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Exploring causal associations between plasma metabolites and attention-deficit/hyperactivity disorder

Shangyun Shi[1†], Ancha Baranova[2,3†], Hongbao Cao[2] and Fuquan Zhang[1,4*]

Abstract

Background Observational studies reported altered levels of plasma metabolites in attention-deficit/hyperactivity disorder (ADHD). We aim to explore the causal link between plasma metabolites and ADHD.

Methods We utilized Mendelian randomization (MR) analysis to assess the causal relationship between plasma metabolites and ADHD and the Genome-wide association study (GWAS) summary datasets were sourced from public databases. GWAS summary datasets were used in the study, including ADHD ($n = 292,548$) and 871 plasma metabolites ($n = 8,299$). Moreover, we used DrugBank and ChEMBL to evaluate whether the identified metabolites are potential therapeutic targets, and in addition, Bayesian colocalization analyses were conducted to assess the shared genetic signals between these metabolites and ADHD.

Results Our MR analysis identified 20 plasma metabolites that conferred protective effects against the risk of ADHD, including dimethylglycine, 3-methoxytyramine sulfate, and adenosine 3',5'-cyclic monophosphate (OR: 0.97–0.98). Additionally, 22 metabolites were associated with an increased risk of ADHD, including N-acetylneuraminate and 3-indoleglyoxylic acid (OR:1.01–1.03). Druggability evaluation showed that 12 of the ADHD-related metabolites have been targeted by pharmacological interventions. For example, doconexent has been used to increase the levels of docosahexaenoic acid. Our reverse MR analysis showed that genetic liability to ADHD may affect the abundance of 91 metabolites. Notably, several plasma metabolites had bidirectional causal associations with ADHD, including docosahexaenoate (DHA; 22:6n3), docosatrienoate (22:3n3), N1-methyladenosine, S-adenosylhomocysteine, and 4-allylcatechol sulfate.

Conclusions Our study supported a causal role of plasma metabolites in the susceptibility to ADHD, and the identified metabolites may provide a new avenue for the prevention and treatment of ADHD.

Clinical trial number Not applicable.

Keywords Attention-deficit/hyperactivity disorder, Plasma metabolites, Mendelian randomization, Causal association

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that typically appears in childhood and may persist into adulthood, with a prevalence rate of up to 5%, its characteristics are inattention, hyperactivity, and impulsivity [1, 2]. People with ADHD may have difficulty concentrating, following instructions, and organizing tasks, and its impact goes beyond individuals, affecting families, teachers, and the broader social structure [3, 4]. The exact causes of ADHD are not yet fully understood, involving genetic, environmental, and neurological factors. Treatment is usually multi-faceted, including a combination of behavioral intervention, psychological education, and medication therapy [5]. The individualized nature of treatment emphasizes the importance of customized interventions for comorbidities and specific symptoms [6].

Advances in neuroimaging and genetic research have greatly enhanced our understanding of ADHD, structural and functional brain imaging has further revealed distinct morphological and functional differences in brain regions governing attention, impulse control, and executive functions among ADHD patients [7–9]. As ADHD is increasingly recognized as a multi-dimensional disorder influenced by both genetic and environmental factors, there has been a growing impetus to explore its underlying biological mechanisms [10].

Metabolites are small molecules formed during biochemical reactions. These molecules may be either intermediates or end products such as amino acids, nucleotides, lipids, hormones, and exogenous substances participating in human metabolism. The levels of individual metabolites are influenced by inherited genetic variants, diet, and other environmental exposures [11]. In previous studies of neuropsychiatric conditions, the levels of plasma or serum metabolites were found altered. Zhang et al. associated the levels of 38 plasma metabolites with an increased risk of dementia [12]. Guo et al. detected 7 specific differential metabolites in bipolar depression, among which glycine may be its characteristic biomarker [13]. In addition, a prospective cohort study found that the metabolite 5-methoxytryptophol in umbilical cord plasma was associated with a reduced risk of ADHD, while tryptophan, 5-HTP, and N-acetyltryptophan were associated with a higher risk of ADHD [14].

For many metabolites, their serum levels are highly heritable, the biological characteristics of metabolites detected in human biological fluids bridge the gap between genotype, environment, and phenotype, and can serve as biomarkers for clinical diagnosis, prognosis, and disease classification [15, 16]. Plasma metabolites may have an impact on neural development, neuronal transmission, and immune regulation within the brain through the bidirectional signaling along the gut-brain axis [17–20]. Metabolomic biomarkers may serve as objective and quantitative indicators of ADHD-related physiological changes [21], helping to distinguish comorbidities and reveal pathological mechanisms.

Mendelian Randomization (MR), now widely used to infer causality from a genetic perspective, has emerged as a crucial tool for evaluating disease causality, with its scope of application encompassing both somatic and mental disorders [22–25]. Leveraging the random assortment of genetic variants in an individual's diploid genome to minimize ADHD–related confounding factors and reverse causality [26–28]. This feature, combined with its use of Genome-Wide Association Study (GWAS) summary data, provides a flexible and convenient approach to analyzing causal relationships between diseases [29]. In MR studies, genetic variants act as instrumental variables, allowing researchers to evaluate causal effects on outcomes, much like randomized clinical trials [30]. This methodology reduces the influence of confounders such as age, drug or environmental exposures, and reverse causation. Therefore, we used the MR method to analyze the genetic link between plasma metabolites and ADHD. We also performed Bayesian colocalization analyses to assess shared genetic signals and determine if identified ADHD - related metabolites could be modulated by pharmacological or other interventions.

Methods

Data sources and study design

The genome-wide association study (GWAS) summary results used for this analysis were all from publicly available data. Demontis et al. expanded the sample size in 2022 [31] which encompassed 38,691 cases and 275,986 control participants, making it one of the most comprehensive GWAS studies on ADHD currently available. Information on ADHD cases was obtained from the Psychiatric Genomics Consortium (https://pgc.unc.edu/), and each participant had a European background.

For metabolites, we focused on data from the Canadian Longitudinal Study of Aging (CLSA). The research targeted 8,299 unrelated European subjects within the CLSA, all of whom underwent genome-wide genotyping and blood metabolite measurement. The CLSA tracks over 50,000 Canadians aged 45–85 (with 50.9% being females) for various types of information such as biological and medical data [32]. Among the plasma metabolites that were tested, those with known identities were distributed across eight super-pathways: lipids, amino acids, xenobiotics, nucleotides, cofactors and vitamins, carbohydrates, peptides, and energy. After excluding the metabolites labeled as "X-" (unknown), we tested 871 metabolites. The statistical summary of GWAS data for each metabolite was taken from the European GWAS website (http://www.ebi.ac.uk/gwas/; registration numb

er from GCST90199621 to GCST90200707). When analyzing the metabolic pathways, we referred to the original research literature, which contained the metabolic pathways of these metabolites. Ethical approval was obtained in all original studies. The flowchart of the current study is described in Fig. 1.

Selection of instrumental variables

We selected single nucleotide polymorphisms (SNPs) that were significantly associated with the phenotype and met genome-wide significance criteria in the exposure dataset. To increase the number of validated instrumental variables (IVs) and enhance statistical power, we applied a threshold of $P < 1 \times 10^{-5}$. In the reverse MR analysis, the threshold for screening SNPs was more stringent, at $P < 5 \times 10^{-8}$. To avoid the inclusion of weak IV that could result in biased effect estimates, SNPs with an F statistic < 10 were excluded. The 1000 Genomes Project Phase 3 (EUR) reference panel was used for SNP selection. To ensure the independence of the IVs, we performed pruning with an r^2 threshold of 0.001 within a 10 Mb window. More details of the selected IVs are presented in Supplementary Table S1-S2.

MR analysis

In this study, we utilized three different models from the TwoSampleMR package in the R studio to investigate causal relationships [33]. The primary method employed was the inverse variance weighted (IVW) approach, which improves the accuracy of estimates by assigning

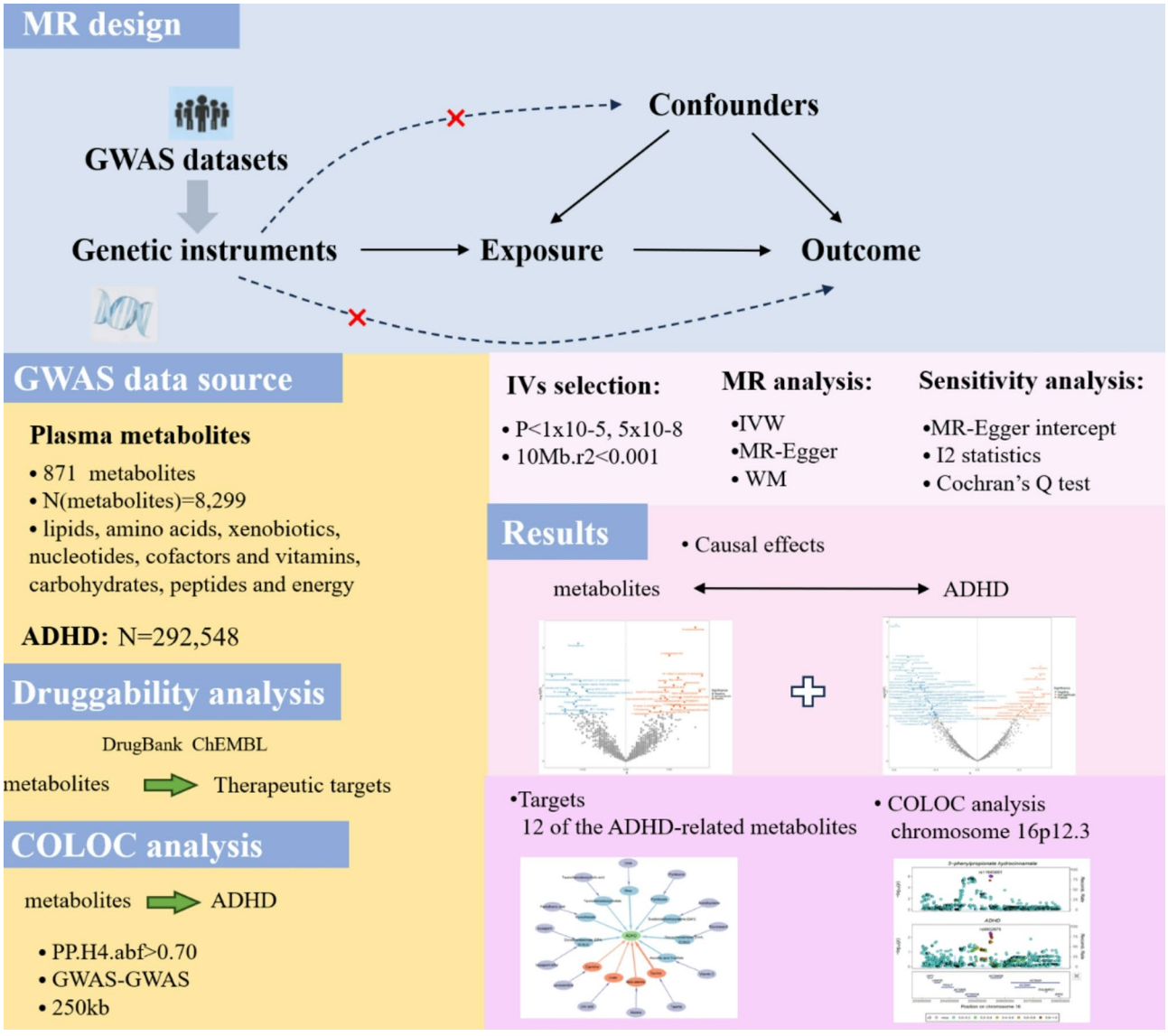

Fig. 1 Flowchart of the study. MR: Mendelian randomization; ADHD: attention-deficit/hyperactivity disorder; GWAS: genome-wide association studies; IVs: instrumental variables; IVW: inverse variance weighted; WM: weighted median

weights to the individual instrumental variables (IVs) based on their precision, helping to minimize random errors. However, the IVW model assumes that all IVs are valid and that their effect on the outcome is mediated solely through the exposure. To verify the robustness of our findings, we also applied the Weighted Median (WM) and MR-Egger methods as supplementary techniques [34, 35]. The WM method gives more weight to IVs with greater precision and provides reliable causal estimates even when some IVs may be invalid. The MR-Egger model, on the other hand, helps to detect and adjust for biases arising from the use of invalid IVs.

For sensitivity analysis, we assessed horizontal pleiotropy using the intercept from the MR-Egger regression [35]. A significant non-zero intercept in this regression indicates the presence of horizontal pleiotropy, suggesting that certain instrumental variables (IVs) may affect the outcome through mechanisms other than exposure. Additionally, we evaluated heterogeneity using Cochran's Q test and the I^2 statistic. A P-value < 0.05 and an I^2 > 0.25 were considered indicative of significant heterogeneity. We used R software and Cytoscape for data lake visualization and plotted related graphs.

Druggability analysis

We explored target and drug data from DrugBank [36] and ChEMBL [37] to evaluate the potential of the identified metabolites as therapeutic targets. These databases emphasize druggable targets by combining insights from text mining, gene function, drug-gene interactions, and expert curation.

Colocalization analysis

Bayesian colocalization analyses were conducted to evaluate the shared genetic signals between metabolites and ADHD [38]. The colocalization analysis was performed on the GWAS summary data with the "coloc" package (v5.1.1) in R Studio, which can calculate the posterior probabilities for the five hypotheses and assess the support for each hypothesis. There were five assumptions in this approach: H0, no SNPs are significantly associated with metabolites or ADHD; H1, the SNP is significantly associated with the metabolites only; H2, the SNP is significantly associated with ADHD only; H3, each SNP is significantly associated with both metabolite and ADHD, but driven by different causal variants; and H4, the SNP is significantly associated with both metabolite and MDD, driven by the same causal variants. We chose a range of 250 kb up and down each SNP to divide the colocalization area, and defined colocalization based on high posterior probability (PP.H4.abf > 0.70). In addition, we analyzed genes within shared chromosomal regions to explore mechanisms and check if they are in causal genes of shared regions.

Results

MR analysis

Using IVW, a total of 42 metabolites were identified as conferring causal effects on ADHD (Table 1; Figs. 2 and 3). 22 metabolites were positively associated with the risk of ADHD, including N-acetylneuraminate and 3-indoleglyoxylic acid (OR: 1.01 ~ 1.03). 20 metabolites were associated with a decreased risk of ADHD, including dimethylglycine, 3-methoxytyramine sulfate (MTS), and adenosine 3',5'-cyclic monophosphate (OR: 0.97 ~ 0.98).

Reverse MR analysis revealed that genetic liability to ADHD is linked to increased levels of 22 metabolites, as well as a reduction in 69 metabolites (Supplementary Table S3 and Supplementary Fig. 1).

The results demonstrated that metabolites predominantly clustered at the lipid and amino acid levels. The implicated metabolic pathways consisted of long-chain polyunsaturated fatty acid biosynthesis, tyrosine metabolism, along with the metabolism of methionine, cysteine, S - adenosylmethionine (SAM), and taurine. For details on other relevant metabolic pathways, see Supplementary Table S4.

Five metabolites had bidirectional causal relationships with ADHD, including docosahexaenoate (DHA; 22:6n3), docosatrienoate (22:3n3), N1-methyladenosine, S-adenosylhomocysteine (SAH), and 4-allylcatechol sulfate.

In the sensitivity analysis, the MR-Egger regression results showed that oleoylcarnitine and docosatrienoate (22:3n3) had horizontal pleiotropy (P-pleiotropy < 0.05). Cochran's Q test and the I^2 statistic indicated potential heterogeneity in the Mendelian randomization estimates (Q_P < 0.05) (Supplementary Table S5-S6).

Druggability evaluation on the potentials of therapeutic targets

The druggability analysis showed that 12 of the ADHD-related metabolites have been targeted by pharmacologic intervention (Fig. 4 and Supplementary Table S7). Doconexent is a drug that serves as a high-docosahexaenoic acid (DHA) supplement, commonly included in a variety of nutritional products to support both a healthy brain and a healthy heart. Icosapent ethyl or ethyl eicosapentaenoic acid is a synthetic derivative of the omega-3 fatty acid eicosapentaenoic acid (EPA). It is used as an adjunct therapy for severe hypertriglyceridemia and to reduce the risk of cardiovascular events in certain patients with elevated triglycerides. In addition, Icosapent is a polyunsaturated fatty acid rich in eicosapentaenoic acid, typically found in fish oil and used in many supplements. Acetylcysteine is an antioxidant and glutathione inducer indicated for mucolytic therapy and the treatment of acetaminophen overdose. Acetylcysteine has also been studied for a wide variety of off-label indications with mixed results.

Table 1 MR analysis of causal effects of plasma metabolites on ADHD

Exposure	Outcome	Q_P	P_pleiotropy	OR [95%CI]	*P*
N-acetylneuraminate	ADHD	0.399	0.215	1.03 [1.01–1.05]	2.89×10^{-4}
Dimethylglycine	ADHD	0.327	0.508	0.98 [0.97–0.99]	7.68×10^{-4}
3-indoleglyoxylic acid	ADHD	0.653	0.211	1.02 [1.01–1.03]	1.59×10^{-3}
N1-methyl-2-pyridone-5-carboxamide	ADHD	0.600	0.459	1.04 [1.01–1.06]	5.47×10^{-3}
3-methoxytyramine sulfate	ADHD	0.079	0.806	0.97 [0.94–0.99]	5.59×10^{-3}
Beta-alanine	ADHD	0.913	0.987	1.02 [1.01–1.04]	6.20×10^{-3}
Docosahexaenoate (DHA; 22:6n3)	ADHD	0.438	0.921	0.97 [0.95–0.99]	6.29×10^{-3}
Adenosine 3',5'-cyclic monophosphate(camp)	ADHD	0.865	0.556	0.98 [0.96–0.99]	7.62×10^{-3}
Carnitine	ADHD	0.471	0.372	1.02 [1.00-1.03]	8.28×10^{-3}
Oleoylcarnitine	ADHD	0.111	0.026	1.03 [1.01–1.05]	9.42×10^{-3}
Docosatrienoate (22:3n3)	ADHD	0.145	9.05×10^{-3}	1.02 [1.01–1.04]	9.78×10^{-3}
5alpha-androstan-3alpha,17beta-diol disulfate	ADHD	0.580	0.642	0.98 [0.97-1.00]	0.011
Ascorbic acid 3-sulfate	ADHD	0.774	0.539	0.97 [0.96–0.99]	0.013
Inosine 5'-monophosphate (IMP)	ADHD	0.540	0.980	1.02 [1.00-1.03]	0.013
Alpha-hydroxyisovalerate	ADHD	0.045	0.874	1.03 [1.01–1.05]	0.014
1-stearoyl-GPG (18:0)	ADHD	0.537	0.065	0.98 [0.97-1.00]	0.014
Palmitoyl dihydrosphingomyelin(d18:0/16:0)	ADHD	0.798	0.060	0.98 [0.97-1.00]	0.014
Taurine	ADHD	0.916	0.582	1.03 [1.01–1.06]	0.014
N1-methyladenosine	ADHD	0.047	0.865	0.98 [0.96-1.00]	0.016
Eicosapentaenoate (EPA; 20:5n3)	ADHD	9.06×10^{-3}	0.279	0.97 [0.95-1.00]	0.017
S-adenosylhomocysteine (SAH)	ADHD	0.073	0.242	0.98 [0.96-1.00]	0.020
2-hydroxy-4-(methylthio)butanoic acid	ADHD	0.022	0.323	1.03 [1.00-1.05]	0.021
Urate	ADHD	0.738	0.850	1.02 [1.00-1.03]	0.021
Lignoceroylcarnitine (C24)	ADHD	0.275	0.889	1.02 [1.00-1.03]	0.022
Glycocholate glucuronide (1)	ADHD	0.771	0.621	1.02 [1.00-1.04]	0.023
Pantothenate	ADHD	0.840	0.833	0.98 [0.96-1.00]	0.026
Prolylglycine	ADHD	0.043	0.771	1.03 [1.00-1.05]	0.027
Pyridoxate	ADHD	0.278	0.344	0.98 [0.95-1.00]	0.031
7-methylguanine	ADHD	0.768	0.613	1.02 [1.00-1.04]	0.035
3-phenylpropionate(hydrocinnamate)	ADHD	0.253	0.193	1.03 [1.00-1.05]	0.036
Taurochenodeoxycholate	ADHD	0.536	0.944	0.98 [0.96-1.00]	0.036
N-acetyl-3-methylhistidine	ADHD	0.967	0.198	1.01 [1.00-1.03]	0.039
3-hydroxy-2-methylpyridine sulfate	ADHD	0.237	0.777	1.03 [1.00-1.05]	0.039
1,7-dimethyluric acid	ADHD	0.796	0.961	0.98 [0.97-1.00]	0.042
1-stearoyl-2-oleoyl-gpc (18:0/18:1)	ADHD	3.52×10^{-3}	0.113	1.02 [1.00-1.04]	0.042
Urea	ADHD	7.20×10^{-3}	0.658	0.97 [0.95-1.00]	0.042
4-oxo-retinoic acid	ADHD	0.310	0.299	0.98 [0.96-1.00]	0.046
Maleate	ADHD	0.233	0.271	0.98 [0.96-1.00]	0.047
1-methylhistidine	ADHD	0.800	0.387	1.02 [1.00-1.03]	0.048
3-formylindole	ADHD	0.652	0.763	1.01 [1.00-1.02]	0.048
4-hydroxycoumarin	ADHD	0.518	0.482	0.98 [0.96-1.00]	0.049
4-allylcatechol sulfate	ADHD	0.088	0.346	0.97 [0.95-1.00]	0.049

ADHD: attention-deficit/hyperactivity disorder; OR: odds ratio; CI: confidence interval; Q_P: Cochran's P-value of heterogeneity analysis; P_pleiotropy: P value of MR-Egger intercept analysis

Colocalization analyses

Evidence from colocalization analysis supported the association of one metabolite, 3-phenylpropionate (hydrocinnamate), with ADHD. Specifically, the colocalization analysis pinpointed a shared genomic region at chromosome 16p12.3 (PP.H4.abf = 0.72). This region encompasses ten protein-coding genes, which are *GP2*, *UMOD*, *PDILT*, *ACSM5*, *ACSM2A*, *ACSM2B*, *ACSM1*, *ACSM3*, *THUMPD1*, and *ERI2* (Fig. 5 and Supplementary Table S8).

Discussion

In this study, we investigated potential links between human plasma metabolites and ADHD by performing a two-sample Mendelian randomization (MR) analysis using GWAS summary statistics. Our analysis

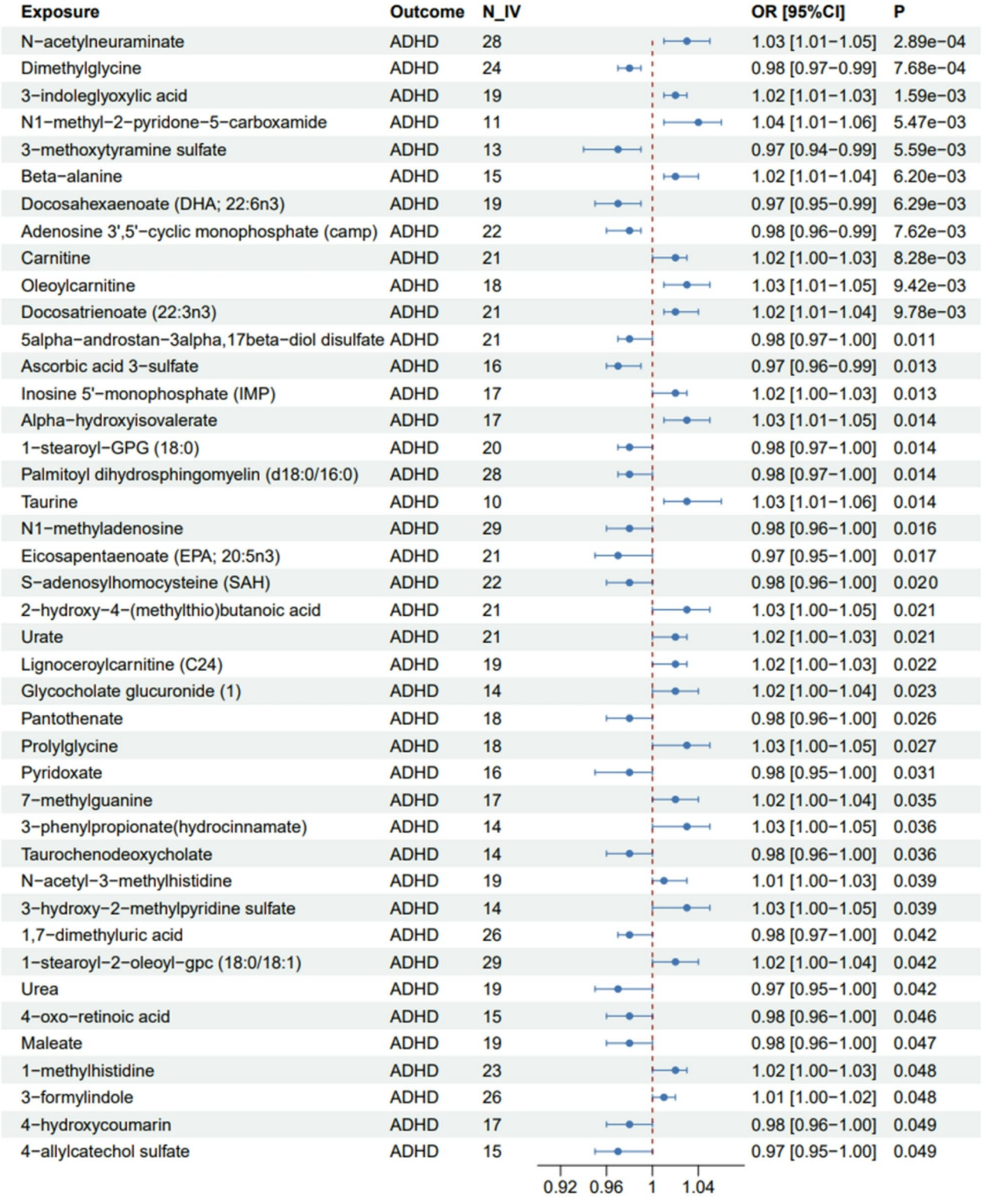

Fig. 2 Forest plot for the causal effects of plasma metabolites on ADHD. ADHD: attention-deficit/hyperactivity disorder; OR: odds ratio; CI: confidence interval; N_IV: number of instrumental variables

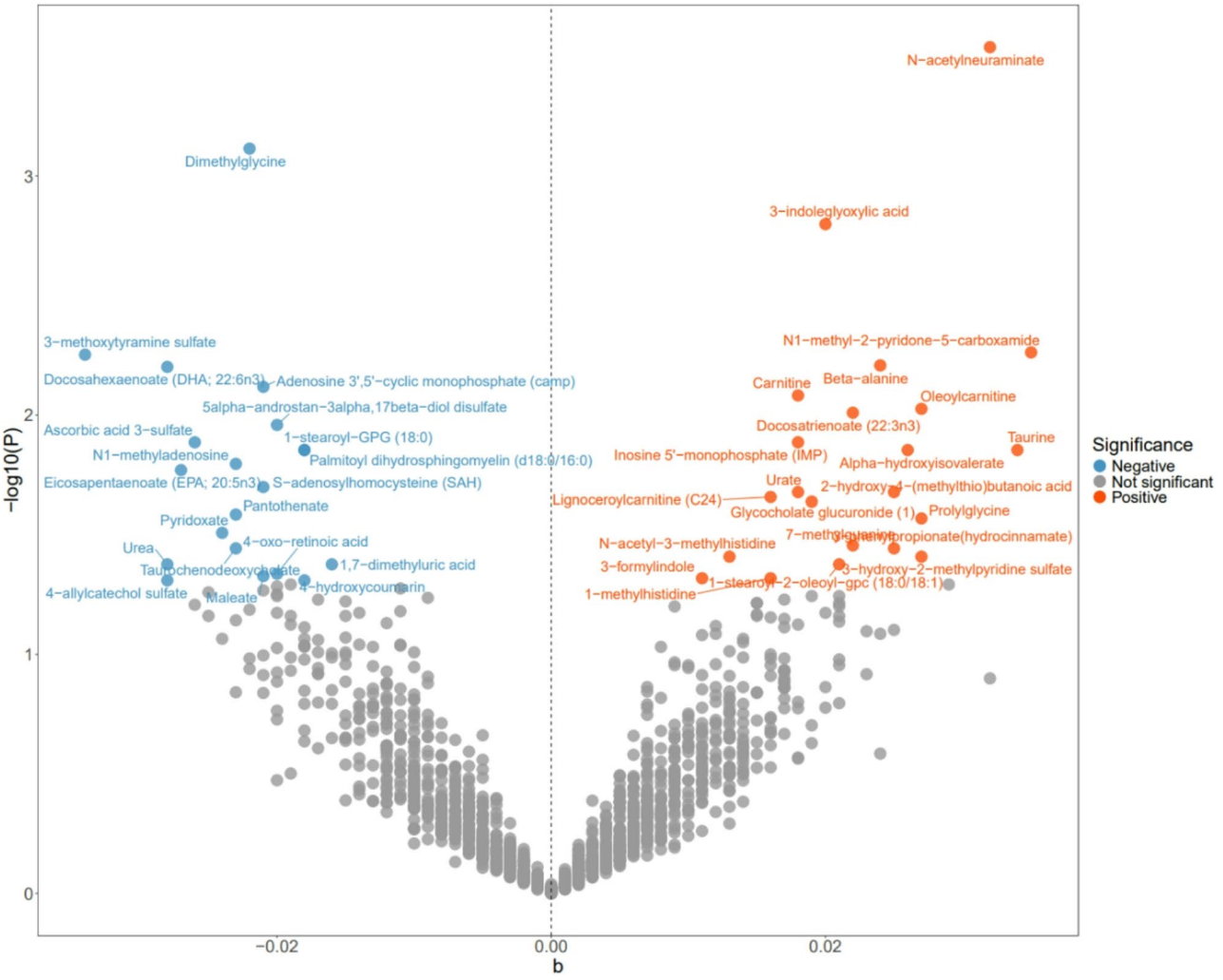

Fig. 3 Volcano plot for the causal effects of plasma metabolites on ADHD. Dot colors indicate different effects: red, positive effect; blue, negative effect

highlighted 42 metabolites whose underlying genetic variation has a causal relationship with ADHD risks. Subsequent druggability assessment emphasizes 12 metabolites associated with ADHD, such as docosahexaenoate (DHA; 22:6n3), ascorbic acid 3-sulfate, and eicosapentaenoate (EPA; 20:5n3), as promising targets for therapeutic interventions. Evidence from colocalization analysis supported the uncovered association of one metabolite, 3-phenylpropionate (hydrocinnamate), with ADHD. Additionally, we found that the genetic variation associated with ADHD also influences the levels of 91 metabolites in plasma.

A total of five metabolites were involved in a bidirectional causal relationship with ADHD, including docosahexaenoate (DHA; 22:6n3), docosatrienoate (22:3n3), N1-methyladenosine, S-adenosyl-homocysteine (SAH), and 4-allylcatechol sulfate, thus, supporting the idea that the metabolism and brain function intertwine. Some other studies have also observed similar phenomena. Yang et al. [39] used different data sources and parameter settings than those in our study, and, therefore, produced results that cannot be directly compared to ours. On the other hand, the study by Jia et al. [40] has reported findings in many ways similar to ours, supporting the effects of carnitine, 5alpha-androstan-3alpha,17beta-diol disulfate, Alpha-hydroxyisovalerate, and urate on ADHD.

In our study, ADHD-related metabolites were mostly belonging to the lipid and amino acid levels, with relevant metabolic pathways involving long-chain polyunsaturated fatty acid biosynthesis, tyrosine metabolism, and the metabolism of methionine, cysteine, SAM, and taurine.

One particular metabolic change of interest was an ADHD associated altreration in plasma levels of MTS, which is a product of tyrosine metabolism and dopamine precursor. Genetic variation supporting higher levels of MTS in plasma was associated with a reduced risk of ADHD. MTS participates in the metabolic pathways of

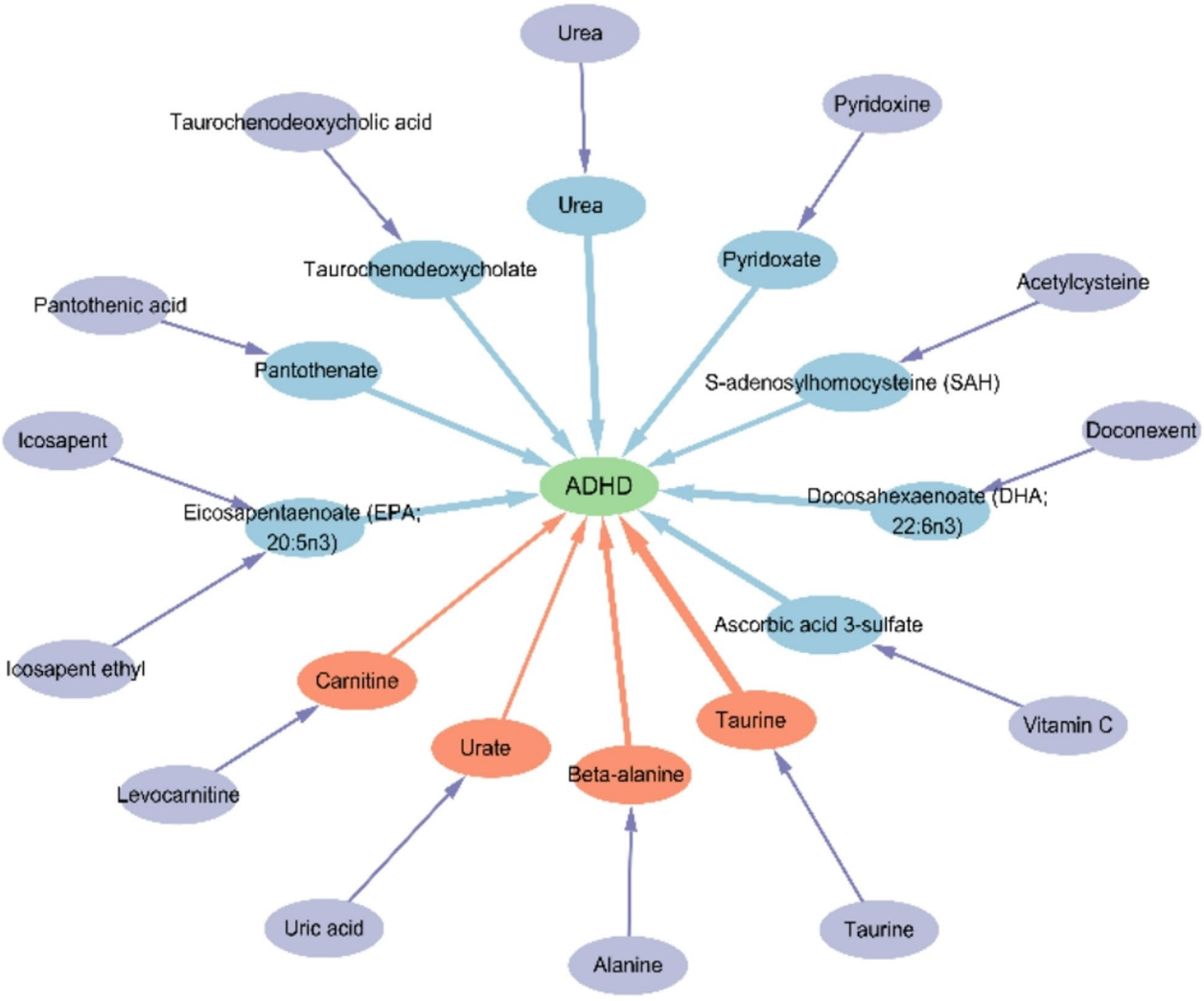

Fig. 4 Druggability of plasma metabolites with a causal effect on ADHD. The purple nodes represent drugs. The blue and red nodes represent metabolites. The green node represents the disease. The red lines are for positive significance and blue for negative significance, lines thicknesses indicate the effect size

neurotransmitters such as dopamine and norepinephrine, as well as in maintenance of their balance, and synergistically regulates neural function [41]. Its levels can serve as a biomarker of neurotransmitter activity [42], especially in neurobiological research involving emotion, motor control, and reward mechanisms. Previous studies have linked MTS to neuroblastoma [43] and the dopamine system altogether to Parkinson's disease [44], suggesting that abnormal changes in MTS may be associated with symptoms, pathophysiological changes, and clinical manifestations of neurodegeneration [45]. Moreover, intraventricular injections of MTS cause an increase in stereotyped behavior, while local injections of MTS are not associated with behavioral changes [46]. At lower concentrations, it dose-dependently reduced movement time in rats [47]. Future studies should explore the mechanisms for the MTS-related effects on the human brain and its specific role in the pathogenesis of ADHD.

In our reverse MR study, it was found that an increase in N-lactoyltyrosine, homovanilate (hva), and 3-methoxytyrosine, which are involved in tyrosine metabolism, are associated with elevated risks of ADHD. The causal link seem to be bidirectional, possibly dependent on neurochemical imbalance, diet, and the functioning of the gut-brain axis [48].

N-acetylneuraminate is a sialic acid derivative that is present in a wide array of mammalian cells, particularly in the central and peripheral neurons, where it plays structural and functional roles in brain development [49]. Sialic acid biosynthesis involves four pathways converging on N-acetylneuraminate synthase (NANS) [49]. Patients with homozygous mutations in the NANS gene have severe developmental delays [50]. Another sialyation

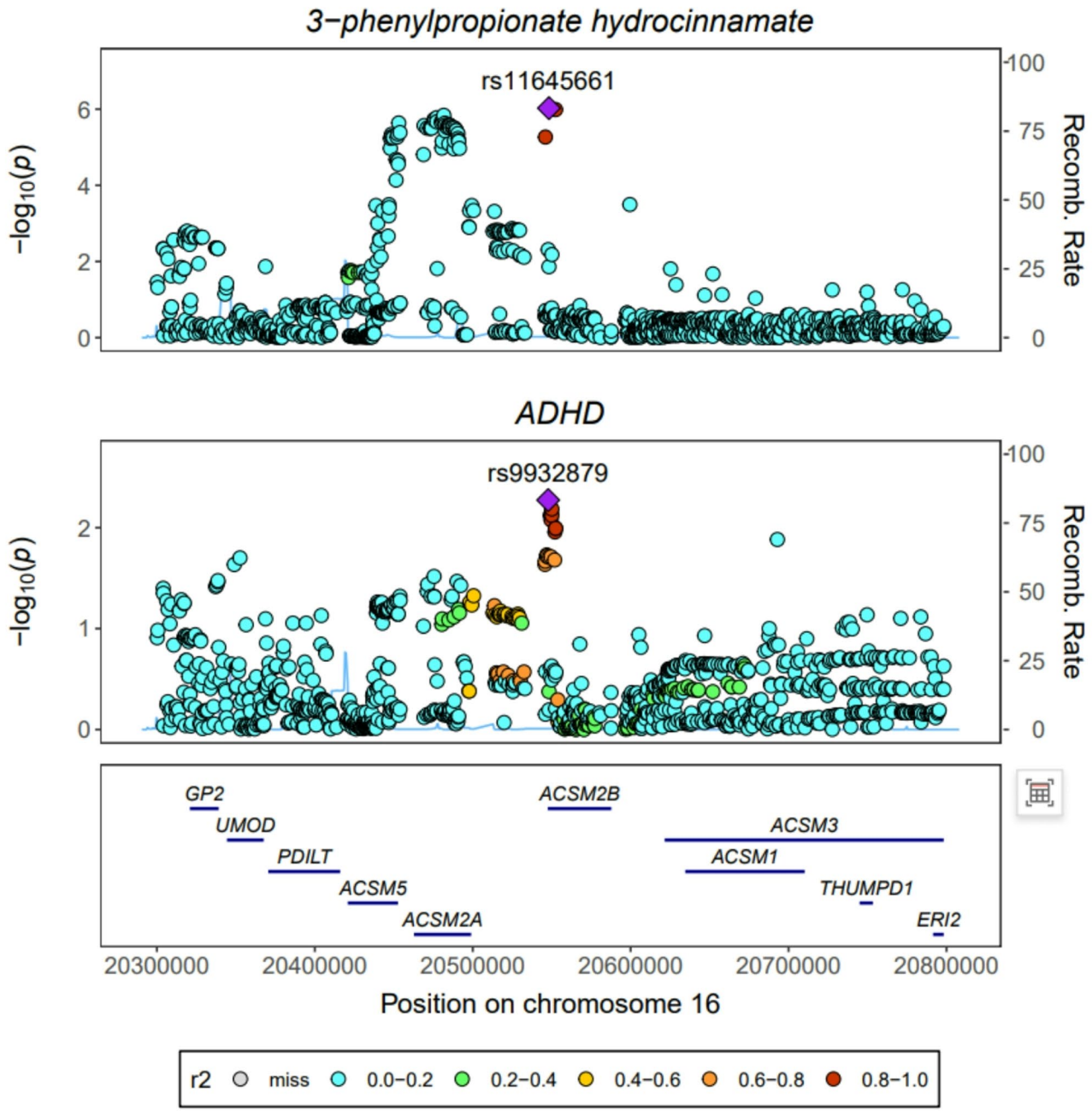

Fig. 5 The colocalized region between metabolites and ADHD. The x-axis represents the genomic coordinates and the y-axis represents the negative log10 transform P value for each genetic variant. ADHD: attention-deficit/hyperactivity disorder

enzyme, alpha-2,8-sialyltransferase, facilitates early brain development by adding polysialic acid to various neuronal proteins, mainly neuronal cell adhesion molecule (NCAM) [51]. Genes of the ST8Sia family were identified as located in susceptibility loci for schizophrenia [52] and autism spectrum disorder [53] and also associated with an increased risk of bipolar disorder [54].

Our MR analysis shows that higher N-acetylneuraminate levels are associated with increased ADHD risks. There's a potential link between the activity of the immune system in brain parenchyma and ADHD symptoms [55]. Abnormally high availability of N-acetylneuraminate may affect the function and development of the nervous system by altering the neuroimmune environment and promoting inflammatory responses [56]. At present, understanding of the relationship between N-acetylneuraminate levels and ADHD is relatively limited, so extension of the research avenue is warranted.

Methionine is an essential amino acid that participates in methyl conversion to homocysteine. Subsequently,

homocysteine is enzymatically converted to cysteine, which can be further converted to taurine. These compounds participate in various physiological processes, through mutual transformation and metabolism forming a complex metabolic network. Augmentation with N-acetylcysteine (NAC) has also been recognized as an approach to treating various mental illnesses, including attention-deficit/hyperactivity disorder, anxiety, bipolar disorder, and depression [57]. Another interesting, potentially therapeutic molecule of methionine pathways is taurine, which may be biosynthesized directly in the tissue of the brain [58]. predominantly in astrocytes, where it takes part in the communication of astrocytes to other cells, especially neurons [59]. A study on magnetic resonance spectroscopy (MRS) a direct correlation between taurine concentrations with glutamate and cannabinoid use frequency [60]. In addition, MRS measurements confirmed that the concentrations of taurine are elevated in the cerebellar vermis of bipolar patients [61], and correlated with disease duration in patients with schizophrenia [62]. Intravenous administration of taurine became popular in general wellness programs but has not been yet tested in individuals with neurological or neuropsychiatric disorders.

Fatty acids are commonly discussed as prominent players in the pathophysiology of ADHD, but specific relationships of particular fatty acids with this condition are not yet clear. Polyunsaturated fatty acids (PUFAs), important components of neuronal membranes, may influence neuronal activity by altering membrane fluidity and function [63]. Both docosahexaenoate (DHA, 22:6n-3) and eicosapentaenoate (EPA, 20:5n-3) are present and abundant in the brain [64, 65], and our MR study suggests that increases in their levels are associated with a reduced risk of ADHD. In a previous observational study, the clinical severity of ADHD was negatively correlated with the levels of EPA and DHA in plasma and the membranes of red blood cells, while the levels of phosphatidylcholine form of DHA in plasma, were significantly correlated with symptoms of inattention and hyperactivity [66]. However, another study showed that the levels of DHA and EPA are positively correlated with inattention [67]. Our reverse MR analysis results indicate that the risks of ADHD causally depend on a reduction in long-chain polyunsaturated fatty acids. These findings suggest that fatty acid metabolism in ADHD patients may be abnormal, and supportive of the pathophysiology of ADHD.

The identified metabolites can be regulated through pharmacological interventions or modifiable factors. Specifically, acetylcysteine is an antioxidant and glutathione inducer indicated for mucolytic therapy and the treatment of acetaminophen overdose. As derivatives of long-chain polyunsaturated fatty acid, doconexent, icosapental ethyl, and icosapental may effectively improve symptoms in ADHD patients.

In the future, more comprehensive validation efforts are required to further explore these causal associations, determine whether drug mediation is indicated, and figure out how to regulate the levels of metabolites within an appropriate range for corresponding prevention. Our research has some limitations. Firstly, the summary datasets used in MR analysis mainly include individuals of European ancestry, which may limit the generalizability of the results to other populations. Future research requires more diverse datasets to validate these findings across different racial groups. Secondly, although MR analysis is a powerful tool for inferring causal relationships, it relies on the hypothesis that the selected instrumental variables are effective and only affect the outcome through exposure. Although we used supplementary methods such as MR Egger to explain pleiotropy, we cannot completely rule out the possibility of residual pleiotropy or confounding. Thirdly, heterogeneity was observed in certain MR estimates, which may stem from differences in genetic tools or underlying biology, and further research is needed to explore these inconsistencies. MR only considers genetic components that contribute to the composition of metabolites and ADHD, so caution should be exercised when interpreting the results. The metabolites may be influenced by other factors such as dietary habits, health status, and BMI. Currently, we cannot conclude whether genetic factors are related to these confounding factors. Finally, although our study identified certain metabolites associated with the risk of ADHD, this mainly provides predictive insights that need to be validated through thorough examination via comprehensive bioinformatics analysis and functional experiments in subsequent research work.

Conclusion

Our research reveals the causal relationship between plasma metabolites and ADHD and emphasizes potential drug intervention strategies. These findings provide valuable clues for developing new diagnostic tools and therapeutic targets, with the potential to optimize ADHD diagnosis and treatment management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06951-9.

Supplementary Material 1

Supplementary Material 2

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Author contributions
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