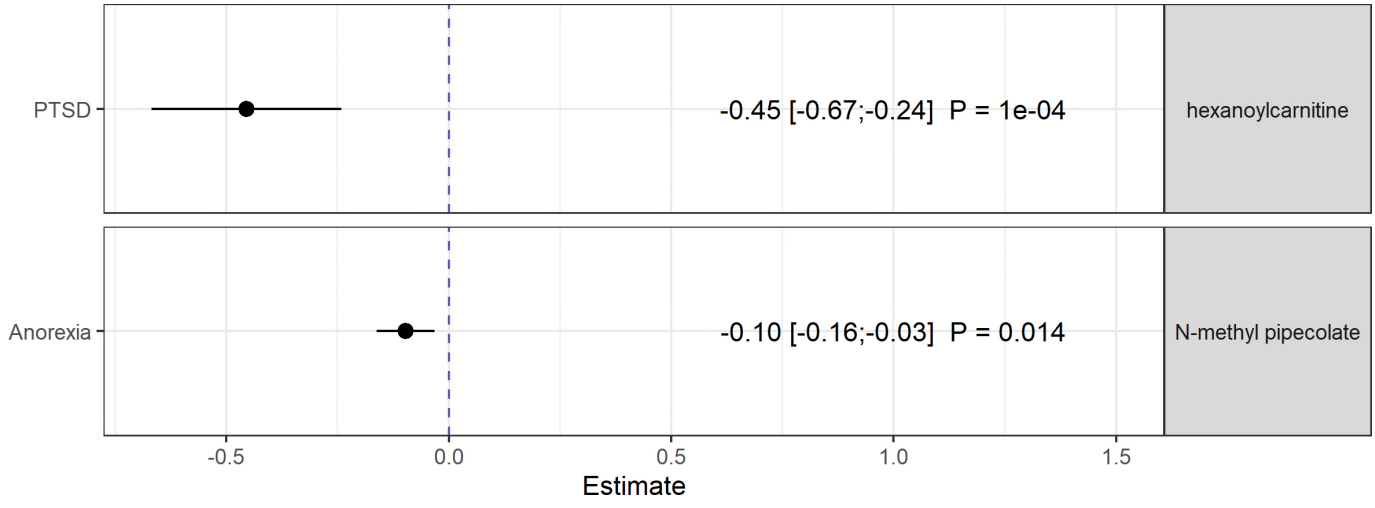

Figure 3 Direct effect estimates and 95% CIs on the log-OR scale derived from meta-analyses based on multivariable Mendelian randomisation analyses considering the mediation effect of bipolar disorder on the relationship of the metabolites hexanoylcarnitine and *N*-methyl pipecolate on post-traumatic stress disorder (PTSD) and anorexia nervosa, respectively. P values were Bonferroni-adjusted.

MR study reported risk effects of plasma *N*-methyl pipecolate on anxious personality.[25] Prior systematic reviews and MR studies investigating the association between metabolites and bipolar disorders did not identify carnitines or *N*-methyl pipecolate as related to the disease.[6 8 9 21] To date, there are no studies that have investigated a link between *N*-methyl pipecolate and anorexia. Therefore, studies of this metabolite or its pathway with regard to bipolar disorder, anorexia and other psychiatric disorders are warranted.

The metabolite O-methyl ascorbate was positively associated with ADHD in our analysis. O-methyl ascorbate occurs naturally as a metabolite of ascorbic acid and has relatively low cytotoxicity. At the same time, it has strong antioxidant stress response capabilities.[26] So far, there are no investigations, which reported an association between O-methyl ascorbate—possibly a proxy for vitamin C levels—and ADHD. Interestingly, there are studies that investigated the role of vitamin C in ADHD and hypothesised that vitamin C deficiency in the brain goes along with an impaired brain development in infants.[27] Changes in oxidative metabolism are considered an important factor in the development of ADHD.[28] Ascorbic acid is an important redox modulator in the brain and thus protect neurons against oxidative lesions.[29] Furthermore, it serves as a cofactor in the regulation of neurotransmitters.

Some prior studies examined the association between serum metabolites and major depression. Using an untargeted whole-metabolome approach, a recent study from a large Dutch clinical cohort found that a wide range of metabolites was dysregulated in depression indicating altered lipid metabolism with downregulation of long-chain fatty acids and upregulation of lysophospholipids.[30] Two prior MR studies on this issue also identified some genetically predicted metabolites from the carnitine metabolism and fatty acid metabolism related to major depression.[9 21] However, the unknown metabolite X-12728, which was related to major depression in the present investigation, was so far not identified as related to major depression.

Strengths and limitations

In this study, we focused on robust and unbiased effect estimates in the context of multiple resources, weak instruments, horizontal pleiotropy and psychiatric mediation mechanisms. Compared with most previous MR studies on this topic, we used a stringent threshold of 5×10^{-8} instead of the frequently used relaxed threshold of 1×10^{-5}, which may violate the relevance assumption and introduce weak instrument bias. Multivariable models, which were mutually adjusted for all assessed and partly dependent metabolites, prevented bias regarding horizontal pleiotropy. A network MR revealed associations between psychiatric disorders and in this way potential mediation mechanisms, which were considered in further multivariable MR analyses. Finally, we combined the results based on two unrelated European cohorts (PGC/iPSYCH and FinnGen) in a meta-analysis to strengthen the evidence.

Some main limitations are to be named. Despite the strict threshold of 5×10^{-8} within the instrument selection process, the conditional F-statistics for several genetic instruments were below 10, indicating a potentially weak instrument bias. However, the results of the recently proposed adIVW method, which is robust to weak instruments and large heterogeneity in instrument strength, consistently supported the findings. In addition, blood metabolites (influenced by several factors) are just a snapshot of a subject's condition at the time of examination. In our analyses, we assumed that the estimates are not distorted on average. Furthermore, we estimated lifetime effects and could therefore not consider possible fluctuations at specific periods of life. The GWASs for psychiatric disorders based on meta-analyses that often combine registry data and observational studies, so that a selection bias cannot be completely ruled out.

Clinical implications

In this study, we were able to identify some new blood metabolites that seems to be causally related to certain psychiatric disorders. However, it is unclear whether these metabolites directly influence disease risk. Rather, the identified metabolites could serve as indicators of the activity of certain biological metabolic pathways that are causally linked to the disease in question. Further studies are needed to investigate whether the identified associations are effects of the metabolites itself or the biochemical pathway regulating the metabolite.

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Contributors CM supervised the entire project and participated with DF in the study design. DF conducted the statistical analyses and prepared the tables and figures. DF and CM were involved in data collection. CM drafted the Introduction and Discussion sections. DF drafted the Methods and Results sections. DF and CM reviewed the drafts and read and approved the final version of the manuscript. DF acted as the guarantor.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Metabolite data can be obtained from https://metabolomips.org/gwas/index.php?task=download. Data regarding mental disorders can be downloaded from PGC (https://www.med.unc.edu/pgc), iPSYCH (https://ipsych.dk/en) and the FinnGen (https://www.finngen.fi/en) projects, respectively.

ORCID iD

Dennis Freuer http://orcid.org/0000-0001-7188-9087

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