Lipids in Health and Disease

REVIEW

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Lipidomics and genomics in mental health: insights into major depressive disorder, bipolar disorder, schizophrenia, and obsessive-compulsive disorder

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Abstract

Introduction This systematic review explores the hypothesis that various lipid categories and lipid metabolism-related genomic variations link to mental disorders, seeking potential clinically useful markers.

Methods We searched PubMed, Scopus, and PsycInfo databases until October 12th, 2024, using terms related to lipidomics, lipid-related genomics, and different mental disorders, i.e., Major Depressive Disorder (MDD), Bipolar Disorder (BD), Schizophrenia (SCZ), and Obsessive–Compulsive Disorder (OCD). Eligible studies were assessed. Extracted data included author, year, methodology, outcomes, genes, and lipids linked to disorders. Bias and evidence certainty were evaluated. The systematic review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and a registered protocol (PROSPERO: CRD42023438862).

Results A total of 27 studies were included. SCZ showed alterations in 77 lipids, including triglycerides (TG), ceramides, and phosphatidylcholine, while MDD and BD exhibited 97 and 47 altered lipids, respectively, with overlap among disorders. Shared genes, such as ABCA13, DGKZ, and FADS, and pathways involving inflammation, lipid metabolism, and mitochondrial function were identified. OCD was associated with sphingolipid signaling and peroxisomal metabolism.

Discussion Lipid signatures in MDD, BD, and SCZ shed light on underlying processes. Further research is needed to validate biomarkers and refine their clinical applications in precision psychiatry.

Highlights

- Various lipid categories can link to mental disorders, being potential clinically useful markers.
- This systematic review comprehensively analyzed the role of lipidomics and lipid-related genomics in Major Depressive Disorder (MDD), Bipolar Disorder (BD), Schizophrenia (SCZ), and Obsessive-Compulsive Disorder (OCD).

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- Specific lipid signatures, such as polyunsaturated fatty acids, high-density lipoproteins (HDL), and arachidonic acid, shed light on the underlying biological processes in MDD, BD, and SCZ.
- Advancing lipidomics research may pave the way for precision psychiatry, enabling personalized diagnostic and therapeutic strategies for mental disorders.

Keywords Metabolomics, Genomics, Schizophrenia, Major Depressive Disorder, Bipolar Disorder, Obsessive–Compulsive Disorder, Lipid Metabolism, Precision Medicine

Introduction

Precision Medicine (PM) has emerged as an innovative approach to disease management, placing utmost importance on individual variability as a pivotal element. Notably, the field of oncology has served as a pioneer domain, leveraging the remarkable progress in molecular biology and bioinformatics [1]. Inspired by the success of precision oncology, other medical disciplines have shown increasing interest in adopting this model: Precision Psychiatry (PP) emerged nearly a decade ago as a field focusing on molecular and biochemical targets in mental disorder [2]. Traditionally, psychiatric diagnoses rely on signs and symptoms categorized under broad syndromic labels, with treatment often guided by a trial-and-error approach. This empirical method exposes patients to unnecessary risks and delays in achieving optimal outcomes [3]. At present, PP has the possibility to focus on molecular and biochemical targets in mental disorders pursuing the conception of more rational drug treatment programs. Moreover, a top-down approach can unravel further pathophysiological elements that account for drug actions and disease processes [4]. These developments provide insights into the underlying pathophysiology, facilitate early detection, and aid in accurate prognosis [5, 6]. Furthermore, PP capitalizes on the synergistic integration of several disciplines, including genetics, neurobiology, pharmacology, and computational biology. The utilization of cutting-edge technologies such as next-generation sequencing, functional imaging, and high-throughput screening enables the identification of genetic variants, biomarkers, and molecular signatures associated with specific mental disorders [7]. Additionally, machine learning approaches have opened avenues for redefining psychiatric taxonomy and therapeutic possibilities [8, 9]. These potential developments may provide valuable insights into the underlying pathophysiology, facilitate early detection, aid in accurate prognosis, and enhance the selection of appropriate therapeutic interventions. Currently, systems biology approaches, such as omics and neuroimaging techniques, are crucial for discovering biomarkers with both translational and clinical potential [7, 10]. Furthermore, the rise of biomarkers in psychiatry has unveiled a remarkably diverse array of elements regarding different aspects of mental disorders [4]. Various categories of biomarkers have been identified, including genetic biomarkers such as single nucleotide variants, insertions or deletions and copy number variants (CNVs) [11]. Additionally, peripheral biomarkers encompassing cytokines [12], markers of oxidative stress [13, 14], and lipids [15] have been explored. Metabolomics, for instance, has been pivotal in uncovering metabolic pathways affected by novel treatments such as ketamine and esketamine, including lipid metabolism and mitochondrial function, which may offer potential biomarkers for treatment-resistant depression [16]. The field of PP also contemplates transcriptome-metabolome profiling [17, 18], as well as central nervous system (CNS) biomarkers derived from neuroimaging techniques [19, 20]. However, it is noteworthy that most of these biomarkers have not yet been proven sufficiently reliable and valid, necessitating further investigation and validation efforts [4]. Current perspectives within the field are striving to delineate specific biotypes for major diagnostic categories, where a convergence of multiple biomarkers could represent a condition-specific "biosignature". Biosignatures represent unique patterns of biological markers that provide valuable insights into the underlying mechanisms and pathophysiology of mental disorders so that a more refined and personalized approach to psychiatric diagnosis and treatment can be pursued. Biomarkers encompass a range of molecular and genetic factors, as well as neuroimaging data, cognitive assessments, and clinical variables. Moreover, biosignatures have the potential to inform prognosis, treatment response prediction, and the development of novel therapeutic interventions [2, 21]. Among the available tools, omics methods, including lipidomics, are particularly important for understanding neurometabolic mechanisms [7].

Over time, metabolomic screening has expanded our understanding of disease dynamics, revealing that metabolite levels are influenced by both genomic (unmodifiable) and environmental (modifiable) factors [22, 23]. The CNS is recognized as the second lipid-rich region within the human body. Lipids are integral to CNS functions, including bioenergetics, membrane integrity, intracellular signaling, synaptic plasticity,

and neurotransmission [24]. They also play a role in energy storage and in regulating pathways critical for neuronal communication [25]. Thus, the diverse functions of lipids in the CNS underscore their significance in supporting the intricate operations of the human brain and nervous system [26]. Therefore, emerging evidence suggests that disturbances in lipid metabolism and functioning may be implicated in several mental disorders, including major depressive disorder (MDD) [27], schizophrenia (SCZ) [28], anxiety disorders, and post-traumatic stress disorder [29]. Although causal models for the pathophysiology of mental disorders remain elusive, lipid-mediated biological processes, such as neuroinflammation, oxidative stress vulnerability, and endocannabinoid system alterations, have been identified as relevant pathways [29]. Current evidence suggests a role of undetected inborn errors of metabolism correlated with psychiatric manifestations in neurodegenerative metabolic conditions such as the Niemann-Pick disease or Acute-Intermittent Porphyria, even in adult mental illnesses such as SCZ [30]. Dysregulation of bioactive lipid mediators, including eicosanoids, sphingolipids, and lipids targeted by phospholipases and lipoprotein lipase (LPL), may contribute to the neuroinflammatory processes underlying MDD and SCZ, highlighting these mediators as potential targets for antidepressant therapies [22, 31, 32]. Obsessive–compulsive disorder (OCD), on its side, despite the current shortage of evidence, has shown alterations of lipid fractions associated with different clinical profiles and constructs such as impulsivity [33], alexithymia [34], panic/anxiety [35], as well as oxidative stress [36], outlining a trans-nosographic relevance of this biochemical domain. The hypothesis underlying this review is that lipid alterations may serve as biomarkers with clinical significance. Unlike previous studies that focused on specific lipid subgroups, this systematic review synthesizes data across a wide range of lipid categories, aiming to provide a comprehensive overview of lipidomics and lipid-related genes in psychiatric disorders. As far as our knowledge extends, the literature currently lacks systematic reviews that incorporates all the known lipid and lipid-related alterations together. This article encompasses a wide range of lipid categories, unlike previous studies that have primarily focused on specific lipid subgroups [22, 37]. Given the significant impact of mental disorders on individuals and society [38], this review aims to clarify the relationship between lipid metabolism and mental disorders, offering insights into its potential for precision psychiatry applications.

Methods

We searched PubMed®, Scopus and PsycInfo® from inception to the 12th of October 2024, using the following terms and their combination: "lipid*", "genom*", "mental disord*", "psychiatr*", "depress*", "bipola*", "schizophr*", "OCD" and "mood disorder*". The precise search strategy can be found in Supplement 1. Two investigators independently screened the abstracts and, if relevant, the full-text articles according to the following eligibility criteria: (i) studies explicitly focusing on lipidomics, genomics, or both in the context of mental disorders, (ii) being observational or randomized controlled trials (RCTs), (iii) including only the diagnoses MDD, bipolar disorder (BD), SCZ or OCD, established through consensus criteria ICD-10 [39], or DSM-IV [40], or DSM-IV-TR [41], or DSM-5 [42], (iv) being written in English, and (v) having full-text availability. Exclusion criteria were: (i) studies that were not RCTs or observational in nature, such as case reports, case series, narrative reviews, opinion pieces, or editorials, (ii) studies where lipidomics or genomics were not the primary focus or where the connection to mental disorders was tangential or secondary, (iii) studies focused on other mental disorders and (iv) studies investigating populations other than humans (animals, invertebrates, etc.). In addition to reviewing individual articles, the two investigators also examined the references cited within those articles to identify any additional relevant studies. When disagreements arose, the third investigator provided input and helped reach a consensus among the team. All included studies were individually summarized in a table. All screened studies, including reasons for exclusion, are presented in Supplementary Table 1.

Parameters extracted from each study included: first author, year of publication, diagnosis involved, diagnostic assessment, sample size, methodology, principal outcomes, and any genes or lipids identified as having a possible alteration associated with the disease. The certainty of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system [43]. We fully complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and checklist [44] (Supplementary Table 2) and registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42023438862) (Fig. 1).

Results

A total of 27 studies were included, all of which highlighted an association between lipids and mental disorders. In an initial study, the lipid profile of patients

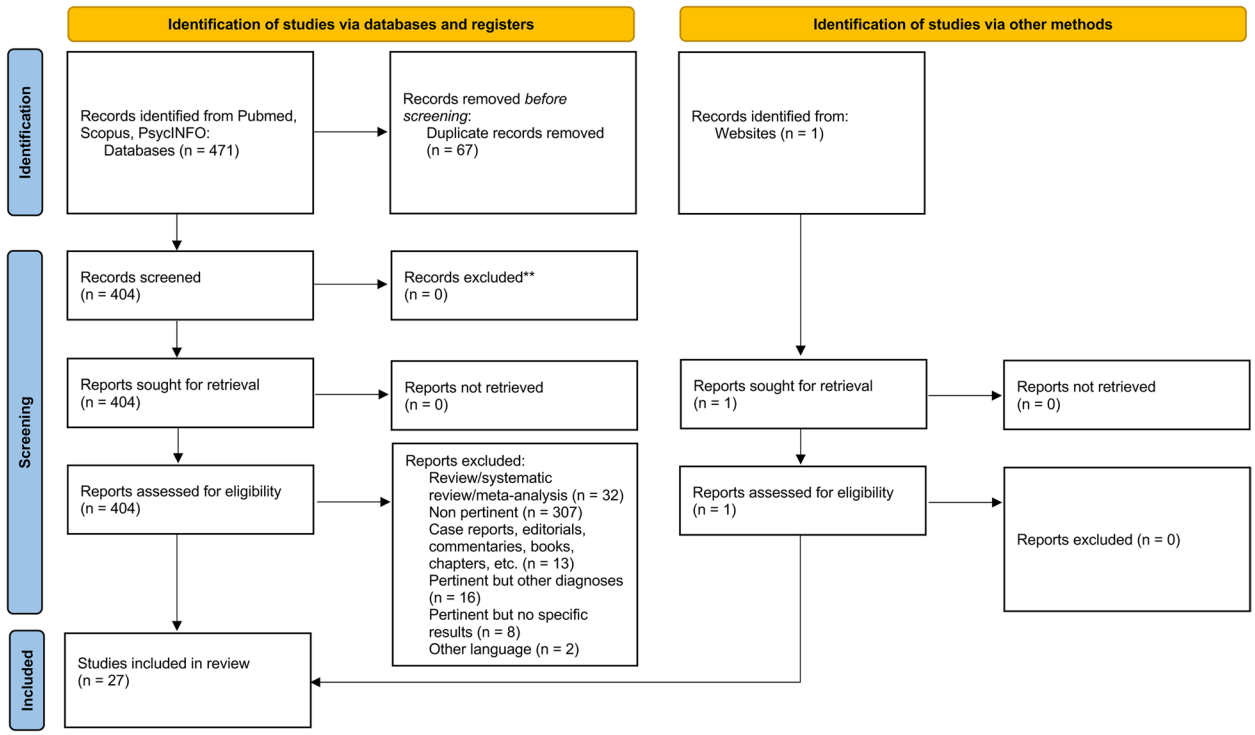

Fig. 1 PRISMA 2020 flow diagram

with SCZ showed quantitative alterations in 77 lipids, including elevated levels of triglycerides (TG), ceramides, phosphatidylcholine, and reduced levels of acylcarnitine and plasmalogen phosphatidylcholine. MDD was associated with alterations in 97 lipids, 30 of which overlapped with SCZ, while BD showed alterations in 47 lipids, 28 of which overlapped with SCZ. Collectively, the three disorders shared common alterations in the levels of 7 lipids [45]. SCZ exhibited specific proteomic alterations, including those related to lipid metabolism, involving apolipoproteins APOC3, APOH, APOB, and six lipid-binding proteins. Additionally, potential metabolic markers of the disease were identified, such as 3OSG, estrone, cholesterol sulfate, 16-a-hydroxypregnenolone, dihydrotestosterone, androstenedione, Vitamin D3, and androsterone sulfate [46]. Additionally, a case–control study observed an association between SCZ and the lipid PC ae C38:6 [47].

Regarding mood disorders, a prospective study on prevalence and incidence rates of late-life depression found reduced high-density lipoproteins (HDL) levels, elevated low-density lipoproteins (LDL) levels, and a U-shaped association between total cholesterol levels and incidence/prevalence of late-life depression. Moreover, the SCL6A4 genotype was identified as a potential mediator of the association between LLD and HDL levels, with the association being significant only in carriers of the S allele [48].

In OCD, peroxisomal metabolism pathways were associated with aggression, sphingolipids with the order dimension, and genetic determinants of lipid metabolism with the hoarding dimension [49].

Other studies identified various gene variants among the lipidomic correlates of mental disorders. The T allele of rs7951870 was associated with elevated plasma Diacylglycerol Kinase Zeta (DGKZ) levels, which were in turn linked to SCZ [50]. Chromosomal rearrangements and translocations of ABCA13 were significantly associated with SCZ, BD, and MDD [51]. The C allele of Rs253 (LPL gene) was significantly associated with SCZ in an observational case–control study [52]. Similar evidence was found for SCZ and autism spectrum disorder (ASD), which correlated with duplications and deletions of genes associated with lipid metabolism [53].

Based on our results, there is substantial evidence from large-scale database analyses and genome-wide association studies.

In MDD, 496 single nucleotide polymorphisms (SNPs) were associated with type II diabetes (T2D) and MDD, with common genes linked to lipid metabolism pathways in both conditions [54]. A causal relationship was also observed between triglyceride levels and depressive symptoms/recurrence of depressive episodes and

suicidality. Conversely, HDL levels showed an inverse association with depressive symptoms [55].

In SCZ, 54 metabolites associated with lipid metabolism, such as acylcarnitine, very-low-density lipoprotein (VLDL), and fatty acids, showed significant associations. Pathways related to LXL/RXR: (liver X receptor/retinoid X receptor) heterodimers, key regulators of steroid metabolism, were found to be upregulated. A post-mortem study of 4 individuals with SCZ versus 4 controls revealed lipid depletion in the dorsolateral prefrontal cortex (dlPFC) of affected patients [56].

Various mental disorders demonstrated significant genetic overlaps with cardiovascular/metabolic phenotypes. For BD, a significant polygenic overlap was identified with traits such as body mass index (BMI), blood pressure, and coronary artery disease, highlighting 129 shared loci related to lipid metabolism, particularly lipoprotein synthesis and metabolism, as well as unsaturated fatty acid biosynthesis [57]. In MDD, a significant polygenic overlap was observed with cardiovascular risk factors and coronary artery disease. Specifically, depression was associated with reduced HDL levels and significant genetic overlap with five cardiovascular risk factors, including T2D, HDL, LDL, total cholesterol (TC), TG, and systolic blood pressure (SBP), with the overlap area located near the FADS2 gene [58]. Moreover, moderate positive genetic correlations were identified between SCZ and plasma lipids such as HDL, TG, LDL, and TC, totaling 945 lipid-related shared loci [59].

Regarding SCZ, a large-scale study found reduced risks of SCZ associated with long-chain omega-3 and omega-6 fatty acids, revealing a key role in desaturation processes linked to the expression of genes in the FADS cluster [60]. In a Mendelian randomization model, HDL and TG levels were associated with SCZ in both East Asian and European populations [61]. Consistently, SCZ, cardiometabolic phenotypes, and inflammation-related traits shared various gene variants, with 10 colocalized SNPs, the strongest association being with SNPs in the brain-derived neurotrophic factor – coding gene (BDNF-coding gene) [62].

Among mood disorders, MDD was characterized by a metabolic signature involving 124 lipids, all related to cellular metabolism, with a significant association with an intestinal dysbiosis profile. Depression was associated with elevated levels of VLDL, HDL-contained TG, IDL, and reduced levels of HDL, omega-6, polyunsaturated fatty acids, apoA1, sphingomyelin, and linoleic acid [63]. MDD was linked to elevated levels of 53 metabolites, including carbohydrates, cofactors, lipid-soluble vitamins, and xenobiotics [64]. A Mendelian randomization study conducted on individuals with various mental disorders highlighted a high risk of MDD associated with hypertriglyceridemia, while HDL cholesterol levels showed an inverse relationship [65]. T2D patients showed a 6% higher risk of MDD, with a causal relationship between T2D and MDD mediated significantly by LDL and TG levels [66]. Complementarily, another study demonstrated that total omega-3 levels could reduce the risk of MDD, with a particularly significant effect for eicosapentaenoic acid. The SNP rs174564 in the FADS cluster gene was identified as a key driver of this effect [67].

In BD, reduced arachidonic acid levels were associated with a higher risk of BD, with a possible impact on lithium response. The FADS rs174592 G allele was associated with increased BD risk and reduced arachidonic acid levels [68]. In another multivariate Mendelian randomization model, hexanoylcarnitine levels were associated with BD [69].

A recent large-scale study identified various lipids associated with different mental disorders, particularly reduced N-acetylornithine in BD and SCZ, reduced docosahexaenoic acid in MDD, increased 3-hydroxybutyrate in depression, increased butyrylcarnitine in SCZ, and reduced 1-arachidonoylglycerophosphocholine in BD. All mediators except N-acetylornithine and 3-hydroxybutyrate were also associated with other non-psychiatric disorders [70]. Finally, among cross-disorder genetic variants emerging from large-scale studies, the rs12721109 polymorphism in the APOC4 gene was found to be shared between cardiovascular diseases and mental disorders such as MDD, PTSD, and SCZ [71].

The main results are summarized in Tables 1 and 2.

Quality assessment tool and risk of bias

All studies addressed an appropriate and focused question. Nevertheless, in case–control studies, the two groups being analyzed were selected from source populations comparable in all respects other than the factor under investigation. The authors formulated a clear research question, supported by pertinent literature in the introduction. Comprehensive and suitable methods, including statistical analyses, were detailed. Conclusions directly addressed the research question. Sample size calculations aligned appropriately with the study design. Limitations pertaining to the study outcomes were thoroughly discussed. The results of individual studies were consistent and mathematically accurate. Even when differences were present, they were not statistically significant. The outcomes are clearly defined in every study, the method of assessment of diagnosis is very reliable in each case, and all psychiatric diagnoses are established through criteria established worldwide. In addition, according to the GRADE system of rating in systematic reviews (Table 3) [43], all included studies

Table 1 Main results of the included studies

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Knight et al., 2009 [51]	FISH analysis and DNA resequencing	DSM-IV, SADS-L	*Discovery Cohort:* Cases:100 Controls: 100 *Test Cohort:* SCZ:1019 BD: 680 MDD: 365 HCs: 2270	Discovery of a chromosomal rearrangement and translocation affecting the ABCA13 gene: rare variants in this gene are significantly associated with SCZ, BD, and show a trend of association with MDD. In a study focused on 21 families of mutation carriers, ABCA13 showed an association with MDD as well	H3609P T4031A R4728X S3704R R4590W
Kim et al., 2011 [48]	Prospective study	GMS diagnostic schedule (GMS B3)	LLD: 521	Associations between lipid traits and prevalent/incident LLD In both depressions 5-HTTLPR modifies the association, whereas HDLc low levels are associated with LLD only in when there is the S-allele TC levels were associated with LLD (but not influenced by 5-HTTLPR genotype	*Prevalent late-life depression* ↓HDL ↑LDL ↑LDL/HDLc ratio TC (U-shaped association) *Incident late-life depression* ↓HDL TC (U-shaped association)
Xie et al., 2011 [52]	RT-PCR	DSM-IV-TR	SCZ: 319 HCs: 575	Significant association between LPL rs253 SNPs and SCZ	rs253 C allele
He et al., 2012 [47]	FIA-MS/MS, bioinformatic approach	DSM-IV, ICD-10	SCZ: 265 HCs: 216	Metabolic deviations detected in SCZ: 4 amino acids and 1 lipid (immune-related signaling and neurotrophin signaling)	PC ae C38:6
Ji et al., 2016 [54]	meta-GWAS statistical analysis	DSM-IV [35]	DIAGRAM and Psychiatric Genomics Consortium studies MDD: 6783 HCs: 50 695	496 SNPs were associated with both T2D and MDD	Enrichment of the lipid metabolism pathways associated with both T2D and MDD
Kushima et al., 2018 [53]	aCGH	DSM-5	ASD: 1132 SCZ: 2519 HCs: 2110	–12 new CNVs loci potentially associated with ASD/SCZ have been identified, including PCSK6 - 11 ASD-associated and 10 SCZ-associated gene sets are involved in lipid metabolism -a genetic overlap between the two conditions was highlighted	*Duplications:* GDPD3, CDIPT, FAM57B *Deletions:* ACACA PIGW TADA2A PIGX PIGZ PCYT1A ZDHHC8 ZDHHC19

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Alinaghi et al., 2019 [50]	qPCR, tetra-ARMS PCR	DSM-5	SCZ: 50 HCs: 50	↑ DGKZ blood expression in SCZ	rs7951870-TT (eQTLS) was associated with higher DGKZ blood expression in SCZ (rs7851870 is significantly associated with an increased expression of several genes, also including LDL receptor related protein-4)
Alemany-Navarro et al., 2020 [49]	SNP-level association analyses, Gene-based association analyses and logistic regressions	*Diagnosis:* DSM-IV *Assessment:* Y-BOCS, DY-BOCS	OCD: 399	Different metabolic dimension-related pathways identified	Peroxisomal lipid metabolism (*aggressive dimension*), sphingolipid signaling pathway (*order dimension*) and of lipid, vitamins and carbohydrate metabolism (*hoarding dimension*)
Maas et al., 2020 [56]	Post-mortem RNA sequencing, GWAS, structural MRI combined with cognitive behavioral data	DSM-IV	*Post-mortem RNA sequencing:* SCZ: 4 HCs: 4 Large scale GWAS dataset *MRI*: SCZ: 50 HCs: 125	-LXR/RXR (cholesterol homeostasis) activation" in SCZ patients -lower lipid content of dlPFC in SCZ patient was associated with efficiency in dlPFC-dependent tasks	54 metabolites related to lipid metabolism (acylcarnitines, VLDL and FA)
Jones et al., 2021 [60]	MR based on GWAS datasets	DSM-IV, ICD-10, DSM-5	Dataset from the Schizophrenia Working Group of the PGC SCZ: 100 410 HCs: 236 642	Protective effects of long-chain omega 3 and long-chain omega-6 fatty acids on SCZ	SNPs in the FADS cluster gene (desaturation steps) Long-chain omega-3 and long-chain omega-6 fatty acid concentrations were associated with a lower risk of SCZ
Rødevand et al., 2021 [57]	MiXerR, cond/conjFDR on GWAS datasets	DSM-IV	Large scale GWAS dataset BD: 20 352 HCs: 31 358	*MiXeR*: polygenic overlap between BD and BMI, SBP, DBP and CAD *FDR*: 129 shared loci between BD and BMI (n = 69), SP (n = 53), DP (n = 53) These loci were related to neurodevelopement, lipid metabolism, chromatin assembly/disassembly and intracellular processes	Shared loci: - lipid biosynthetic processes, - unsaturated fatty acid biosynthesis, - chylomicrons -lipoproteins

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
So et al., 2021 [55]	MR analysis on large-scale GWAS dataset		Large scale GWAS dataset MDD: 195 309 HCs: 458 055	-TG increase causally related to: depressive symptoms, self-reported DSH/suicide, MDD, number of low-mood episodes -HDL-c causally associated with MDD and inverse causal association with depressive symptoms	TG, HDL-c
Aoki et al., 2022 [61]	MR	N/A	PGC	Significant genetic correlation between SCZ and metabolic syndrome traits were found. No causal relationship was found at MR analysis The direction of the association was consistent in East Asian and European subsamples	HDLc TG
Perry et al., 2022 [62]	LDSR based on GWAS datasets	DSM-IV, ICD-10, DSM-5	SCZ 40,675 HCs: 64,643	Shared genes between SCZ, cardiometabolic and inflammation-related traits	10 colocalized SNPs (involved in neurologic/cardiometabolic functioning) Strongest evidence of colocalization involves BDNF SNPs
Torgersen et al., 2022 [58]	MiXerR, cond/conjFDR on GWAS datasets	DSM-IV, ICD-10, DSM-5	Large scale GWAS dataset MDD: 121 198 HCs: 329 421	Shared genetic architecture identified between depression and CAD and CVD risk factors, most strongly with BMI and BP	*MiXeR* Polygenic overlap between MDD and BMI, SBP, and DBP *CondFDR* MDD-related loci conditional on TC, TG, T2D, LDL, HDL, CRP and vice versa *ConjFDR* Depression, CAD and 5 CVD risk factors (T2D, HDL, LDL, TC, TG and SBP) were associated with largely overlapping regions on Chr 11. FADS2 was the nearest gene for all the lead SNPs Depression in this study is associated with lower levels of HDL

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Amin et al., 2023 [63]	MR, 1H-NMR (metabolite profiling), Metabolome-Wide association Analysis	ICD-10	Large scale GWAS dataset MDD: 59 851 HCs: 113 154	A Metabolic signature of 124 was significantly associated with MDD, all belonging to the energy and lipid metabolism pathways The metabolic shift characterizing MDD was consistent with the gut dysbiosis, bacteria associated with healthy lipid profile (↑HDL, ↓VLDL) were decreased in MDD	*Mendelian Randomization*: changes in lipids appear to be associated with MDD-related genes ↑ 27 VLDL particles ↓ 18 HDL particles ↑ triglyceride content in HDL ↓5 IDL particles ↑ triglyceride content in IDL ↑ Total MUFA and MUFA/total FA ↓ linoleic acid ↓ omega-6 FA ↓PUFA/total fatty acid ↓ apoA1, ↓ sphingomyelins
Huang et al., 2023 [66]	MR	Self-reported clinical assessment	Different GWAS dataset MDD: 12,588 HCs: 85,914 T2D: 36,614 HCs: 155,150	Genetically predicted T2D was significantly associated with MDD, not vice versa	T2D patients show a 6% elevated risk of MDD The causal relation between T2D and MDD is significantly mediated by LDL-c and TG
Jia et al., 2023 [70]	MR	N/A	GWAS Datasets	5 established and three novel metabolites were associated with mental disorder. 6 out of 8 metabolites were lipids, with 3-Hydroxybutyrate, N-acetylornithine, and butyrylcarnitine having no adverse side effects in a model designed to assess metabolite-targeted interventions All mediators, except for N-acetylornithine and 3-Hydroxybutyrate, have additional associations with other non-psychiatric disorders	N-acetylornithine: ↓ BD, SCZ docosahexaenoic acid: ↓ MDD 3-Hydroxybutyrate: ↑MDD Butyrylcarnitine: ↑ SCZ 1-arachidonoylglycerophosphocholine: ↓ BD Sphingomyelins: ↑ AN

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Kopylov et al., 2023 [46]	quantitative proteomic and metabolomic assay, high throughput genotyping (GWAS)	DSM-IV, ICD-10, DSM-5	SCZ: 77 HCs: 61	Three omics layers (metabolomic, genomic and proteomic) were integrated highlighting strict implication of lipid transports, oxidative stress, imbalance in steroidogenesis and associated impartments of thyroid hormones in the production of a SCZ specific pattern	*Proteomic analysis* APOC3, APOH, APOB *PPI assessment* enzyme regulatory activity including inhibitory activity (n = 9 proteins), heparin binding (n = 4 proteins) and steroid and lipids binding (n = 6 proteins). Among the other pathways identified regulation, assembly, remodeling, and clearance of LDL and VLDL particles was present in SCZ *Metabolomic markers:* 3OSG, estrone, cholesterol sulfate, 16-a-hydroxypregnenolone, dihydrotestosterone, androstenedione, Vitamin D3, androsterone sulfate
Li et al., 2023 [65]	MR	N/A	PGC and Alzheimer Disease Genetics Consortium (ADGC)	Univariable and Multivariable MR showed significant associations between lipid traits and different mental disorders There is a significant relationship among genetically anticipated MDD and hyperTG risk	*Univariable MR* HDL-c: ↓ risk AD, PTSD LDL-c: ↓ risk MDD, increased risk of AD TG: ↑ MDD, AD, and ↓ panic disorder TC: ↓ PTSD Multivariable MR HDL-c ↓ risk of PTSD, AD TG ↑ risk of MDD, ↓panic disorder HDL-c ↓ risk for MDD
Rødevand et. al., 2023 [59]	MiXerR, cond/conjFDR on recent GWAS datasets	N/A	PGC – SCZ dataset SCZ: 53,386 HCs: 77,258	MiXerR analysis estimated moderate positive genetic correlations within the shared components of SCZ and blood lipid levels (HDL, TG, LDL, and TC). A total of 945 lipid-related shared loci between SCZ and cardiovascular disease (CVD) were identified (conjFDR < 0.05)	Several shared lipid-related loci were identified between CVD phenotypes and SCZ, particularly in relation to blood lipid levels: HDL (n = 304), TG (n = 307), LDL (n = 158), and TC (n = 176)

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Tkachev et al., 2023 [45]	LC–MS	*Diagnosis:* DSM-IV, ICD-10 *Assessment:* PANSS	Cases: 980 HCs: 572 SCZ, MDD, BD	–77 lipids were found to be significantly altered in SCZ -Lipidome alterations in BD (n = 184) and MDD (n = 256) were similar in SCZ	*SCZ* ↑Cer, ↑TG and ↑PC, ↓CAR and ↓PC-P *MDD* 30 lipids out of 97 overlapping with SCZ *BD* 28 lipids out of 47 overlapping with SCZ 7 lipids overlapping between all 3 disorders
van der Spek et al., 2023 [64]	LC–MS and MR	Various quantitative methods for assessing depressive symptoms	6 cohort studies were included Metabolome-wide association analysis conducted in a cohort of 13,596 individuals	MDD is associated with elevated levels of 53 metabolites, including amino acids, carbohydrates, cofactors, vitamins, lipids, and xenobiotics *These metabolites are either directly derived from food or are products of host and gut microbial metabolism of food-derived compounds*	After adjustment for antidepressant use: 2-aminooctanoate, 10-undecenoate (11:1n1), 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1),1-linoleoyl-GPA (18:2) Higher levels of 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1) and retinol were associated with an increased risk of depression, while for the other lipids were associated with a decreased risk After adjustment for other medication use, including lipid-lowering medication, antihypertensive medication, antidiabetic medication, BMI and current smoking:10-undecenoate (11:1n1) (undecylenic acid),1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1) (Lecithin),1-linoleoyl-GPA (18:2) (lysophosphatidic acid)
Carnegie et al., 2024 [67]	MR	N/A	Different GWAS datasets Outcome samples MDD: 116,209 HCs: 314,566 rMDD:17,451 HCs: 62,482	Omega-3 FA, in particular eicosapentaenoic acid, may play a role in the etiology of depression	Multivariable MR total omega-3 FA: ↓ odds of MDD The largest points estimates were observed for eicosapentaenoic acid FADS gene cluster (rs174564) has been highlighted as a key driver of this effect

Table 1 (continued)

Authors	*Methods*	*Clinical Assessment*	*Sample and Diagnosis*	*Principal outcomes*	*Genes/Variants and/or Lipids*
Chen et al., 2024 [71]	LDSC analysis FUMA analysis	N/A	PGC	Neuropsychiatric disorders show extensive genetic overlap with cardiovascular disorders. This association was particularly relevant for ADHD, MDD and PTSD	Among the shared independent significant SNPs: APOC4 gene (rs12721109)
Freuer & Meisinger, 2024 [69]	Multivariable MR	N/A	Outcome sample from the PGC/iPSYCH/FinnGen datasets	Genetically predicted levels of 6 metabolites were associated with ADHD, BD, anorexia nervosa, MDD, PTSD and SCZ	Butyrilcarnitine—PTSD Hexanoylcarnitine -PTSD, BD
Stacey et al., 2024 [68]	MS and MR analysis	N/A	PGC outcome sample BD: 41,917	33 metabolites were associated with BD Taken together, these findings suggest that the conversion of LA into ARA by the FADS1/2/3 cluster genes may play a key role in BPD etiology	↓ ARA = ↑ BD risk The effect was observed in both ARA free form and as side chain of 11 different complex lipids Metabolites such as ARA might be associated with better response to lithium G allele of rs174592 (FADS 1/2/3 cluster) is associated with higher risk of BD and lower levels of plasma ARA

Abbreviations: 1H-NMR protonic nuclear magnetic resonance, *3OSG* 3-O sulfogalactosylceramide, *aCGH* microarray-based comparative genomic hybridization, *ADHD* Attention-deficit/hyperactivity disorder, ARA arachidonic acid, *ASD* autism spectrum disorder, *BD* bipolar disorder, *BDNF* brain-derived neurotrophic factor, *BMI* body mass index, *BP* blood pressure, *CAD* coronary artery disease, *CAR* acylcarnitine, *Cer* ceramide, *Chr* chromosome, *CNVs* copy number variations, *cond/conjFDR* conjunctional false discovery rate, *CRP* C-reactive protein, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *DGKZ* diacylglycerol kinase, *DSH* deliberate self-harm, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *eQTLS* expression quantitative trait loci, *FA* fatty acids, *FADS* Fatty acid desaturase, *FIA-MS/MS* flow injection analysis–tandem mass spectrometry, *GWAS* genome-wide association study, *HCs* healthy controls, *HDL* high-density lipoprotein, *ICD* International Classification of Diseases, *LC–MS* liquid chromatography coupled with untargeted mass spectrometry, *LDL* low-density lipoprotein, *LDSR* linkage disequilibrium score regression, *LPL* lipoprotein lipase, *LXR/RXR* liver X receptor/retinoid X receptor, *MDD* major depressive disorder, *MiXerR* bivariate causal mixture model, *MR* mendelian randomization, *MRI* magnetic resonance imaging, *MS* mass-spectrometry, *MUFA* monounsaturated fatty acids, *OCD* obsessive–compulsive disorder, *PC* phosphatidylcholine, *PGC* psychiatric genomics consortium, *PCP* phosphatidylcholine plasmalogen, *PCSK6* proprotein convertase subtilisin/kexin type 6, *PPI* protein–protein interaction, *PTSD* post-traumatic stress disorder, *PUFA* polyunsaturated fatty acids, *qPCR* quantitative polymerase chain reaction, rMDD recurrent major depressive disorder, *SADS-L* Schedule for Affective Disorders and Schizophrenia – lifetime version, *SBP* systolic blood pressure, *SCZ* schizophrenia, *SNPs* single nucleotide polymorphism, *T2D* type 2 diabetes, *TG* triglycerides, *TC* total cholesterol, *tetra-ARMS PCR* tetra-primer amplification refractory mutation system-polymerase chain reaction, *VLDL* very-low-density lipoprotein, *Y-BOCS* Yale Brown Obsessive–Compulsive Scale, *DY-BOCS* Dimensional Yale-Brown Obsessive–Compulsive Scale

show consistent findings with no publication bias, no severe limitations, and no severe indirectness. Despite the potentially very high quality of evidence of the studies included, the GRADE system requires all non-RCT studies to have a baseline rating of "low". Nevertheless, the certainty of evidence was kept on "low" based on specific factors, including the robustness of statistical methodologies, the presence of consistent and reproducible findings, and the use of large-scale datasets in genetic studies, which strengthened the confidence in the observed associations. These adjustments align with GRADE principles, allowing greater confidence in evidence when indirectness or imprecision is mitigated by methodological rigor and biological plausibility of results. In addition, the three authors who independently performed the GRADE followed it according to its original guidelines. Possibly, this may have led to an underestimation of the quality of the studies included. RCTs are costly and time-consuming, thus employing alternative methods to enhance causal inference from observational data could aid in assessing whether such trials might be potentially justified. These observations underline the need for a more specific tool in this sense. We assessed the quality of the GWAS studies we included with the quality of genetic studies (Q-Genie) tool [72], which indicated a moderate quality for each study, corresponding the low quality of the evidence according to the GRADE assessment. Ultimately, considering all the included studies, their appropriateness of diagnosis as well as appropriate control of confounding, and other aspects of design, conduct, and analysis that influence the risk of bias, we can conclude that the quality of evidence is low according to the GRADE, but potentially higher considering that GWASs have important translational consequences in clinical terms, and considering the lack of a specific tool for assessing quality of evidence in systematic reviews concerning GWASs and genetic studies.

Discussion

Despite the heterogeneity of the results, the findings are promising and hold significant potential. This review encompasses current literature, offering a comprehensive analysis of cutting-edge research. Of the 27 articles included, 10 studies [45–48, 55, 56, 60, 63, 64, 68] provided lipid measurements, while the remaining focused on lipid metabolism-related genes. The evidence is synthesized with a focus on each specific mental disorder.

Major depressive disorder

As far as MDD is concerned, many authors have found genetic overlaps between this mental disorder and common many authors have found genetic overlaps between this disorder and common metabolic conditions. ABCA13 has been associated with MDD, highlighting the potential role of lipid transmembrane transport in its pathophysiology [51]. Shared genetic architecture has also been identified between MDD, coronary artery disease (CAD), and cardiovascular disease (CVD) risk factors, particularly with BMI and blood pressure [58]. Variants linked with increased risk for depression were also associated with increased risk of CAD, and higher TG, LDL and C-reactive protein (CRP) levels, while there was an opposite or mixed pattern of effect direction for other traits. Moreover, depression was associated with lower levels of HDL, and TG increase is causally related to depressive symptoms and self-reported deliberate self-harm, or suicide [55]. A significant relationship between depression and the risk of hypertriglyceridemia has also been confirmed by Li et al., highlighting the role of genetic determinants of HDL, LDL, and TG levels in a Mendelian randomization model [65]. Late-life depression has shown associations with reduced HDL, elevated LDL, and a U-shaped relationship with total cholesterol [48]. As highlighted by Chen and colleagues, among the shared genetic variants between cardiovascular disorders and neuropsychiatric conditions, the APOC4 rs12721109 is particularly relevant for major depression, ADHD, and PTSD [71]. These findings align with the growing interest in lipid metabolism within the study of mood disorders. A GWAS meta-analysis identified 496 SNPs shared between T2D and MDD, supporting overlapping genetic susceptibility [54]. Huang et al. (2023) further expanded this evidence by demonstrating that patients with T2D have a 6% increased risk of developing depression. [66]. This cause-effect relationship can be mediated by LDL and triglyceride levels, according to the Mendelian randomization model developed by the authors [66]. Collectively, these findings suggest shared genetic and metabolic pathways between MDD and systemic diseases. In some cases, different medical conditions could potentially feed off each other [73, 74], or create a vicious multisystemic circle. Moreover, both cardiovascular risk factors [75] and MDD [76] seem to be influenced by inflammation and the immune system, these findings encourage further exploration of these relations under the lens of lipidomics [77]. Focusing on lipid levels, animal studies conducted on mice (LDL receptor gene knock-out) consistently outlined a link between hypercholesterolemia, depressive-like behavior [78, 79], and LDL-dependent monoamine oxidase (MAO)-A and MAO-B-activity-increase in the hippocampal region [79]. A lipidomic-based approach may extend beyond MDD to other disorders, such as SCZ, as lipid profiles often overlap across conditions [62]. Notably, a Mendelian randomization study demonstrated that cardiometabolic traits genetically predict inflammation-related insulin resistance, with HDL and TG levels

Table 2 Summary of pathways/gene sets, genes and lipids related to MDD, BD, SCZ, and OCD

Disorder	*Pathways/Gene Sets*	*Genes/SNPs*	*Lipids*
Major Depressive Disorder	tricarboxylic acid cycle/energy metabolism	FADS2 rs174564 rs12721109 (APOC4 gene)	TG, HDL, LDL, TC, VLDL, IDL, ↑MUFA, ↓PUFA and ↓ omega-6 FA, omega-3 FA, ↓ APOA, ↓sphingomyelins, 2-aminooctanoate, 10-undecenoate (11:1n1), 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1),1-linoleoyl-GPA (18:2), docosahexaenoic acid, 3-Hydroxybutyrate
Bipolar Disorder	lipids biosynthetic process, unsaturated FA biosynthesis, chylomicrons and triglyceride-rich lipoprotein particles, protein-lipid complexes, omega-3 FA	ABCA13 rs174592-G (FADS cluster gene)	Arachidonic Acid, Hexanoylcarnitine, N-acetylornithine, 1-arachidonoylglycerophosphocholine
Schizophrenia	LDL and VLDL, LXR/RXR, glycerolipids, phospholipids, glycerophospholipids, FA, cardiometabolic and inflammation-related traits	ABCA13, LPL (rs253-CC), FADS cluster gene, APOC3, APOH, APOB, DGKZ (rs7851870-TT)	VLDL, HDL, TG, LDL, TC, FA, short-chain PUFA, ↑Cer, ↑PC, ↑TG, ↓ CAR and ↓ PC-P, PC ae C38:6, 3OSG, estrone, cholesterol sulfate, 16A OH-Preg, DHT, A4, Vitamin D3, androsterone sulfate, N-acetylornithine, Butyrylcarnitine
Obsessive–Compulsive Disorder	Peroxisomal lipids, sphingolipids, lipophilic vitamins		

Abbreviations: ↑ increased blood levels, ↓ decreased blood levels, *16A OH-Preg* 16-alpha-hydroxypregnenolone, *3OSG* 3-O-sulfogalactosylceramide, *A4* androstenedione, *ABCA13* ATP binding cassette subfamily A Member 13, *APOA1* apolipoprotein A1, *APOB* apolipoprotein B, *APOC3* apolipoprotein C3, *APOH* apolipoprotein H, *CAR* acylcarnitine, *Cer* ceramides, *DGKZ* diacylglycerol kinase zeta, *DHT* dihydrotestosterone, *FA fatty acids, FADS* fatty acid desaturase, *FADS2* Fatty Acid Desaturase 2, *HDL* high-density lipoprotein, *IDL* intermediate-density lipoprotein, *LDL* low-density lipoprotein, *MUFA* monounsaturated fatty acids, *PC-P* phosphatidylcholine plasmalogen, *PC* phosphatidylcholine, *PUFA* polyunsaturated fatty acids, *TC* total cholesterol, TG triglycerides, *VLDL* very low-density lipoproteins

Table 3 Grade certainty of evidence of included studies

Study	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Knight et al., 2009 [51]	Discovery of a chromosomal rearrangement and translocation affecting the ABCA13 gene: rare variants in this gene are significantly associated with SCZ, BD, and show a trend of association with MDD. In a study focused on 21 families of mutation carriers, ABCA13 showed an association with MDD as well	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Kim et al., 2011 [48]	Associations between lipid traits and prevalent/incident LLD In both depressions 5-HTTLPR modifies the association, whereas HDLc low levels are associated with LLD only in when there is the S-allele TC levels were associated with LLD (but not influenced by 5-HTTLPR genotype	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Xie et al., 2011 [52]	Significant association between LPL rs253 SNPs and SCZ	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
He et al., 2012 [47]	Metabolic deviations detected in SCZ: 4 amino acids and 1 lipid (immune-related signaling and neurotrophin signaling)	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Ji et al., 2016 [54]	496 SNPs were associated with both T2D and MDD	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Kushima et al., 2018 [53]	–12 new CNVs loci potentially associated with ASD/SCZ have been identified, including PCSK6 - 11 ASD-associated and 10 SCZ-associated gene sets are involved in lipid metabolism -a genetic overlap between the two conditions was highlighted	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Alinaghi et al., 2019 [50]	↑ DGKZ blood expression in SCZ	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Alemany-Navarro et al., 2020 [49]	Different metabolic dimension-related pathways identified	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW

Table 3 (continued)

Study	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Maas et al., 2020 [56]	-LXR/RXR (cholesterol homeostasis) activation" in SCZ patients -lower lipid content of dlPFC in SCZ patient was associated with efficiency in dlPFC- dependent tasks	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Jones et al., 2021 [60]	Protective effects of long-chain omega 3 and long-chain omega-6 fatty acids on SCZ	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Rødevand et al., 2021 [57]	MiXeR: polygenic overlap between BD and BMI, SBP, DBP and CAD FDR: 129 shared loci between BD and BMI (n = 69), SP (n = 53), DP (n = 53) These loci were related to neurodevelopement, lipid metabolism, chromatin assembly/disassembly and intracellular processes	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
So et al., 2021 [55]	-TG increase causally related to: depressive symptoms, self-reported DSH/suicide, MDD, number of low-mood episodes -HDL-c causally associated with MDD and inverse causal association with depressive symptoms	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Aoki et al., 2022 [61]	Significant genetic correlation between SCZ and metabolic syndrome traits were found. No causal relationship was found at MR analysis The direction of the association was consistent in East Asian and European subsamples	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Perry et al., 2022 [62]	Shared genes between SCZ, cardiometabolic and inflammation-related traits	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Torgersen et al., 2022 [58]	Shared genetic architecture identified between depression and CAD and CVD risk factors, most strongly with BMI and BP	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW

Table 3 (continued)

Study	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Amin et al., 2023 [63]	A Metabolic signature of 124 was significantly associated with MDD, all belonging to the energy and lipid metabolism pathways The metabolic shift characterizing MDD was consistent with the gut dysbiosis, bacteria associated with healthy lipid profile (↑HDL, ↓VLDL) were decreased in MDD	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Huang et al., 2023 [66]	Genetically predicted T2D was significantly associated with MDD, not vice versa	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Jia et al., 2023 [70]	5 established and three novel metabolites were associated with mental disorder. 6 out of 8 metabolites were lipids, with 3-Hydroxybutyrate, N-acetylornithine, and butyrylcarnitine having no adverse side effects in a model designed to assess metabolite-targeted interventions All mediators, except for N-acetylornithine and 3-Hydroxybutyrate, have additional associations with other non-psychiatric disorders	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Kopylov et al., 2023 [46]	Three omics layers (metabolomic, genomic and proteomic) were integrated highlighting strict implication of lipid transports, oxidative stress, imbalance in steroidogenesis and associated impartments of thyroid hormones in the production of a SCZ specific pattern	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Li et al., 2023 [65]	Univariable and Multivariable MR showed significant associations between lipid traits and different mental disorders There is a significant relationship among genetically anticipated MDD and hyperTG risk	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW

Table 3 (continued)

Study	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Rødevand et. al., 2023 [59]	MiXerR analysis estimated moderate positive genetic correlations within the shared components of SCZ and blood lipid levels (HDL, TG, LDL, and TC). A total of 945 lipid-related shared loci between SCZ and cardiovascular disease (CVD) were identified (conjFDR < 0.05)	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Tkachev et al., 2023 [45]	–77 lipids were found to be significantly altered in SCZ -Lipidome alterations in BD (n = 184) and MDD (n = 256) were similar in SCZ	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
van der Spek et al., 2023 [64]	MDD is associated with elevated levels of 53 metabolites, including amino acids, carbohydrates, cofactors, vitamins, lipids, and xenobiotics These metabolites are either directly derived from food or are products of host and gut microbial metabolism of food-derived compounds	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Carnegie et al., 2024 [67]	Omega-3 FA, in particular eicosapentaenoic acid, may play a role in the etiology of depression	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Chen et al., 2024 [71]	Neuropsychiatric disorders show extensive genetic overlap with cardiovascular disorders. This association was particularly relevant for ADHD, MDD and PTSD	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Freuer & Meisinger, 2024 [69]	Genetically predicted levels of 6 metabolites were associated with ADHD, BD, anorexia nervosa, MDD, PTSD and SCZ	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW
Stacey et al., 2024 [68]	33 metabolites were associated with BD Taken together, these findings suggest that the conversion of LA into ARA by the FADS1/2/3 cluster genes may play a key role in BPD etiology	Non-RCT	No serious risk of bias	Not at all	Not serious	Not at all	⊕⊕◯◯ LOW

being associated with SCZ. This association appears to be mediated by inflammation, further underscoring the multifactorial etiology of this disorder [80].

Adopting a metabolomics perspective, various lipid metabolites, including lecithin and lysophosphatidic acid, have shown significant associations with MDD, suggesting potential metabolic markers for depression [64]. Carnegie et al. highlighted a protective role of omega-3 fatty acids, particularly eicosapentaenoic acid, which may primarily be mediated by genetic variations in FADS cluster genes, such as rs174564, a key member of the desaturase family [67]. Recent studies also identified docosahexaenoic acid as protective and 3-hydroxybutyrate as a risk factor for depression [70]. Docosahexaenoic acid, in terms of plasma levels, has already been associated with several polymorphisms in the FADS genes [81], supporting a potential link between the findings of various studies where polymorphisms and lipid levels have been separately correlated with major depression.

Tkachev et al. found 97 lipids linked to MDD through LC–MS, with overlap observed in lipids associated with SCZ and BD [45]. While a specific biosignature for each condition may exist, the complexity of underlying genetic pathways makes it difficult to identify. As biological profiling advances, the relationship between diagnoses and underlying biology may become more complex to predict. Pursuing a similar purpose, Amin et. al identified a metabolic signature of 124 lipids significantly associated with MDD, all belonging to the energy and lipid metabolism pathways [63]. Profiles remained similar both when excluding those with antidepressant use instead of adjusting for antidepressants, and between lifetime and recurrent MDD. On the one hand, these findings show how lipidomics may extend our current comprehension of MDD; on the other they raise the possibility of identifying a lipidic biosignature in MDD, independently from treatment and the number of episodes lifetime.

Bipolar disorder

Knight and Pickard have emphasized the association between ABCA13 variants and BD, highlighting its role in lipid transmembrane transport and neurometabolic implications [51]. Interestingly, in a mouse model, ABCA13 has been found to mediate synaptic vesicle transport in cortical neurons [82], suggesting possible specific neurometabolic implications for the variants of this gene. The FADS cluster gene has also been implicated, with arachidonic acid levels linked to BD risk and lithium response [68].

Considering metabolites, levels of hexanoylcarnitine have been associated with the diagnosis of BD [69], while N-acetylornithine and 1-arachidonoylglycerophosphocholine appear to reduce the risk [70]. Overlap in lipid profiles between BD and SCZ suggests shared pathways, with 28 lipids common to both disorders and 7 shared across BD, MDD, and SCZ [45]. In addition, these authors found 7 lipids overlapping between BD, MDD and SCZ corroborating the possible implication that some of the underlying mechanisms may transcend the diagnostic categories.

The overlap in lipid profiles between BD and SCZ suggests shared biological pathways contributing to these disorders. Understanding these shared and unique lipid dysregulations can help elucidate the underlying biological mechanisms and inform the development of targeted treatments. Rødevand et al. found that omega-3 FA metabolism and other pathways are overrepresented in genes shared between BD and other conditions like type 2 diabetes (T2D) and coronary artery disease (CAD) [57]. Genes linked to BD and lipid-related traits are associated with lipid biosynthesis, while those shared with T2D and CAD are more specifically linked to unsaturated FA biosynthesis. The association between BD and lipids like total cholesterol and LDL involves functions related to chylomicrons, TG-rich lipoprotein particles, and protein-lipid complexes. These results suggest a complex interplay between genetic factors involved in lipid metabolism and the development of BD, providing insights into potential shared pathways and mechanisms underlying these conditions, as has previously explained for depression, but with different pathways and lipids involved. Further research is needed to elucidate the precise mechanisms underlying these associations and their implications for understanding and managing BD, lipid-related traits, and associated metabolic disorders.

Schizophrenia

Most of the studies included in this review have focused on SCZ. Genetic variations, including ABCA13 and the rs253 SNP within the LPL gene, underline the role of lipid metabolism in SCZ [51, 52]. LPL encodes an enzyme involved in lipid metabolism, further supporting the role of lipid dysregulation in SCZ. PC ae 38:6, a glycerophospholipid involved in immune-related and neurotrophin signaling pathways, was significantly altered in SCZ patients and neuroleptic-free probands [47]. Linkage disequilibrium score regression (LDSR) based on GWASs identified 10 colocalized SNPs, with the strongest evidence involving 7 SNPs, 4 of which are related to BDNF, a key factor in both neurological and cardiometabolic diseases [62, 83]. Together with these SNPs, DGKZ is expressed in a significantly higher manner in SCZ vs controls [50]. Diacylglycerol kinases (DGKs) are a family of enzymes that play a crucial role in lipid signaling pathways by converting diacylglycerol (DAG) to phosphatidic acid (PA). DGKZ is encoded by a polymorphic gene and

has been implicated in various cellular processes, including signal transduction, membrane trafficking, and lipid homeostasis. The DGKZ rs7951870 has been significantly associated with DGKZ blood expression. Moreover, the rs7951870-TT genotype is associated with elevated expressions of several genes, including LRP4, encoding the LDL receptor-related protein 4, a protein involved at different levels in hippocampal neuroplasticity [84]. The comorbidity between SCZ, cardiometabolic, and inflammation-related traits suggests that lipid transport and dysregulation may collectively contribute to the disorder's development.

Several copy number variations (CNVs) associated with SCZ, ASD, or both were identified, including duplications in GDPD3 (glycerophospholipid metabolism) and deletions in ACACA (fatty acid synthesis). Genes like PIGW, PIGX, PIGZ (glycosylphosphatidylinositol anchor biosynthesis), and PCYT1A (phosphatidylcholine synthesis) were also implicated [53]. Over the years, SCZ and ASD have shown several meeting places that require new approaches aimed at investigating both similarities and differences between the two conditions [85]. Kushima's et al. work provides promising results that suggest a future role for lipidomics in this field to better describe and predict these two conditions from a biological perspective [53]. Post-mortem RNA sequencing revealed LXR/LXR activation in SCZ, which promotes cholesterol efflux and fatty acid synthesis, linking lipid metabolism dysregulation to SCZ pathology [56]. Activation of these receptors promotes heterodimerization, resulting in cholesterol efflux from the cell in the form of HDL, inhibition of uptake, and increased FA synthesis. In a subsequent step, they further explored this discovery by conducting a GWAS and, ultimately, an association study using brain MRI data contained in a database that included cognitive test results. The results revealed a broad involvement of lipid metabolism, which may be implicated in the pathology of SCZ. Of the 56 metabolites identified through the GWAS, 54 were associated with lipid metabolism pathways. Furthermore, the brain MRI analysis showed a correlation between SCZ and reduced lipid content in the dlPFC, which was associated with poorer performance on cognitive tests that assess task-switching abilities. These findings provide compelling evidence linking lipid metabolism to SCZ and its associated cognitive impairments. The observed correlation between reduced lipid content in the dlPFC and poorer cognitive performance suggests a potential mechanism through which lipid dysregulation in specific brain regions may contribute to cognitive deficits in individuals with SCZ. Omega-3 and omega-6 fatty acids, primarily driven by SNPs in the FADS cluster gene, showed protective effects in SCZ. Difficulties in converting short-chain polyunsaturated fatty acids (PUFAs) to long-chain PUFAs may contribute to lipid metabolism alterations in SCZ [60, 86]. The authors found that the observed effects were driven mainly by SNPs in the FADS cluster gene [60], encoding desaturases crucial in the long-chain PUFAs synthesis [86]. Interestingly, the FADS cluster gene has been associated with decreased PUFAs to total FA ratio in depression as well [63], where SNPs in the FADS2 gene overlapped between depressive symptoms and cardiometabolic changes [58], highlighting once again the complexity of the yet to be understood biological correlates in psychiatry.

Indeed, there is an association between SCZ and dyslipidemia, although a causal relationship has not been established [80, 87]. However, it has been found that a genetically predicted phenotype related to inflammation-induced insulin resistance, as well as levels of HDL cholesterol and TG [61] are associated with these diagnoses [80]. In this regard, Rødevand et al. identified 945 lipid-related loci shared between cardiovascular phenotypes and SCZ, particularly involving plasma lipids such as LDL, HDL, TG, and TC [59]. Despite these findings implying that the association with inflammation-related insulin resistance suggests a potential shared pathophysiological mechanism between SCZ and metabolic disturbances, shared genetic etiology is not the most likely mechanism underlying associations between SCZ and CVD [88], nor there is evidence of a causal effect of SCZ on cardiometabolic traits, or vice versa [87]. Indeed, the heightened susceptibility to cardiometabolic diseases in individuals with SCZ can be attributed to factors such as lifestyle, diet, adverse effects of antipsychotic medications, and shared mechanisms involving mild systemic inflammation. The results suggest that genetically determined dyslipidemia patterns associated with SCZ can potentially become specifically associated with the disease, considering that SCZ, CVD, and diabetes likely have distinct etiologies [45]

On this line, possibly, research is already moving on several proteomic and metabolomic elements have been discovered and integrated into the proposed framework of SCZ, indicating their involvement in the pathways discussed earlier. These elements likely form the central core of disrupted biological processes associated with the disorder. In one study of our review, 10 lipid metabolites were characterized with the highest difference between the control group and patients with SCZ: 3-O sulfogalactosylceramide (3OSG), estrone, cholesterol sulfate, 16-a-hydroxypregnenolone, dihydrotestosterone, androstenedione, Vitamin D3, androsterone sulfate [46]. To complement these findings, a recent metabolomic study conducted on GWAS datasets highlighted a protective role of N-acetylornithine levels (as seen in BD) and an increased risk associated with higher levels

of butyrylcarnitine [70]. Proteomic analysis showed a significant association of SCZ with APOC3, APOH, APOB, which are related to lipid metabolism (cholesterol uptake and dependent steroidogenesis) and synthesis and transport of ligands acting in chronic inflammatory reactions. The interaction between the CNS, endocrine functions and immune response has been clinically observed and investigated for nearly a century by psychoneuroimmunoendocrinology [89], and in this field the application of -omics techniques may broaden the horizons for a more comprehensive view of both psychiatric and medical conditions.

In conclusion, substantial evidence highlights the involvement of lipid metabolism in the pathophysiology of SCZ. Genetic variations, such as ABCA13 and rs253 in the LPL gene, alongside lipid dysregulation in glycerophospholipids and brain regions, contribute to SCZ susceptibility and cognitive impairments. The interplay between genetic, environmental, and lifestyle factors, including inflammation and antipsychotic effects, underscores the complexity of SCZ. Proteomic and metabolomic findings further support lipid metabolism's role, offering potential avenues for understanding and managing the disorder.

OCD

Only one study in this review focused on OCD [49]. Currently, the association analyses of SNPs yielded no significant results, despite the enrichment analyses showing an involvement of the peroxisomal lipid metabolism pathway in the aggressive dimension, the sphingolipid signaling pathway in the order dimension, and lipid, vitamin, and carbohydrate metabolism in the hoarding dimension. According to these results, further confirmatory studies should be encouraged to gain a deeper understanding of the biological markers in OCD.

Future developments

The shared lipid biomarkers identified across disorders, such as alterations in glycerophospholipids, triglycerides, and fatty acids, highlight common metabolic pathways underlying mental disorders. These findings suggest potential clinical applications, including the development of lipid-based biomarkers for diagnostic precision and personalized treatment strategies. For example, the overlap of lipid markers like PUFAs and sphingolipids across SCZ and BD could provide insights into shared pathophysiological mechanisms, aiding in early diagnosis or risk stratification. Furthermore, specific biomarkers, such as ABCA13 and LPL variants or alterations in lipid-binding proteins (e.g., APOC3, APOH), may offer opportunities to monitor treatment response or predict therapeutic outcomes, particularly for disorders like SCZ and MDD. Despite these promising prospects, the clinical translation of lipidomics remains limited due to variability in methodologies, lack of standardization, and the need for longitudinal studies to validate these markers in diverse populations. As lipidomics continues to advance, integrating these findings with genomic and proteomic data could refine psychiatric diagnoses, identify distinct biotypes, and facilitate the transition toward precision psychiatry. Collaborative efforts between researchers and clinicians will be pivotal to harnessing the full potential of lipid-based biomarkers in mental health care.

Conclusions

This systematic review underscores the critical involvement of lipid metabolism and lipid-related genes in MDD, BD, SCZ, and OCD. Across the 27 studies included, overlapping genetic and lipidomic patterns suggest shared and disorder-specific pathways that contribute to their pathophysiology.

In MDD, genetic overlaps with metabolic conditions such as cardiovascular disease and type 2 diabetes were identified, mediated by lipid dysregulation, including TG, LDL, and HDL. Specific lipid signatures have been linked to depression, independent of treatment and episode recurrence, pointing toward potential biosignatures.

BD showed associations with arachidonic acid and lipid-related genes, including ABCA13 and the FADS cluster, suggesting shared molecular mechanisms with SCZ and other metabolic traits like type 2 diabetes. The overlap in lipid profiles between BD and SCZ highlights common lipid dysregulation pathways, while unique lipidomic markers offer insights into BD-specific mechanisms.

SCZ exhibited the most robust evidence, with alterations in apolipoproteins (APOC3, APOH, APOB), lipid-binding proteins, and specific metabolites such as acylcarnitines and glycerophospholipids. Dysregulation in lipid metabolism, inflammation, and brain lipid content was linked to cognitive impairments and systemic metabolic disturbances. Shared genetic loci between SCZ and cardiometabolic traits further underscore the role of lipid dysregulation in its pathophysiology.

Although only one study addressed OCD, it identified peroxisomal and sphingolipid pathways linked to specific clinical dimensions, warranting further investigation. These findings demonstrate the value of lipidomics and genomics in uncovering the complex biological mechanisms underlying mental disorders. Further studies are needed to validate lipid signatures, explore their interactions with genetic and environmental factors, and advance their integration into precision psychiatry. Lipidomics offers promising opportunities for biomarker discovery, diagnosis, and the development of targeted

interventions, paving the way for a deeper understanding of psychiatric conditions.

Limitations and strengths

The discussed review sheds light on the intricate relationship between lipid metabolism and genetic factors in major mental disorders like MDD, BD, SCZ, and OCD. However, acknowledging its limitations is vital for a balanced view. Focusing on specific disorders limits broader applicability, and heterogeneity in methods and sample sizes complicates consistent conclusions. Associations are explored, but causation remains unestablished, requiring more experimental and longitudinal research. From a methodological point of view, non-standardized lipidomic approaches hinder direct comparisons, while confounding factors such as medication, lifestyle, nutrition and genetic predisposition for metabolic disorders affect observational study results. Despite these challenges, the review highlights gaps in understanding lipid metabolism and gene-environment interactions, emphasizing the need for deeper exploration. Nevertheless, the review provides an overall look at this field showing strengths that advance our understanding of this field. It offers a comprehensive analysis of cutting-edge research, aiding the interpretation of novel findings. Diverse methodologies like GWAS and large datasets enhance insights into lipid-related pathways, improving statistical power and generalizability. Moreover, the identified overlapping lipid profiles between disorders suggest shared molecular pathways and have the potential to serve as forerunners for the identification of new biomarkers or biosignatures. Understanding lipid metabolism through "-omics" techniques advance our knowledge of biological mechanisms, paving the way for new treatment strategies and drug discovery. In conclusion, despite limitations, the review's strengths provide a foundation to comprehend how lipid metabolism and genetic factors interact in major mental disorders. This paves the way for future research and improved mental health strategies.

Abbreviations

3OSG	3-O Sulfogalactosylceramide
ABCA13	ATP binding cassette transporter A13
APOB	Apolipoprotein B
APOC3	Apolipoprotein C3
APOH	Apolipoprotein H
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CAD	Coronary artery disease
CNS	Central nervous system
CNVs	Copy number variations
CRP	C-reactive protein
CVD	Cardiovascular disease
DAG	Diacylglycerol
DGKs	Diacylglycerol kinase
DGKZ	Diacylglycerol kinase zeta
dlPFC	Dorsolateral prefrontal cortex
FA	Fatty acids
FADS	Fatty acid desaturase
GWAS	Genome-wide association studies
HDL	High-density lipoproteins
-MS	Liquid chromatography-mass spectrometry
LDL	Low-density lipoproteins
LDSR	Linkage disequilibrium score regression
LPL	Lipoprotein lipase
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
OCD	Obsessive-compulsive disorder
PA	Phosphatidic acid
PM	Precision medicine
PP	Precision psychiatry
PUFA	Polyunsaturated fatty acids
qPCR	Quantitative polymerase chain reaction
SCZ	Schizophrenia
SNP	Single-nucleotide polymorphism
T2D	Type 2 diabetes
TG	Triglycerides

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

Conceptualization: S.F. and M.N.M.; Data curation: M.N.M. and J.F.A.; Formal Analysis: M.N.M, A.D.C., and J.F.A.; Investigation: M.N.M. and J.F.A; Methodology: M.N.M, A.D.C, G.P., S.F., and J.F.A.; Validation: G.G., M.B., G.P.; Writing – original draft: M.N.M. and J.F.A; Writing – review and editing: all authors; Supervision: M.S, C.G., S.F.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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