ITALIAN JOURNAL OF PSYCHIATRY
2025;11:52-63; doi: 10.36180/2421-4469-2025-653

Future research perspectives on energy metabolism and mood disorders: a brief narrative review on metabolic status, mitochondrial hypothesis and potential biomarkers

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Summary

Mood disorders are complex and heterogeneous conditions influenced by environmental, genetic, and neurobiological factors. Their aetiopathogenesis is highly intricate and not yet fully elucidated. A growing body of evidence highlights the crucial role of altered energy metabolism and inflammation within the central nervous system in the pathophysiology of mood disorders, identifying these pathways as promising therapeutic targets and diagnostic indicators.

Although the hypothesis linking energy metabolism, inflammation, and mood disorders is gaining attention, the current literature regarding metabolic biomarkers remains fragmented, limited, and far from being clinically applicable.

This narrative review aims to offer a more comprehensive overview of the interactions between energy metabolism, inflammation, and mood disorders. Specifically, it discusses the possibility of identifying a panel of metabolic biomarkers associated with mood disorders, which could facilitate the development of a multi-parametric test. Such a test would integrate various biological markers into a single platform, thus providing clinicians with a versatile tool capable of supporting diagnosis, monitoring disease progression, predicting treatment responses, and determining prognosis.

Compared to existing literature, this review uniquely emphasizes the translational potential and clinical applicability of metabolic biomarkers, highlighting novel pathways and providing a clearer vision for future research and clinical practice in mood disorders.

Keywords: mood disorders, major depressive disorder, bipolar disorder, metabolic dysfunction, mitochondrial dysfunction, biomarkers

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How to cite this article:
Socci V, Fagnani L, Barlattani T, et al. Future research perspectives on energy metabolism and mood disorders: a brief narrative review on metabolic status, mitochondrial hypothesis and potential biomarkers. Italian Journal of Psychiatry 2025;11:52-63; https://doi.org/10.36180/2421-4469-2025-653

INTRODUCTION

Major depressive disorder (MDD) and bipolar disorder (BD) are considered among the leading cause of disability worldwide and major contributors to the overall global burden of disease (WHO). For instance, it is estimated that 5% of adults suffer from depression globally. Mood disorders (MDs) can have dramatic effects on all aspects of life, including performance at school, productivity at work, relationships, and the ability to participate in the community. Despite their high prevalence and considerable negative impact on the health of individuals and society, the complexity and heterogeneity of these conditions continue to present substantial challenges to fully elucidating their pathophysiology, although significant advances in understanding

their neurobiological underpinnings have been made. Due to the heterogeneous and complex nature of MDs resulting in a variety of endophenotypes and clinical pictures, the outcome of current treatments is far from optimal, as only one-third of patients show remission after first-line treatment. Further, there are no currently available objective methods to assess subtypes, severity, or response to treatment.

The complex physiopathology of MDs includes a combination of genetic and/or acquired factors involving the whole organism. As a result, MDs are now considered as systemic diseases characterized by systemic biological alterations, supported by accumulating evidence highlighting associations between MDs and metabolic, inflammatory, and immune dysregulation. The literature of the last few decades has begun to reveal a bidirectional relationship between various metabolic alterations and mood symptoms. Studies have shown elevated whole-blood glucose levels in patients with depression[1], indicative of insufficient glucose metabolism in the body; in addition, diabetic patients have an increased risk of depression[2]. The negative consequences of abnormal glycemic control on brain function are mediated, in part, by insulin, glucose, growth factors, cortisol, cytokines, and reactive oxygen species[3], thus suggesting a complex interplay between brain functioning and energy metabolism. More recently, altered mitochondrial function and a resulting bioenergetic imbalance have been associated with the molecular pathophysiology of depression[4].

Within the bounds of a 'precision medicine' perspective, a detailed characterisation of the disorder's endophenotypes has become a major challenge. Precision medicine, which aims to tailor diagnosis and treatment strategies based on individual biological variability, has begun transforming clinical approaches in various medical fields; however, its integration into psychiatry remains in early stages. Recent studies suggest that metabolic dysfunction could represent a promising area for precision psychiatry, as metabolic biomarkers might facilitate patient stratification, predict treatment responses, and improve prognostic assessments [5].

This review aims to highlight the main evidence on the existing relationships between bioenergetic metabolism and MDs, together with the main shared biological mechanisms. Current limitations on the search for diagnostic and prognostic biomarkers in mood disorders will also be highlighted, emphasising the potential of mitochondria as a source of possible biomarkers. Finally, this paper will discuss some valuable implications for future research.

METHODS

This narrative review was conducted through a structured literature search in the PubMed database. Relevant articles were identified using key search terms, including "mood disorders," "major depressive disorder," "bipolar disorder," "metabolic dysfunction," "lipid regulation," "glucose regulation," "energy metabolism," "mitogenesis," "mitophagy," and "biomarkers." These terms were combined using Boolean operators (AND/OR) to refine the search results and enhance specificity. Inclusion criteria consisted of original research articles, systematic reviews, meta-analyses, and narrative reviews published in English. Priority was given to recent publications, primarily from the last 10 years, although foundational studies and highly cited articles from earlier periods were also considered. Relevant references cited in the selected articles were reviewed to identify additional pertinent studies.

ASSOCIATIONS BETWEEN METABOLIC DYSFUNCTION AND MOOD DISORDERS

Research so far provides evidence for a bidirectional association between metabolic alterations and mood disorders[6]. As suggested by longitudinal investigations[7], different metabolic dysregulations may predict a more chronic course of depressive disorders. Similarly, compared to the general population, BD patients exhibit higher rates of metabolic disease, hypertension and cardiovascular disease one year prior to diagnosis, suggesting that metabolic disturbances could precede clinical manifestations or reflect systemic vulnerability associated with BD [8,9]. Compared to healthy controls, a 4-fold higher rate of early death has been indicated in individuals with MDs, partly attributable to a significantly higher prevalence of metabolic disturbances such as hyperglycemia and dyslipidemia in this clinical group[10,11]

Compared with the general population worldwide, the prevalence rates of depression could be up to three times higher in patients with type 1 diabetes mellitus (DM) and twice as high in people with type 2 diabetes[2]. Clinically significant depressive symptoms are highly prevalent in patients with DM[12] and appeared to be associated with increased incident type 2 DM over a 3-year follow-up period[6]. However, most studies remain correlational, and a clear causal direction remains to be established. Sex-specific differences have been documented, with female diabetic patients exhibiting higher vulnerability to developing depression compared to their male counterparts[13]. Similarly, a strong association between BD and DM has been described, with significantly higher prevalence rates of DM in BD patients compared to the general population[14,15], as well as higher rates of DM in patients with DM than in non-diabetic individuals[16]. A population-based study with a longitudinal cohort design reported that patients with newly diagnosed BD had a higher risk of DM relative to both the general population and patients with schizophrenia across the 3-year prodromal period[8].

Regarding lipid regulation in patients with mood disorders, in a longitudinal cohort analyses report that patients with MDD had both a higher prevalence (14.4% vs. 7.9%) and incidence (3.6% vs. 2.6%) of hyperlipidemia compared to controls [17]. Similarly, the prevalence and incidence of hyperlipidemia for BD were 13.5% and 4.37%, respectively[18]. Moreover, compared to patients with schizophrenia, BD individuals had an increased OR of hyperlipidemia 1 year prior to receiving their respective psychiatric diagnosis (OR: 1.22 95%CI: 1.09–1.36)[8]. These findings suggest that dyslipidemia may serve as an early clinical

marker and contribute to mood dysregulation through altered metabolic pathways. At the same time, a higher risk of subsequent MDD has been reported in individuals with newly diagnosed hyperlipidemia[19] or baseline low HDL [20]. Lower levels of cholesterol have also been associated with alexithymia and suicidality, possibly mediated through alterations in serotonergic neurotransmission pathways.[21,22]. Furthermore, dyslipidemia characterized by elevated triglycerides and reduced high-density lipoprotein cholesterol (HDL-C) has been consistently associated with increased risk for depressive episodes and symptom severity, indicating a potential mechanistic role in the pathophysiology of mood disorders. [23,24] Alterations in polyunsaturated fatty acids (PUFA) have also been reported in patients with mood disorders. In this respect, relative to healthy controls, patients with MDD exhibit significantly lower levels of omega-3 PUFA levels[25] and an altered ratio of omega-PUFA with higher amounts of omega-6 vs omega-3 PUFA[26] have been showed in patients with MDD. Also, a meta-analysis of patients with BD reported significantly lower levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) compared to control subjects, reinforcing lipid metabolism abnormalities' role in MD pathogenesis. [27].

Collectively, although with high heterogeneity, meta-analyses showed associations between MDD and increased total cholesterol, triglycerides, low HDL, low high-density lipoprotein cholesterol (LDL-C) and low omega-3 PUFA[28,29]. These findings highlight the potential clinical utility of routine metabolic screening and targeted interventions in patients with mood disorders. However, to clarify the causal nature and precise underlying mechanisms linking metabolic dysfunction and mood disorders, further prospective and experimental studies are essential

PATHOPHYSIOLOGICAL LINKS AND SHARED MECHANISMS BETWEEN METABOLIC DYSFUNCTION AND MOOD DISORDERS

Studies investigating the metabolic profile in individuals with MDD and BD are increasingly elucidating a complex relation between metabolic dysfunction and mood disorders, suggesting the existence of potential shared biological mechanisms.

Among the proposed pathophysiological links and shared mechanisms between metabolic dysfunction and mood disorders, a critical candidate for a common pathway could be the chronic activation of the stress system. As previously discussed, prolonged activation of the stress system contributes to metabolic disturbances and neurobiological changes relevant for mood regulation [30–32]. Moreover, chronic stress increases the production of pro-inflammatory cytokines that are involved in the pathophysiology of both DM and depression. Inflammatory cytokines may interact with neurotransmitter metabolism, neuroendocrine function and synaptic plasticity that are relevant for the pathophysiology of depressive disorders[33] as well as with the functioning of the pancreatic β-cells, thus promoting insulin resistance [34].

Neuroinflammation has emerged as another crucial pathophysiological link between metabolic dysfunction and mood disorders. Recent evidence indicates elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in patients with major depressive disorder (MDD) and bipolar disorder (BD). For instance, increased cerebrospinal fluid concentrations of IL-6 and TNF-α were reported in MDD patients compared to healthy controls, strongly supporting a neuroinflammatory component in depression [35]. Similarly, Solmi et al. [36] observed that IL-6 and TNF-α levels were significantly elevated in BD patients during mood episodes, with IL-6 remaining elevated even during euthymic periods, suggesting persistent immune activation in BD. However, despite these findings, considerable debate remains regarding the specificity of inflammatory biomarkers. Elevated cytokine levels have also been reported in other psychiatric disorders, such as schizophrenia and anxiety disorders, as well as various medical conditions, complicating their clinical utility as specific diagnostic or prognostic biomarkers for mood disorders [37].

Insulin receptors are expressed in brain regions such as the nucleus accumbens (NAc), the ventral tegmental area (VTA), the amygdala, and the raphe nuclei that are associated with depressive symptoms and mood disorders [38]. Repeated periods of hypoglycemia/hyperglycemia, lacunar infarcts, and generalised microvascular dysfunction have been shown to impact brain function in regions that are associated with mood and cognition, such as the pre-frontal cortex (PFC) and HC[39].

Another proposed pathophysiological link concerns brain cholesterol metabolism due to its role in regulating critical processes such as synaptic transmission, axonal and dendrite formation, and membrane-bound proteins[40]. Further, research showed associations between deficits in fatty acids and altered DA and serotonin neurotransmission in the frontal cortex, with potential implications for cognitive and emotional functioning[41].

Further, metabolic dysfunction, including obesity, glycemic control, and insulin resistance, have been associated with a shift of gut microbiota[42]. The gut microbiome is increasingly recognized as a key regulator of brain function through multiple pathways, including modulation of neurotransmitter synthesis, neuroinflammation, and metabolic homeostasis. Emerging evidence suggests that dysbiosis—an imbalance in microbial composition—may directly influence mood disorders via gut-brain axis mechanisms involving altered intestinal permeability, immune dysregulation, and neuroactive metabolite production [43]. Specifically, altered gut microbiota has been shown to affect the synthesis of neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA), as well as short-chain fatty acids (SCFAs), which play essential roles in mood regulation and cognitive function [44]. Patients with mood disorders frequently exhibit reduced microbial diversity and specific changes in microbial populations, including decreased levels of beneficial bacteria (e.g, *Bifidobacterium*, *Lactobacillus*) and increased levels of pro-inflammatory species

(e.g, *Enterobacteriaceae*) [45,46]. These microbial imbalances are linked to increased gut permeability ("leaky gut"), systemic inflammation, and altered neuroendocrine responses, all of which may contribute to depressive symptoms and treatment resistance [47]. Given the relevance of microbiota-brain interactions, therapeutic interventions targeting the microbiome, such as probiotics, prebiotics, dietary adjustments, and fecal microbiota transplantation (FMT), represent promising avenues for novel treatments of mood disorders. However, further studies are required to confirm their clinical efficacy and clarify the underlying biological mechanisms [48].

METABOLIC BIOMARKERS IN PATIENTS WITH MOOD DISORDERS

In recent years, the involvement of the inflammatory system in mood disorders has become increasingly relevant since many studies have indicated reciprocal associations between inflammatory diseases/biomarkers and mood alterations. Cytokine levels show significant variability in mood disorder patients. Elevated levels of pro-inflammatory molecules in subjects with MDs have been reported, including pro-inflammatory cytokines (i.e, IL-4, TNF-, IL-1, IL-6), soluble receptors of IL-2 and TNF-type 1 (sIL-2R and sTNFR1, respectively) and reactive protein C (CRP). Furthermore, significant variability in cytokine profiles has been observed also in different clinical phase (i.e, depression, mania, and euthymia), suggesting variable involvement of inflammatory dysfunctions in different mood states and severity[49]. Currently, there is substantial evidence for an association between pro-inflammatory cytokines and depressive episodes, specifically IL-1, IL-6, TNF-types, and CRP as the most reliable biological markers[50].

However, the specificity and sensitivity of these inflammatory biomarkers for mood disorders remain unclear, as elevated cytokine levels also been consistently reported also in other psychiatric disorders, such as obsessive-compulsive disorder, anxiety, schizophrenia, and post-traumatic stress disorder (PTSD)[51,52]. A recent systematic review and meta-analysis further emphasized that abnormal cytokine levels, including IL-6 and TNF-α, are prevalent across various psychiatric disorders, reinforcing concerns about their specificity as biomarkers for mood disorders [53]. Additionally, methodological issues such as diurnal variation in cytokine secretion, differences in assay techniques, medication status, and the presence of comorbid medical conditions may significantly influence cytokine measurements, complicating their interpretation and clinical applicability [54]. For instance, diurnal variations can significantly alter cytokine concentrations, with peak levels typically occurring in the early morning hours, potentially confounding the interpretation of clinical data if sampling times are inconsistent across studies. Similarly, variations in assay sensitivity, specificity, and reproducibility between different laboratory methods can further complicate the comparison of cytokine levels across studies, making it difficult to establish standardized reference values[55]. A recent study by Chumakov et al. found that in patients with paranoid schizophrenia, IL-6 levels were associated with cognitive impairments, but these levels varied significantly depending on clinical status and treatment, underscoring the complexity of using cytokines as reliable biomarkers [56]. Recent studies have also highlighted that elevated levels of inflammatory markers, such as IL-6 and CRP, are associated with a range of psychiatric conditions beyond mood disorders, further challenging their specificity as biomarkers for depression or bipolar disorder. For instance, increased IL-6 levels have been observed in patients with schizophrenia and PTSD, suggesting a shared inflammatory pathway across these disorders. A meta-analysis by Zhou et al. confirmed that IL-6 levels are elevated in schizophrenia, particularly during acute episodes, and tend to decrease following antipsychotic treatment, indicating that IL-6 may serve as a state-dependent marker rather than a disorder-specific biomarker [57].

Therefore, current research efforts are increasingly focused on exploring how inflammatory mechanisms interact with other biological systems involved in the pathophysiology of mood disorders. in particular, inflammatory alterations associated with neurotransmitters and neurotrophins dysfunctions, chronic hypothalamic-pituitary-adrenal (HPA) axis activation, purinergic system abnormalities, and increased oxidative stress. In this respect, as suggested by several findings, altered activation of the HPA axis may promote an inflammatory state that, in turn, might contribute to the development and/or progression of the depressive pathology through an alteration of the neuroplasticity caused by reduced brain-derived neurotrophic factor (BDNF) activity[58]. For these reasons, peripheral BDNF was proposed as a potential diagnostic, prognostic, and therapeutic biomarker for MDs, particularly associated with disease severity and response to treatments[59]. However, results are still inconclusive[60]; this neurotrophin is involved in a variety of body functions, and reduced blood BDNF levels have been reported in a multitude of neuropsychiatric and neurodegenerative diseases, as well as in medical diseases, thus making circulating BDNF a non-specific biomarker. Although reduced peripheral BDNF levels have consistently been observed in patients with mood disorders, including major depressive disorder and bipolar disorder, recent evidence highlights that such reductions are also common in other psychiatric conditions like schizophrenia, anxiety disorders, and post-traumatic stress disorder, further challenging its specificity as a diagnostic biomarker [61,62]. Moreover, peripheral BDNF concentrations are influenced by several confounding variables such as age, sex, pharmacological treatments (especially antidepressants), lifestyle factors including physical activity, and the presence of medical comorbidities (e.g, cardiovascular diseases and metabolic disorders), complicating its clinical interpretation [61,63] Therefore, given these limitations, current research suggests incorporating BDNF measurements within multimodal biomarker panels, which combine multiple biological and clinical indicators, potentially enhancing diagnostic and prognostic accuracy in mood disorders [64].

The association between glucose or lipid biomarkers and the

risk of depression has been investigated with inconsistent results. Several investigations showed a positive association between glucose levels and the risk of depression[11,65,66]. However, a negative[6] and a null association[67] were also reported. Similarly, among lipid biomarkers, a positive association was shown for triglycerides, whereas a negative association was shown for HDL-C [11,65,66], although with some inconsistencies[68].
Such inconsistencies may reflect several confounding variables and methodological differences among studies, including diverse study populations (differences in age, sex, and ethnicity), variability in diagnostic criteria, presence of metabolic and psychiatric comorbidities, medication use, and lifestyle factors such as diet and physical activity. For instance, a recent large-scale cohort study found that elevated levels of glucose and triglycerides and lower levels of HDL-C were associated with an increased risk of depression; significantly, these biomarker levels were also associated with an increased risk of other psychiatric conditions such as anxiety and stress-related disorders, with no differences among disorders, suggesting a generalized role of these metabolic biomarkers across psychiatric conditions [69]. Additionally, recent evidence from drug-free patients newly diagnosed with major depressive disorder highlighted that lipid parameters, including triglycerides and HDL-C, were significantly correlated with depressive symptom severity, further reinforcing the potential influence of metabolic factors on mood disorders and emphasizing the need to consider patient-specific metabolic profiles in clinical assessments [70].
Again, this raises many concerns about the specificity of biomarkers for mood disorders.

THE MITOCHONDRIAL HYPOTHESIS

Undoubtedly, when addressing energy metabolism, it is impossible not to consider mitochondria, rightly recognised as the energy powerhouses of the cell. Their role is not limited to energy production through ATP synthesis. Still, they also participate in amino acid, lipid, and steroid metabolism, regulate calcium levels in cells, produce free radicals, and control apoptosis. As a result, mitochondrial dysfunction disrupts not only energy generation but also several other critical cellular functions. The number of mitochondria in a cell is primarily related to its energy needs.
Neurons are exceptionally energy-demanding cells. Proper mitochondrial function is essential to manage the high energy demands required for sustaining neurotransmitter release, neurogenesis, dendritogenesis, synaptogenesis, and glial functions. Neuronal mitochondria are preferentially localized to synaptic regions, where they meet the high energy demands of neurotransmission and synaptic plasticity [71,72]. Moreover, mitochondria are not static but are actively transported along axons and dendrites to regions with high energy demands. This dynamic distribution ensures that the energy supply meets the localised metabolic needs of neurons.
The mitochondrial hypothesis of mood disorders suggests that disturbances in mitochondrial function are central to the pathophysiology of psychiatric conditions such as MD and BD. Mitochondrial quality control is primarily regulated through the processes of formation of new mitochondria, mitogenesis, and the removal of defective mitochondria, mitophagy. The balance between mitogenesis and mitophagy plays a pivotal role in sustaining normal cellular function and preventing mood disorders[73].
Mitochondrial biogenesis ensures a constant supply of healthy mitochondria. A reduction in this process could lead to energy deficits, fatigue, and cognitive decline frequently observed in MD patients. Conversely, mitophagy removes dysfunctional mitochondria, preventing oxidative stress and neuroinflammation, common in MD and BD [74]. Disruptions in mitophagy are linked to increased mitochondrial damage, which exacerbates the oxidative imbalance seen in depressive and bipolar patients.
Additionally, mitochondrial dynamics, which involve the continuous fission and fusion of mitochondria, are critical for maintaining mitochondrial integrity and function. In mood disorders, alterations in these dynamic processes have been observed, where excessive fission or impaired fusion can lead to mitochondrial fragmentation and dysfunction[75]. These disruptions are thought to compromise neuronal resilience and adaptability, making the brain more vulnerable to stress and mood dysregulation. Recent human studies have indeed confirmed altered mitochondrial dynamics in peripheral cells, such as dermal fibroblasts from bipolar patients, demonstrating increased mitochondrial fragmentation and impaired fusion processes associated with early disease phases and symptom severity [76]
The balance between mitogenesis and mitophagy is tightly regulated by several factors, which are mainly sustained by the general energy demand sensor AMPK (adenosine monophosphate-activated protein kinase), the key regulator of mitogenesis PGC-1α (peroxisome proliferator-activated receptor-γ coactivator 1 α) and the PINK1/Parkin pathway, which governs mitophagy[77].
AMPK is a central energy sensor that plays a crucial role in maintaining cellular energy homeostasis, particularly in regulating mitochondrial function. In the context of BD, AMPK's ability to regulate energy production and its involvement in oxidative stress and inflammation make it a significant factor in the disorder's pathophysiology[77]. Clinically, altered AMPK activity could explain the distinct energy fluctuations between manic and depressive phases of BD. During manic episodes, hyperactivation of mitochondria and increased ATP production could be associated with excessive AMPK signaling, leading to increased cellular energy availability and heightened neuronal activity. Conversely, during depressive episodes, reduced AMPK activation might result in diminished mitochondrial biogenesis, impaired energy metabolism, fatigue, psychomotor retardation, and cognitive difficulties, symptoms frequently observed in depressive phases [78]. These fluctuations make AMPK an attractive target for pharmacological interventions aimed at stabilizing energy homeostasis in BD patients.

One of AMPK's primary roles is to promote mitochondrial biogenesis and improve mitochondrial function, which it achieves by activating PGC-1α, a key regulator of mitochondrial health. This regulation is especially relevant in bipolar disorder, where energy dysregulation is a hallmark, particularly the distinct energy imbalances observed between manic and depressive episodes.

In manic phases of bipolar disorder, mitochondrial activity and ATP production are often increased, and AMPK activation can help manage excessive energy demands while protecting cells from oxidative damage. Conversely, during depressive phases, mitochondrial dysfunction and decreased energy production are prominent. AMPK activation in this context can stimulate mitochondrial biogenesis and improve cellular energy availability, potentially alleviating symptoms related to fatigue and lethargy. Moreover, AMPK is closely linked to the regulation of inflammation and oxidative stress, both of which are elevated in BD. By activating anti-inflammatory pathways and reducing reactive oxygen species (ROS) production, AMPK helps mitigate the cellular damage associated with chronic inflammation and oxidative stress, which are prevalent in mood disorders. Given these roles, AMPK is a promising therapeutic target for modulating mitochondrial function and restoring energy balance in bipolar disorder[79].

Mitochondrial biogenesis within cells is primarily regulated by PGC-1α, a PGC family transcriptional regulator which indirectly promotes nuclear transcription of genes involved in energy metabolism and mitogenesis. It operates primarily through its interaction with a group of nuclear transcription receptors known as peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-dependent receptors that regulate genes involved in metabolism, with three main subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ. PGC-1α acts as a co-activator for these PPARs, enhancing their activity and linking environmental signals, such as physical exercise or metabolic stress, to the expression of specific genes[80–82]. PPAR subtypes, such as PPAR- β/δ, are critical regulators of lipid metabolism, mitochondrial function, and energy balance, especially in the context of metabolic diseases. PGC-1α enhances the activity of these receptors, particularly during exercise or metabolic stress, which activates a cascade of gene expressions related to energy homeostasis and mitochondrial biogenesis[82,83].

In the brain, PGC-1α is integral to mitochondrial biogenesis and dynamics, ensuring the proper number, structure, and function of mitochondria, PGC-1α influences the mitochondrial electron transport chain, promoting efficient energy production and the buffering of ROS, which, if unregulated, can lead to oxidative damage and inflammation [84,85]. Furthermore, PGC-1α's role extends beyond energy regulation to the modulation of inflammatory pathways. Inflammatory markers, often elevated in psychiatric disorders such as bipolar disorder, are linked to metabolic dysregulation. PGC-1 alpha helps counteract this by promoting anti-inflammatory effects, particularly in muscle and adipose tissues, through its interaction with PPAR-gamma. This reduces the production of pro-inflammatory cytokines and enhances the body's resilience to metabolic challenges, including obesity and insulin resistance[86]. In the context of neuropsychiatric conditions, such as bipolar disorder, this regulation of energy and inflammation suggests that PGC-1 alpha is essential not only for maintaining metabolic balance but also for protecting against cellular damage that can exacerbate psychiatric symptoms.

Clinically, alterations in PGC-1α expression and signaling have been associated with depressive symptoms such as fatigue, reduced motivation, impaired cognition, and increased inflammatory markers, particularly in peripheral tissues and blood samples from patients with mood disorders. Decreased PGC-1α mRNA expression has been specifically observed in patients with major depressive disorder, notably in those with psychotic depression, while variations in the PGC-1α gene have been associated with differential therapeutic responses to lithium in patients with bipolar disorder [87,88]. Although direct post-mortem evidence from human brain tissues remains limited, altered peripheral and genetic indicators of PGC-1α activity suggest its role in mitochondrial dysfunction, potentially contributing to mood dysregulation and cognitive impairment observed clinically. Therefore, targeting the PGC-1α pathway may represent a promising therapeutic approach to ameliorate metabolic, cognitive, and mood-related symptoms in individuals with MDD and BD. By regulating energy production, reducing oxidative stress, and modulating inflammation, PGC-1 alpha provides a comprehensive mechanism through which the brain maintains homeostasis and responds to environmental changes, particularly in the face of psychiatric and neurodegenerative disorders[89–91].

The PINK1/Parkin pathway is central to the regulation of mitophagy, a selective form of autophagy responsible for identifying and degrading damaged or dysfunctional mitochondria to maintain cellular homeostasis. PINK1 (PTEN-induced kinase 1), a mitochondrial serine/threonine-protein kinase, accumulates on the outer mitochondrial membrane when mitochondria become damaged or depolarised. When mitochondria lose their membrane potential, PINK1 stabilises on the outer membrane and recruits Parkin, an E3 ubiquitin ligase, to the site of damage[92,93]. This pathway facilitates the removal of damaged mitochondria, preventing their accumulation and the resulting cellular damage caused by increased oxidative stress and impaired energy production[94]. Impaired mitophagy, resulting from dysfunction in the PINK1/Parkin pathway, can lead to accumulation of damaged mitochondria, worsening oxidative stress and energy deficits, as can be commonly observed in BD and MDD[95,96].

Clinically, impaired mitophagy via the PINK1/Parkin pathway has been associated with cognitive deficits, increased symptom severity, and reduced responsiveness to conventional antidepressant therapies, potentially contributing to treatment resistance and chronicity in mood disorders. Notably, patients with major depressive disorder exhibit altered levels of mitophagy-related proteins, such as elevated PINK1 and reduced Parkin in peripheral blood cells, correlating with disease severity [97].

In MDD, growing evidence points to impaired mitophagy as a significant factor in disease progression. Mitochondrial dysfunction, often observed in MDD, is marked by reduced ATP production, increased oxidative stress, and the release of pro-inflammatory signals due to the accumulation of defective mitochondria. This dysfunction is closely linked to common MDD symptoms, such as fatigue, cognitive decline, and mood disturbances. The failure to adequately clear damaged mitochondria amplifies oxidative damage and promotes a pro-inflammatory environment, both of which are known to contribute to the pathophysiology of MDs. Moreover, the persistence of malfunctioning mitochondria disrupts neuronal function and exacerbates neuroinflammation, which are crucial contributors to the severity and progression of depressive episodes[98,99]. Consequently, targeting the proteins and pathways involved in mitophagy offers a promising therapeutic approach to address mitochondrial dysfunction and reduce neuroinflammation in MDs [100,101].

EXPLOITING MITOCHONDRIA AS SOURCE OF POTENTIAL SPECIFIC BIOMARKERS OF MDS

The scientific literature broadly supports the close connection between energy metabolism, cellular functionality, and mitochondrial dynamics. While this relationship is well-established, particularly in relation to alterations in mitochondrial homeostasis, the scientific community still lacks sufficiently valid diagnostic tools for MDs. As discussed in previous sections, associations with glycaemic and lipid profiles are often conflicting or inconclusive. Similarly, alterations in inflammation markers, such as CRP and pro-inflammatory cytokines, lack the diagnostic specificity needed to establish positive predictive value for accurate diagnosis[102,103].

However, there is still potential for progress in this area. Mitochondrial biomarkers are increasingly recognised for their potential to improve the diagnosis and monitoring of MDs[104]. One of the most promising biomarkers under investigation is circulating cell-free mitochondrial DNA (ccf-mtDNA), which has shown elevated levels in patients with MDs, especially during depressive episodes or mood swings in BD. Elevated ccf-mtDNA levels have been associated with both disease severity and episode recurrence, making it a potential marker for not only diagnosing MDs but also tracking the course of the illness [105]. Its non-invasive nature (via blood samples) makes it particularly appealing for longitudinal monitoring and potentially for predicting the onset of depressive or manic episodes. Similarly, mitochondrial DNA copy number (mtDNAcn) has emerged as a key biomarker, offering insights into mitochondrial health and overall cellular energy production. In MDs, altered mtDNAcn has been found in peripheral blood, suggesting that it reflects a bioenergetic disturbance in these conditions. A meta-analysis by Calarco et al. (2024)[106] found that mtDNAcn could be used to differentiate between mood disorders like MDD and BD. Decreased mtDNAcn, often associated with metabolic inefficiency and oxidative stress, is indicative of a more severe or chronic mood disorder course. Additionally, the same meta-analysis highlighted significant variability of mtDNAcn across different subtypes of mood disorders, reinforcing the need for further research to establish its diagnostic accuracy and clinical specificity[106]. The ability to track mtDNAcn over time may be exploited to assess treatment response, as restoration of mitochondrial function could signal an improvement in clinical outcomes.

Beyond genetic markers, reduced mitochondrial respiration in the blood cells of patients with MDD and BD reflects systemic metabolic dysregulation[107]. These mitochondrial disturbances are proposed to correlate with the severity of depressive or manic episodes, providing a potential diagnostic tool for differentiating between MDs subtypes. However, clinical translation of mitochondrial respiration measures faces significant technical and methodological challenges, such as the need for specialised equipment, variability across measurement protocols, and a current lack of methodological standardization. These factors limit feasibility in routine clinical practice, indicating that additional studies are necessary to enhance practicality and reproducibility [108]. The reversibility of the mitochondrial disturbance in response to mood stabilisers and antidepressants may be used to monitor treatment efficacy.

Emerging evidence also points to the role of mitochondrial oxidative stress and the accumulation of mitochondrial DNA mutations as further biomarkers. These mutations may lead to increased oxidative damage, which has been implicated in the neuroinflammatory processes that contribute to MDs[109].

The growing body of research on mitochondrial biomarkers underscores their potential for improving both the diagnosis and monitoring of MDs. Biomarkers like ccf-mtDNA and mtDNAcn offer non-invasive, easily measurable indicators of disease severity and treatment response. At the same time, mitochondrial respiration and oxidative stress markers provide deeper insight into the cellular dysfunctions associated with these conditions. These developments suggest that mitochondrial biomarkers could play a critical role in transitioning toward more personalised and precise treatments for MDs, allowing for earlier detection, improved differentiation between mood disorder subtypes, and more effective long-term monitoring. Nevertheless, given the early stage of research, further longitudinal validation studies and standardisation of measurement techniques are essential before mitochondrial biomarkers can be reliably integrated into clinical practice. Currently, these biomarkers should be viewed as complementary research tools rather than definitive diagnostic measures

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

The scientific literature in recent years provides evidence of the highly complex and multifactorial nature of MDs, whose aetiology and pathophysiology appear to be tightly regulated by complex interactions among endocrine, immune, metabolic systems, inflammatory status and trophic factor activity. The link between energy metabolism, inflammation and MDs is slowly maturing in the face of scientific evidence, butscien-

tific literature is nonetheless patchy and fragmented. Although numerous efforts have been made in this direction, to date, no methods are available to objectively assess clinical subtypes, severity, or response to treatment. Presumably, in the context of psychiatric disorders, the likelihood of a single biomarker being clinically useful, thus endowed with high predictive power, is low. Therefore, the application of advanced methods to the analysis of panels of biomarkers may be of crucial importance to provide a greater understanding of multiple biological alterations related directly or indirectly to energy metabolism that contribute to the heterogeneity of the disorder's phenomenology as well as to treatment response. However, the clinical integration of biomarker panels requires validation through rigorous prospective studies with clearly defined clinical populations, standardised collection protocols, replicable analytical procedures, and predefined statistical approaches to assess predictive accuracy and clinical utility (e.g, sensitivity, specificity, predictive values). Such validation studies should also include external validation cohorts to confirm generalisability and reproducibility of findings across diverse clinical settings, thus ensuring practicality, reliability, and cost-effectiveness in routine clinical practice.

In this context, research efforts should be addressed to significantly extend the understanding of the biological mechanisms underlying MDs through the analysis of a large panel of biomarkers. Advanced, high-throughput analytical methods (e.g, genomics, transcriptomics, proteomics, metabolomics) will provide an impressive amount of data for a more detailed and in-depth characterisation of energy metabolism, mitochondrial function and inflammation associated with MD onset and clinical outcome. T Nevertheless, the feasibility and accessibility of these high-throughput technologies in psychiatric research remain challenging due to technical complexity, costs, and the need for specialised infrastructure and trained personnel. Future research should explicitly address these barriers to facilitate broader adoption of these methodologies in clinical psychiatry. This will provide the most informative panel of biomarkers significantly associated with the clinical phenotypes, cognitive and psychosocial functioning, and lifestyles of individuals with MDs, as well as potential diagnostic implications. These profiles could be instrumental in identifying more homogenous, clinically distinct sub-groups to be included in studies on therapeutic efficacy and individualising treatment interventions in the clinical setting. Specifically, machine learning and computational approaches could support the integration and interpretation of multi-dimensional biomarker data, facilitating translation into clinical decision-making.

In addition, future studies should include longitudinal designs to highlight potential trajectories of the metabolic profile along with the clinical course and pharmacological treatment. Prospective cohort studies employing repeated measures of metabolic, inflammatory, and mitochondrial biomarkers at multiple time points alongside detailed clinical, cognitive, and lifestyle assessments are particularly recommended. By evaluating patterns of association between analytical, clinical, and lifestyle-related variables over time, it will be possible to contribute to the identification of the most critical targets of treatment programs, further increasing our knowledge of modifiable factors as targets for intervention. Such a holistic approach will allow the identification of moderating factors and potential predictors of therapeutic efficacy, with relevant implications for the definition of risk, protective, and treatment biomarkers.

Research in this field will be crucial in addressing the challenges of the increased incidence of MDs, contributing to the advancement of knowledge of their aetiopathogenesis and the development of innovative methodological and technological solutions for their management.

Finally, a significant limitation of this manuscript is its methodological approach as a narrative review rather than a systematic review or meta-analysis. The choice of a narrative review was primarily guided by the broad scope and the exploratory intent of synthesizing heterogeneous literature on emerging metabolic and mitochondrial biomarkers in mood disorders. Consequently, inclusion criteria were purposefully broad to capture a wide spectrum of studies. However, this approach inherently carries the risk of selection and interpretation biases. To mitigate this issue, efforts were made to systematically select peer-reviewed literature prioritizing recent, high-quality original research articles, systematic reviews, and meta-analyses from authoritative databases (PubMed, Scopus), clearly highlighting the limitations of current evidence. Future work employing systematic reviews or meta-analytical methodologies would be valuable for quantitatively assessing the strength and consistency of evidence regarding metabolic biomarkers in mood disorders.

Abbreviations

MDD: major depressive disorder; BD: bipolar disorder; MDs: mood disorders; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PUFA: polyunsaturated fatty acids; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; SNS: sympathetic nervous system; NAc: nucleus accumbens; VTA: ventral tegmental area; PFC: pre-frontal cortex; HC: hippocampus; IL-1: Interleukin-1; IL-6: Interleukin-6, TNF: tumor necrosis factor; CRP: reactive protein C; BDNF: brain-derived neurotrophic factor; HPA: hypothalamic-pituitary-adrenal axis; TG: triglycerides; ATP: adenosine triphosphate; AMPK: adenosine monophosphate-activated protein kinase; ROS: reactive oxygen species; PPARs: peroxisome proliferator-activated receptors; PINK1: PTEN-induced kinase 1; ccf-mtDNA: cell-free mitochondrial DNA; mtDNAcn: mitochondrial DNA copy number.

Conflict of interest statement

The authors confirm that there is no conflict of interest related to the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contributions

VS: Conceptualization, Methodology, Writing-Original manuscript; LF: Conceptualization, Methodology, Writing-Original manuscript; TB: Methodology, Writing-Review and Editing; GC: Supervision, Writing-Review and Editing; AR: Supervision, Writing-Review and Editing; FP: Conceptualization, Supervision, Writing-Review and Editing

References

1. Bekhbat M, Treadway MT, Goldsmith DR, et al. Gene signatures in peripheral blood immune cells related to insulin resistance and low tyrosine metabolism define a sub-type of depression with high CRP and anhedonia. Brain Behav Immun 2020;88:161–5. https://doi.org/10.1016/j.bbi.2020.03.015.
2. Roy T, Lloyd CE. Epidemiology of depression and diabetes: A systematic review. J Affect Disord 2012;142:S8–21. https://doi.org/10.1016/s0165-0327(12)70004-6.
3. Hendrickx H, McEwen BS, Ouderaa F van der. Metabolism, mood and cognition in aging: The importance of lifestyle and dietary intervention. Neurobiol Aging 2005;26:1–5. https://doi.org/10.1016/j.neurobiolaging.2005.10.005.
4. Kuffner K, Triebelhorn J, Meindl K, et al. Major Depressive Disorder is Associated with Impaired Mitochondrial Function in Skin Fibroblasts. Cells 2020;9:884. https://doi.org/10.3390/cells9040884.
5. Shih P an (Betty). Metabolomics Biomarkers for Precision Psychiatry. Adv Exp Med Biol 2019;1161:101. https://doi.org/10.1007/978-3-030-21735-8_10.
6. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008;299:2751–9. https://doi.org/10.1001/jama.299.23.2751.
7. Marijnissen RM, Vogelzangs N, Mulder ME, et al. Metabolic dysregulation and late-life depression: a prospective study. Psychol Med 2016;47:1041–52. https://doi.org/10.1017/s0033291716003196.
8. Chen P-H, Tsai S-Y, Pan C-H, et al. High Risk and Trajectories of Physical Illnesses before the Diagnosis of Bipolar Disorder. J Affect Disord 2021;281:99–108. https://doi.org/10.1016/j.jad.2020.11.127.
9. Lee H, Han D, Rhee SJ, et al. Alterations in blood proteins in the prodromal stage of bipolar II disorders. Scientific Reports 2022 12:1 2022;12:1–10. https://doi.org/10.1038/s41598-022-07160-0.
10. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic Syndrome and Metabolic Abnormalities in Bipolar Disorder: A Meta-Analysis of Prevalence Rates and Moderators. American Journal of Psychiatry 2013;170:265–74. https://doi.org/10.1176/appi.ajp.2012.12050620.
11. Watson KT, Simard JF, Henderson VW, et al. Incident Major Depressive Disorder Predicted by Three Measures of Insulin Resistance: A Dutch Cohort Study. American Journal of Psychiatry 2021;178:914–20. https://doi.org/10.1176/appi.ajp.2021.20101479.
12. Ali S, Stone MA, Peters JL, et al. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabetic Medicine 2006;23:1165–73. https://doi.org/10.1111/j.1464-5491.2006.01943.x.
13. Deischinger C, Dervic E, Leutner M, et al. Diabetes mellitus is associated with a higher risk for major depressive disorder in women than in men. BMJ Open Diabetes Res Care 2020;8:e001430. https://doi.org/10.1136/bmjdrc-2020-001430.
14. Calkin C V, Gardner DM, Ransom T, et al. The relationship between bipolar disorder and type 2 diabetes: More than just comorbid disorders. Ann Med 2012;45:171–81. https://doi.org/10.3109/07853890.2012.687835.
15. Chien I-C, Chang K-C, Lin C-H, et al. Prevalence of diabetes in patients with bipolar disorder in Taiwan: a population-based national health insurance study. Gen Hosp Psychiatry 2010;32:577–82. https://doi.org/10.1016/j.genhosppsych.2010.09.005.
16. Wändell P, Ljunggren G, Wahlström L, et al. Diabetes and psychiatric illness in the total population of Stockholm. J Psychosom Res 2014;77:169–73. https://doi.org/10.1016/J.JPSYCHORES.2014.06.012.
17. Chien I-C, Lin C-H, Chou Y-J, et al. Increased risk of hyperlipidemia in patients with major depressive disorder: A population-based study. J Psychosom Res 2013;75:270–4. https://doi.org/10.1016/j.jpsychores.2013.06.003.
18. Hsu J-H, Chien I-C, Lin C-H. Increased risk of hyperlipidemia in patients with bipolar disorder: a population-based study. Gen Hosp Psychiatry 2015;37:294–8. https://doi.org/10.1016/j.genhosppsych.2015.04.003.
19. Chuang C-S, Yang T-Y, Muo C-H, et al. Hyperlipidemia, statin use and the risk of developing depression: a nationwide retrospective cohort study. Gen Hosp Psychiatry 2014;36:497–501. https://doi.org/10.1016/j.genhosppsych.2014.05.008.
20. Almeida OP, Yeap BB, Hankey GJ, et al. HDL cholesterol and the risk of depression over 5 years. Mol Psychiatry 2013;19:637–8. https://doi.org/10.1038/mp.2013.113.
21. De Berardis D, Marini S, Piersanti M, et al. The Relationships between Cholesterol and Suicide: An Update. ISRN Psychiatry 2012;2012:387901. https://doi.org/10.5402/2012/387901.
22. De Berardis D, Serroni N, Campanella D, et al. Alexithymia and its relationships with C-reactive protein and serum lipid levels among drug naïve adult outpatients with major depression. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1982–6. https://doi.org/10.1016/j.pnpbp.2008.09.022.
23. Oh J, Kim T-S. Serum lipid levels in depression and suicidality: The Korea National Health and Nutrition Examination Survey (KNHANES) 2014. J Affect Disord 2017;213:51–8. https://doi.org/10.1016/j.jad.2017.02.002.
24. Meijer A, Zuidersma M, de Jonge P. Depression as a non-causal variable risk marker in coronary heart disease. BMC Med 2013;11:130. https://doi.org/10.1186/1741-7015-11-130.
25. Müller CP, Reichel M, Mühle C, et al. Brain membrane lipids in major depression and anxiety disorders. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 2015;1851:1052–65. https://doi.org/10.1016/j.bbalip.2014.12.014.
26. Shanmugam N, Reddy MA, Guha M, et al. High Glucose-Induced Expression of Proinflammatory Cytokine and Chemokine Genes in Monocytic Cells. Diabetes 2003;52:1256–64. https://doi.org/10.2337/diabetes.52.5.1256.
27. McNamara RK, Welge JA. Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder. Bipolar Disord 2016;18:300–6. https://doi.org/10.1111/bdi.12386.
28. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care 2012;35:1171–80. https://doi.org/10.2337/dc11-2055.

29 Lin P-Y, Huang S-Y, Su K-P. A Meta-Analytic Review of Polyunsaturated Fatty Acid Compositions in Patients with Depression. Biol Psychiatry 2010;68:140–7. https://doi.org/10.1016/j.biopsych.2010.03.018.

30 Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–81. https://doi.org/10.1038/NRENDO.2009.106.

31 Herbert J, Goodyer IM, Grossman AB, et al. Do Corticosteroids Damage the Brain? J Neuroendocrinol 2006;18:393–411. https://doi.org/10.1111/j.1365-2826.2006.01429.x.

32 Moulton CD, Costafreda SG, Horton P, et al. Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes. Brain Imaging Behav 2015;9:651–62. https://doi.org/10.1007/s11682-014-9348-2.

33 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24–31. https://doi.org/10.1016/j.it.2005.11.006.

34 Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2013;36:166–75. https://doi.org/10.2337/dc12-0702.

35 Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun 2019;81:24–40. https://doi.org/10.1016/J.BBI.2019.06.015.

36 Solmi M, Suresh Sharma M, Osimo EF, et al. Peripheral levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β across the mood spectrum in bipolar disorder: A meta-analysis of mean differences and variability. Brain Behav Immun 2021;97:193–203. https://doi.org/10.1016/J.BBI.2021.07.014.

37 Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Molecular Psychiatry 2018 25:6 2018;25:1301–11. https://doi.org/10.1038/s41380-018-0096-3.

38 Figlewicz DP, Evans SB, Murphy J, et al. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. Brain Res 2003;964:107–15. https://doi.org/10.1016/s0006-8993(02)04087-8.

39 Zhang S, Zhang Y, Wen Z, et al. Cognitive dysfunction in diabetes: abnormal glucose metabolic regulation in the brain. Front Endocrinol (Lausanne) 2023;14:1192602. https://doi.org/10.3389/fendo.2023.1192602.

40 Petrov AM, Kasimov MR, Zefirov AL. Brain Cholesterol Metabolism and Its Defects: Linkage to Neurodegenerative Diseases and Synaptic Dysfunction. Acta Naturae 2016;8:58–73. https://doi.org/10.32607/20758251-2016-8-1-58-73.

41 Chalon S, Vancassel S, Zimmer L, et al. Polyunsaturated fatty acids and cerebral function: Focus on monoaminergic neurotransmission. Lipids 2001;36:937–44. https://doi.org/10.1007/s11745-001-0804-7.

42 Lanthier N, Delzenne N. Targeting the Gut Microbiome to Treat Metabolic Dysfunction-Associated Fatty Liver Disease: Ready for Prime Time? Cells 2022;11:2718. https://doi.org/10.3390/cells11172718.

43 McGuinness AJ, Loughman A, Foster JA, et al. Mood Disorders: The Gut Bacteriome and Beyond. Biol Psychiatry 2024;95:319–28. https://doi.org/10.1016/j.biopsych.2023.08.020.

44 Cryan JF, O'riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877–2013. https://doi.org/10.1152/PHYSREV.00018.2018/ASSET/IMAGES/LARGE/Z9J0041929160006.JPEG.

45 Cheung SG, Goldenthal AR, Uhlemann AC, et al. Systematic Review of Gut Microbiota and Major Depression. Front Psychiatry 2019;10:34. https://doi.org/10.3389/FPSYT.2019.00034.

46 Valles-Colomer M, Falony G, Darzi Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nature Microbiology 2019 4:4 2019;4:623–32. https://doi.org/10.1038/s41564-018-0337-x.

47 Van Ameringen M, Turna J, Patterson B, et al. The gut microbiome in psychiatry: A primer for clinicians. Depress Anxiety 2019;36:1004–25. https://doi.org/10.1002/DA.22936.

48 Ng QX, Lim YL, Yaow CYL, et al. Effect of Probiotic Supplementation on Gut Microbiota in Patients with Major Depressive Disorders: A Systematic Review. Nutrients 2023;15:1351. https://doi.org/10.3390/NU15061351/S1.

49 Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 2009;116:214–7. https://doi.org/10.1016/j.jad.2008.12.001.

50 Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 2016;21:1696–709. https://doi.org/10.1038/mp.2016.3.

51 Miller AH. Beyond depression: the expanding role of inflammation in psychiatric disorders. World Psychiatry 2020;19:108–9. https://doi.org/10.1002/wps.20723.

52 Michopoulos V, Powers A, Gillespie CF, et al. Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. Neuropsychopharmacology 2017;42:254–70. https://doi.org/10.1038/npp.2016.146.

53 Zhang Y, Wang J, Ye Y, et al. Peripheral cytokine levels across psychiatric disorders: A systematic review and network meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2023;125:110740. https://doi.org/10.1016/J.PNPBP.2023.110740.

54 Koola MM. Cytokines in Schizophrenia: Hope or Hype? Indian J Psychol Med 2016;38:97. https://doi.org/10.4103/0253-7176.178766.

55 Yang H, Engeland CG, King TS, et al. The relationship between diurnal variation of cytokines and symptom expression in mild obstructive sleep apnea. J Clin Sleep Med 2020;16:715. https://doi.org/10.5664/JCSM.8332.

56 Chumakov E, Dorofeikova M, Tsyrenova K, et al. A Cross-Sectional Study on Associations Between BDNF, CRP, IL-6 and Clinical Symptoms, Cognitive and Personal Performance in Patients With Paranoid Schizophrenia. Front Psychiatry 2022;13. https://doi.org/10.3389/FPSYT.2022.943869.

57 Zhou X, Tian B, Han H Bin. Serum interleukin-6 in schizophrenia: A system review and meta-analysis. Cytokine 2021;141:155441. https://doi.org/10.1016/J.CYTO.2021.155441.

58 Wohleb ES, Franklin T, Iwata M, et al. Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci 2016;17:497–511. https://doi.org/10.1038/nrn.2016.69.

59 Dimitriadis M, van den Brink RHS, Comijs HC, et al. Prognostic effect of serum BDNF levels in late-life depression: Moderated by childhood trauma and SSRI usage? Psychoneuroendocrinology 2019;103:276–83. https://doi.org/10.1016/j.psyneuen.2019.02.003.

60 Polyakova M, Stuke K, Schuemberg K, et al. BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. J

Affect Disord 2015;174:432–40. https://doi.org/10.1016/j.jad.2014.11.044.
61 Liberona A, Jones N, Zúñiga K, et al. Brain-Derived Neurotrophic Factor (BDNF) as a Predictor of Treatment Response in Schizophrenia and Bipolar Disorder: A Systematic Review. Int J Mol Sci 2024;25:11204. https://doi.org/10.3390/IJMS252011204.
62 Mora C, Zonca V, Riva MA, et al. Blood biomarkers and treatment response in major depression. Expert Rev Mol Diagn 2018;18:513–29. https://doi.org/10.1080/14737159.2018.1470927.
63 Phillips C. Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection. Neural Plast 2017;2017. https://doi.org/10.1155/2017/7260130.
64 Strawbridge R, Young AH, Cleare AJ. Biomarkers for Depression: Recent Insights, Current Challenges and Future Prospects. Focus (Madison) 2018;16:194–209. https://doi.org/10.1176/APPI.FOCUS.16206.
65 Han K-M, Kim MS, Kim A, et al. Chronic medical conditions and metabolic syndrome as risk factors for incidence of major depressive disorder: A longitudinal study based on 4.7 million adults in South Korea. J Affect Disord 2019;257:486–94. https://doi.org/10.1016/j.jad.2019.07.003.
66 Mast BT, Miles T, Penninx BW, et al. Vascular Disease and Future Risk of Depressive Symptomatology in Older Adults: Findings from the Health, Aging, and Body Composition Study. Biol Psychiatry 2008;64:320–6. https://doi.org/10.1016/j.biopsych.2008.01.025.
67 Vogelzangs N, Beekman ATF, Boelhouwer IG, et al. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. J Clin Psychiatry 2011;72:598–604. https://doi.org/10.4088/JCP.10m06559.
68 Vogelzangs N, Beekman ATF, Boelhouwer IG, et al. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. J Clin Psychiatry 2011;72:598–604. https://doi.org/10.4088/JCP.10m06559.
69 Chourpiliadis C, Zeng Y, Lovik A, et al. Metabolic Profile and Long-Term Risk of Depression, Anxiety, and Stress-Related Disorders. JAMA Netw Open 2024;7:e244525–e244525. https://doi.org/10.1001/JAMANETWORKOPEN.2024.4525.
70 Liu J, Li Z, Xiao L, et al. Association between lipid parameters and severity of depressive symptoms in patients with first-diagnosed drug-free major depressive disorder 2024. https://doi.org/10.21203/RS.3.RS-3956327/V1.
71 Misgeld T, Schwarz TL. Mitostasis in Neurons: Maintaining Mitochondria in an Extended Cellular Architecture. Neuron 2017;96:651–66. https://doi.org/10.1016/j.neuron.2017.09.055.
72 Duarte F V, Ciampi D, Duarte CB. Mitochondria as central hubs in synaptic modulation. Cellular and Molecular Life Sciences 2023 80:6 2023;80:1–21. https://doi.org/10.1007/S00018-023-04814-8.
73 Fisar Z, Hroudová J. Common aspects of neuroplasticity, stress, mood disorders and mitochondrial functions. Activitas Nervosa Superior Rediviva 2010;52.
74 Giménez-Palomo A, Dodd S, Anmella G, et al. The Role of Mitochondria in Mood Disorders: From Physiology to Pathophysiology and to Treatment. Front Psychiatry 2021;12:546801. https://doi.org/10.3389/fpsyt.2021.546801.
75 Manji H, Kato T, Di Prospero NA, et al. Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci 2012;13:293–307. https://doi.org/10.1038/nrn3229.
76 Marques AP, Resende R, Silva DF, et al. Mitochondrial Alterations in Fibroblasts of Early Stage Bipolar Disorder Patients. Biomedicines 2021;9. https://doi.org/10.3390/BIOMEDICINES9050522.
77 Iorio R, Celenza G, Petricca S. Mitophagy: Molecular Mechanisms, New Concepts on Parkin Activation and the Emerging Role of AMPK/ULK1 Axis. Cells 2021;11:30. https://doi.org/10.3390/cells11010030.
78 Scaini G, Andrews T, Lima CNC, et al. Mitochondrial dysfunction as a critical event in the pathophysiology of bipolar disorder. Mitochondrion 2021;57:23–36. https://doi.org/10.1016/J.MITO.2020.12.002.
79 Morris G, Walder K, McGee SL, et al. A model of the mitochondrial basis of bipolar disorder. Neuroscience & Biobehavioral Reviews 2017;74:1–20. https://doi.org/10.1016/j.neubiorev.2017.01.014.
80 Fuentes E, Guzmán-Jofre L, Moore-Carrasco R, et al. Role of PPARs in inflammatory processes associated with metabolic syndrome (Review). Mol Med Rep 2013;8:1611–6. https://doi.org/10.3892/mmr.2013.1714.
81 Kim J-C. The effect of exercise training combined with PPARγ agonist on skeletal muscle glucose uptake and insulin sensitivity in induced diabetic obese Zucker rats. J Exerc Nutrition Biochem 2016;20:42–50. https://doi.org/10.20463/jenb.2016.06.20.2.6.
82 Cheng C-F, Ku H-C, Lin H. PGC-1α as a Pivotal Factor in Lipid and Metabolic Regulation. Int J Mol Sci 2018;19:3447. https://doi.org/10.3390/ijms19113447.
83 Coll T, Rodriguez-Calvo R, Barroso E, et al. Peroxisome Proliferator-Activated Receptor (PPAR)β /δ: A New Potential Therapeutic Target for the Treatment of Metabolic Syndrome. Curr Mol Pharmacol 2009;2:46–55. https://doi.org/10.2174/1874-470210902010046.
84 Nierenberg AA, Ghaznavi SA, Sande Mathias I, et al. Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha as a Novel Target for Bipolar Disorder and Other Neuropsychiatric Disorders. Biol Psychiatry 2018;83:761–9. https://doi.org/10.1016/j.biopsych.2017.12.014.
85 d'Angelo M, Castelli V, Catanesi M, et al. PPARγ and Cognitive Performance. Int J Mol Sci 2019;20:5068. https://doi.org/10.3390/ijms20205068.
86 Fidaleo M, Fanelli F, Ceru M, et al. Neuroprotective Properties of Peroxisome Proliferator-Activated Receptor Alpha (PPARα) and its Lipid Ligands. Curr Med Chem 2014;21:2803–21. https://doi.org/10.2174/09298673216661403031434553455.
87 Ryan KM, Patterson I, McLoughlin DM. Peroxisome proliferator-activated receptor gamma co-activator-1 alpha in depression and the response to electroconvulsive therapy. Psychol Med 2019;49:1859–68. https://doi.org/10.1017/S0033291718002556.
88 Geoffroy PA, Etain B, Lajnef M, et al. Circadian genes and lithium response in bipolar disorders: associations with PPARGC1A (PGC-1α) and RORA. Genes Brain Behav 2016;15:660–8. https://doi.org/10.1111/GBB.12306.
89 Altinoz MA, Ozpinar A. PPAR-δ and erucic acid in multiple sclerosis and Alzheimer's Disease. Likely benefits in terms of immunity and metabolism. Int Immunopharmacol 2019;69:245–56. https://doi.org/10.1016/j.intimp.2019.01.057.
90 Wójtowicz S, Strosznajder AK, Jeżyna M, et al. The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders. Neurochem Res 2020;45:972–88. https://doi.org/10.1007/s11064-020-02993-5.
91 Andreazza AC, Young LT. The neurobiology of bipolar disorder: identifying targets for specific agents and synergies for combination treatment. Int J Neuropsycho-

pharmacol 2013;17:1039–52. https://doi.org/10.1017/s1461145713000096.

92 Song Y, Cao H, Zuo C, et al. Mitochondrial dysfunction: A fatal blow in depression. Biomedicine & Pharmacotherapy 2023;167:115652. https://doi.org/10.1016/j.biopha.2023.115652.

93 Mishra SR, Mahapatra KK, Behera BP, et al. Mitochondrial dysfunction as a driver of NLRP3 inflammasome activation and its modulation through mitophagy for potential therapeutics. The International Journal of Biochemistry & Cell Biology 2021;136:106013. https://doi.org/10.1016/j.biocel.2021.106013.

94 Li X, Huang L, Lan J, et al. Molecular mechanisms of mitophagy and its roles in neurodegenerative diseases. Pharmacol Res 2021;163:105240. https://doi.org/10.1016/j.phrs.2020.105240.

95 Scaini G, Mason BL, Diaz AP, et al. Dysregulation of mitochondrial dynamics, mitophagy and apoptosis in major depressive disorder: Does inflammation play a role? Mol Psychiatry 2021;27:1095–102. https://doi.org/10.1038/s41380-021-01312-w.

96 Mani S, Swargiary G, Chadha R. Mitophagy impairment in neurodegenerative diseases: Pathogenesis and therapeutic interventions. Mitochondrion 2021;57:270–93. https://doi.org/10.1016/j.mito.2021.01.001.

97 Xu W, Gao W, Guo Y, et al. Targeting mitophagy for depression amelioration: a novel therapeutic strategy. Front Neurosci 2023;17:1235241. https://doi.org/10.3389/FNINS.2023.1235241/XML/NLM.

98 Zhang Y. Parkin, a Parkinson's disease-associated protein, mediates the mitophagy that plays a vital role in the pathophysiology of major depressive disorder. Neurochem Int 2024;179:105808. https://doi.org/10.1016/j.neuint.2024.105808.

99 Jhuo C, Chen C, Tzen JTC, et al. Teaghrelin protected dopaminergic neurons in MPTP-induced Parkinson's disease animal model by promoting PINK1/Parkin-mediated mitophagy and AMPK/SIRT1/PGC1-α-mediated mitochondrial biogenesis Environ Toxicol 2024;39:4022–34. https://doi.org/10.1002/tox.24275.

100 Tripathi A, Scaini G, Barichello T, et al. Mitophagy in depression: Pathophysiology and treatment targets. Mitochondrion 2021;61:1–10. https://doi.org/10.1016/j.mito.2021.08.016.

101 Mangrulkar S V, Wankhede NL, Kale MB, et al. Mitochondrial Dysfunction as a Signaling Target for Therapeutic Intervention in Major Neurodegenerative Disease. Neurotox Res 2023;41:708–29. https://doi.org/10.1007/s12640-023-00647-2.

102 Osimo EF, Pillinger T, Rodriguez IM, et al. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun 2020;87:901. https://doi.org/10.1016/J.BBI.2020.02.010.

103 Kohler O, Krogh J, Mors O, et al. Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. Curr Neuropharmacol 2016;14:732–42. https://doi.org/10.2174/1570159X14666151208113700.

104 Pei L, Wallace DC. Mitochondrial Etiology of Neuropsychiatric Disorders. Biol Psychiatry 2018;83:722–30. https://doi.org/10.1016/J.BIOPSYCH.2017.11.018.

105 Jeong H, Dimick MK, Sultan A, et al. Peripheral biomarkers of mitochondrial dysfunction in adolescents with bipolar disorder. J Psychiatr Res 2020;123:187–93. https://doi.org/10.1016/j.jpsychires.2020.02.009.

106 Calarco CA, Keppetipola SM, Kumar G, et al. Whole blood mitochondrial copy number in clinical populations with mood disorders: A meta-analysis. Psychiatry Res 2024;331:115662. https://doi.org/10.1016/j.psychres.2023.115662.

107 Zvěřová M, Hroudová J, Fišar Z, et al. Disturbances of mitochondrial parameters to distinguish patients with depressive episode of bipolar disorder and major depressive disorder. Neuropsychiatr Dis Treat 2019;15:233–40. https://doi.org/10.2147/NDT.S188964.

108 Gumpp AM, Behnke A, Bach AM, et al. Mitochondrial bioenergetics in leukocytes and oxidative stress in blood serum of mild to moderately depressed women. Mitochondrion 2021;58:14–23. https://doi.org/10.1016/J.MITO.2020.12.009.

109 Allen J, Romay-Tallon R, Brymer KJ, et al. Mitochondria and Mood: Mitochondrial Dysfunction as a Key Player in the Manifestation of Depression. Front Neurosci 2018;12:386. https://doi.org/10.3389/fnins.2018.00386.