# Advances in the Association and Mechanisms of Abnormal Lipid Metabolism and Depression Development: A Postprint

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## Abstract

Lipid metabolism is a critical physiological process in the human body, and its disturbance is closely associated with the onset and progression of depression. Nevertheless, systematic syntheses of these associations remain insufficient. This article comprehensively examines alterations in lipid metabolism in patients with depression and elaborates in detail on diseases that exhibit comorbid relationships with both lipid metabolism disturbance and depression, such as overweight, obesity, and metabolic syndrome. Additionally, this review summarizes five underlying mechanisms linking abnormal lipid metabolism to depression development: overexpression of the SNCA gene and abnormal accumulation of $\alpha$-Syn, ferroptosis, gut microbiota dysbiosis, mitochondrial quality control system dysfunction, and chronic stress. Finally, this article proposes future research directions, aiming to provide new perspectives and a research foundation for the early diagnosis and treatment of depression.

## Full Text

### Review and Monograph: Research Progress on the Association and Mechanisms Between Abnormal Lipid Metabolism and Depressive Disorder Development

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**Abstract**

Lipid metabolism is a key physiological process in the human body, and its disruption is closely linked to the onset and progression of depression. Nevertheless, a systematic collation of these associations is currently inadequate. This article comprehensively explores changes in lipid metabolism among patients with depression and elaborates on disorders that are comorbidly associated with depression through lipid metabolism disturbances, such as overweight, obesity, and metabolic syndrome. Additionally, the article summarizes five intrinsic mechanisms through which abnormal lipid metabolism is associated with depressive development: overexpression of the SNCA gene and abnormal accumulation of $\alpha$-synuclein, ferroptosis, gut microbiota dysbiosis, impairment of mitochondrial quality control systems, and chronic stress. Finally, this article suggests future research directions aimed at providing new perspectives and a research foundation for the early diagnosis and treatment of depression.

**Keywords:** Depression; Lipid metabolism; Mechanism; Alpha-synuclein; Polyunsaturated fatty acids

Depression is a serious mental health disorder characterized by low mood, loss of interest, sleep disturbances, and other symptoms that severely interfere with daily functioning and quality of life, potentially leading to suicide. The WHO states that the disease affects approximately 280 million people globally (3.8% of the population), making it one of the leading causes of morbidity and disability worldwide [1]. By 2030, the global disease burden of depression is projected to increase further [2]. The main pathological features of depression involve multiple dimensions, including neurobiology, neurochemistry, neuroendocrinology, genetics, and psychosocial factors. Recent studies have found that the occurrence and development of depression are related to abnormal lipid metabolism, involving processes such as overexpression of the alpha-synuclein gene (SNCA) and abnormal accumulation of $\alpha$-synuclein ($\alpha$-Syn) [3], ferroptosis [4], gut microbiota disturbance [5], mitochondrial quality control system dysfunction [6], and chronic stress [7]. However, current research on the impact of abnormal lipid metabolism on depression onset and progression remains limited, and the related mechanisms in depression pathogenesis are still unclear. Therefore, this article reviews and summarizes relevant studies on abnormal lipid metabolism and depression, attempting to elucidate how lipid metabolism abnormalities affect depression progression and their underlying mechanisms, thereby providing possible approaches for early diagnosis, progression delay, and prognosis improvement in depression.

## 1. Lipid Metabolism Changes in Depressed Patients

Lipids are essential components of cell membranes and play crucial roles in myelination, neurotransmission, synaptic plasticity, energy metabolism, and inflammatory responses, making them vital for maintaining normal physiological functions. Abnormal lipid metabolism refers to disturbances in lipid synthesis, decomposition, transport, or utilization, leading to altered lipid levels, distribution, or function that negatively impacts various body systems, including brain function impairment and the development of neuropsychiatric disorders [8].

The most obvious characteristic of abnormal lipid metabolism is weight change. Some depressed patients experience weight gain, possibly related to emotional eating, lack of exercise, and adverse drug reactions, while others show weight loss, potentially due to decreased appetite, somnolence, and increased metabolic rate caused by anxiety and depressive states [9]. Antidepressant use is a potential cause of weight changes in depressed patients. A meta-analysis by Andres et al. [9] indicated that antidepressants such as mirtazapine, paroxetine, and amitriptyline cause weight gain, while fluoxetine and bupropion are associated with weight loss. Gafoor et al. [10] prospectively examined 10 years of primary care electronic health records and found a strong association between antidepressants and weight gain, with the risk of antidepressant-induced weight gain persisting for at least 5 years, among which mirtazapine had the highest incidence ratio for weight gain. Weight changes can predict depression risk; a retrospective cohort study analyzing 1.1 million people revealed a U-shaped association between weight change and depression risk, with the lowest risk observed when weight change remained stable between -5% and 5% [11].

Compared with other tissues, the brain contains diverse lipid components that play important roles in neuronal function. Changes in brain lipid composition can affect perception and emotional behavior, leading to depressive moods. Large amounts of lipids in the brain are used to construct and maintain myelin, and myelination and oligodendrocyte dysfunction can be observed in many psychiatric disorders. In major depressive disorder (MDD) patients, reduced myelination and dysregulation of lipids and polyunsaturated fatty acids (PUFA) have been observed [12]. Clinical blood lipid measurements show that compared with healthy individuals, MDD patients have elevated triglyceride (TG) levels and significantly decreased serum total cholesterol (TC) and very low-density lipoprotein (VLDL) levels [13]. Additionally, in MDD patients, lower levels of high-density lipoprotein (HDL) and TC, along with higher TG levels, indicate greater depression severity and poorer prognosis [14]. Broader non-clinical lipidomics studies across various lipid categories have shown that MDD patients exhibit decreased ether phospholipid and acylcarnitine levels and increased ceramide levels, with ceramide C18:0 and C20:0 serving as potential diagnostic biomarkers for depression [15].

PUFA includes $\omega$-3 PUFA and $\omega$-6 PUFA. Studies have shown that compared with healthy individuals, depressed patients have lower $\omega$-3 PUFA levels in

blood and tissues, along with a higher $\omega$-6/$\omega$-3 ratio [16]. Furthermore, PUFA can serve as an indicator for assessing depression symptom severity, with low $\omega$-3 PUFA levels often indicating worsening depressive symptoms [17]. Antidepressants cause changes in blood lipid composition and have complex effects on lipid metabolism. For example, after treatment with selective serotonin reuptake inhibitors (SSRI), depressed patients show increased blood TC, TG, and low-density lipoprotein (LDL) levels, raising the risk of metabolic diseases such as non-alcoholic fatty liver disease [18]. Conversely, Hummel et al. [14] demonstrated that symptom improvement after antidepressant treatment is accompanied by improved LDL/HDL ratios, thereby reducing atherosclerosis risk. However, most studies have not compared treated depressed patients with healthy controls, hindering research on antidepressant effects on lipid metabolism [19]. In summary, depressed patients exhibit significant changes in body weight and lipid levels, distribution, and function, which may correlate with depression progression and severity.

## 2. Depressive Symptoms in Lipid Metabolism-Related Diseases

Lipid metabolism-related diseases and depressive symptoms have a close relationship, often influencing each other and forming comorbidities. Here, we briefly discuss the connections between overweight, obesity, metabolic syndrome (MetS), and depression.

### 2.1 Overweight, Obesity, and Depression

Overweight is defined as BMI between 25.0-29.9 kg/m$^2$, and obesity as BMI $\geq$ 30.0 kg/m$^2$. Although BMI cannot accurately measure individual fat distribution and muscle mass, most high-BMI patients accompany ectopic fat accumulation—fat deposition in harmful locations such as arteries and the liver. This abnormal fat accumulation triggers inflammatory responses and immune system abnormalities, considered primary inducers of depression in overweight and obese patients [7]. Additionally, fat interferes with serotonin (5-HT) synthesis, an important neurotransmitter associated with depression development [22]. Rodent studies have revealed that long-term high-fat diet-induced obesity increases anxiety and depression-like behaviors related to neuroadaptations in brain reward circuits [23]. In human studies, the causal relationship between diet-induced obesity and depression is indirect; saturated fat intake positively correlates with plasma levels of acute-phase reactant C-reactive protein (CRP) [24], which increases depression risk by upregulating pro-inflammatory cytokines and causing peripheral inflammation. Studies show that even mild peripheral inflammation can lead to neuroinflammatory responses and immune dysregulation, producing depression-like behaviors [21]. Furthermore, obesity may cause psychosocial issues such as social discrimination, self-negation, and social barriers, which increase depression risk. Conversely, depressive moods may affect dietary choices and eating behaviors, creating a vicious cycle.

### 2.2 MetS and Depression

MetS is a common clinical lipid metabolism disorder typically presenting as a cluster of factors including obesity (especially abdominal obesity), hypertension, hyperglycemia, elevated TG, and low HDL cholesterol. Studies have found a bidirectional relationship between MetS and depression: MetS patients have 1.27-fold and 1.49-fold higher depression risk in cross-sectional and cohort studies, respectively, while depression increases MetS risk by 34% and 52% in cross-sectional and cohort studies [25]. The association between MetS and depression may be attributed to shared pathophysiological mechanisms. Increased HPA axis activity in depressed patients may affect MetS through influences on lipid metabolism and blood pressure regulation. For example, HPA axis overactivation elevates cortisol and cortisone levels, causing fat redistribution and central obesity [26]. Autonomic nervous system dysregulation is also an important intersection in MetS-depression comorbidity; overactive sympathetic nervous system (SNS) increases MetS risk by elevating fatty acid release and inhibiting insulin release, while SNS overactivity may disrupt neurotransmitter release and reuptake, increasing depression risk [27]. Additionally, chronic low-grade inflammatory responses involve inflammatory mediators such as leukocytes and CRP that regulate neural conduction, endocrine function, and cell signaling, indirectly affecting physical and mental health [20].

## 3. Mechanisms of Lipid Metabolism in Depression Onset and Progression

The association between lipid metabolism and depression progression is complex and multifaceted, with lipid metabolism disturbances affecting depression through multiple pathways. We explore these mechanisms through five aspects: SNCA gene overexpression and $\alpha$-Syn abnormal accumulation, ferroptosis, gut microbiota dysbiosis, mitochondrial quality control system dysfunction, and chronic stress.

### 3.1 Lipid Metabolism and SNCA Gene Overexpression with $\alpha$-Syn Abnormal Accumulation

$\alpha$-Syn is a lipophilic neuronal protein encoded by the SNCA gene, consisting of 140 amino acids that primarily aggregates at presynaptic terminals, regulating synaptic transmission and plasticity. Recent studies show that SNCA not only affects neurodegenerative diseases like Parkinson' s but also participates in mood disorders such as depression. Upregulated SNCA expression and abnormal $\alpha$-Syn accumulation have been observed in both MDD patients and animal models [3]. Lipid membrane composition and structure significantly influence $\alpha$-Syn binding; specific lipids such as phospholipids (PL), ceramides, sphingolipids (SL), and cholesterol affect $\alpha$-Syn conformation and promote abnormal aggregation, accelerating neuronal injury and depression progression. Studies show that ceramides and certain PL components like phosphoglycerides and phospho-

inositides can participate in cell signal transduction by activating or inhibiting protein kinase C (PKC), PI3K/AKT pathways, thereby regulating SNCA gene transcription and expression [28]. SL includes more C20 SL and less C16 SL; $\alpha$-Syn binding to lipid membranes is influenced by SL content, with higher proportions of C20 SL on lipid membranes facilitating $\alpha$-Syn binding and formation of larger aggregates [29]. Cholesterol regulates lipid membrane fluidity and stability, and its content also affects $\alpha$-Syn binding; higher cholesterol content promotes $\alpha$-Syn binding to membranes and helps form stable aggregates [30]. Additionally, lipid membrane pH can affect $\alpha$-Syn binding patterns and affinity by regulating surface charge states; under low pH conditions, lipid membranes carry more positive charges, facilitating binding with negatively charged $\alpha$-Syn [29]. Lipid metabolism abnormalities cause pathological $\alpha$-Syn accumulation and gliosis, impairing amygdala and hippocampal function. In these regions, overexpressed $\alpha$-Syn and lipid metabolism abnormalities affect synaptic protein levels, reducing synapsin 1 (Syn1), synapsin 2 (Syn2), and vesicle-associated membrane protein 2 (Vamp2) at synaptic terminals, leading to synapse loss and neuronal death [31]. Meanwhile, SNCA overexpression activates the complement system, inducing microglial proliferation and increasing pro-inflammatory cytokines such as IL-1$\beta$, IL-6, and TNF-$\alpha$, which induce neuroinflammation and affect neuronal survival [3].

Studies show that Hashi' s Shugan Jianpi Decoction can treat perimenopausal depression by downregulating $\alpha$-Syn and elevating Syn1 levels [32]; stearoyl-CoA desaturase (SCD) inhibitors can reduce $\alpha$-Syn cytotoxicity by decreasing oleic acid production [33]. Based on these findings, targeting enzymes or lipid transporters involved in lipid metabolism may represent a potential strategy to reduce abnormal $\alpha$-Syn aggregation and exert antidepressant effects. Lipid metabolism abnormalities contribute to depression onset and progression by mediating SNCA overexpression and $\alpha$-Syn abnormal accumulation. Additionally, lipidomics analysis serves as a valuable tool for studying lipid changes in depression, assessing their impact on $\alpha$-Syn-dependent synaptic activity, and helping predict and improve depression prognosis.

### 3.2 Lipid Metabolism and Ferroptosis

Ferroptosis refers to cell death caused by abnormal iron accumulation. Studies have found abnormal iron increases in the hippocampus and prefrontal cortex (PFC) of depressed patients [34]. Additionally, depression patients exhibit lipid metabolism abnormalities related to iron metabolism disturbances, including altered lipid structure and composition and increased lipid peroxidation, suggesting ferroptosis may participate in depression pathogenesis [4].

Abnormal iron accumulation changes lipoprotein content and proportions in serum. Lipoproteins play important roles in the brain, and their alterations affect cerebral lipid metabolism and neurological function, thereby influencing depression onset and development [35]. Lipoproteins are also the main cholesterol carriers, affecting neuronal membrane stability and functional maintenance

by altering cholesterol levels, subsequently causing mood changes. Lipid peroxidation is a primary feature of ferroptosis, with excessive lipid peroxide accumulation occurring through two mechanisms: enzymatic and non-enzymatic pathways. The enzymatic pathway involves fatty acid enzymes catalyzing PUFA conversion to phospholipid hydroperoxides (PLOOH). The GPX4 pathway, regulated by glutathione peroxidase 4 (GPX4), maintains cell membrane integrity by clearing intracellular peroxidized lipids. When GPX4 activity is inhibited or inactivated, the clearance capacity for peroxidized lipids decreases, exacerbating cell membrane damage and ultimately causing cell death [36]. Due to their multiple unsaturated double bonds, PUFA are the most sensitive lipids in ferroptosis and more susceptible to oxidative damage [37], explaining the lower $\omega$-3 and $\omega$-6 PUFA levels in depressed patients [16]. Additionally, PUFA oxidation products can serve as GPX4 substrates, so PUFA oxidation degree affects GPX4 pathway activity. The non-enzymatic pathway involves the Fenton reaction caused by iron metabolism disorders, where free $Fe^{2+}$ promotes oxygen radical generation, triggering lipid peroxidation. This increases levels of oxidized lipid metabolites such as oxidized lipid aldehydes and hydroxyl lipids, causing lipid oxidative damage, destroying cell membrane integrity and stability, and ultimately leading to cell death [37]. Therefore, inhibiting ferroptosis may be effective for depression treatment; ferroptosis inhibitors can exert antidepressant effects by reducing free $Fe^{2+}$ and inhibiting lipid peroxide deposition. Current studies show that sodium hydrosulfide can reduce iron deposition and lipid peroxidation, increase GPX4 and glutamate reverse transporter SLC7A11 expression, and significantly alleviate depression-like behaviors in type 1 diabetic mice [38]. The iron chelator deferoxamine can reverse damage induced by chronic unpredictable mild stress (CUMS) in mice [39]. The free radical scavenger edaravone can improve depression-like behaviors in chronic social defeat stress (CSDS) mice by increasing expression of ferroptosis-related proteins Sirt1, Nrf2, HO-1, and GPX4 [40]. In summary, ferroptosis promotes depression onset and development by altering lipid structure and composition and increasing lipid peroxidation through enzymatic and non-enzymatic pathways, with ferroptosis inhibitors offering new therapeutic approaches.

### 3.3 Lipid Metabolism and Gut Microbiota Dysbiosis

Based on the "brain-gut axis" theory, changes in gut microbiota quantity, composition, and metabolism regulate brain emotions through pathways including the enteric nervous system, autonomic nervous system, endocrine system, and immune system. Compared with healthy individuals, depressed patients exhibit disturbances in Lachnospiraceae, Lactobacillaceae, Streptococcaceae, Erysipelotrichaceae, and Ruminococcaceae, with reduced microbial diversity [5]. Lipid metabolism disorders cause gut microbiota dysbiosis, thereby affecting depression onset and development. Zou et al. [41] found that mice fed a high-cholesterol diet for 6 weeks showed decreased relative abundance of Akkermansia muciniphila (AKK) and exhibited depression-like behaviors. Human studies have observed reduced Bacteroides abundance in severely obese

patients, negatively correlating with serum glutamate levels; higher glutamate levels produce depressive moods by altering neurotransmitter metabolism and neuronal excitability [42]. Conversely, gut microbiota dysbiosis also affects lipid metabolism, leading to depression. Rodent studies show that AKK can reduce fat accumulation, improve blood lipid levels, and increase fat oxidation, positively regulating lipid metabolism [43]. Additionally, AKK significantly improves depression-like behaviors in mice and restores abnormal changes in depression-related neurotransmitters such as 5-HT, corticosterone, dopamine (DA), and brain-derived neurotrophic factor (BDNF) [44]. Jiang et al. [45] found that post-stroke depression rats exhibited gut microbiota disturbances, with the most significant changes in Firmicutes, which altered short-chain fatty acids (SCFAs) and subsequently affected PFC lipid metabolism, particularly glycerophospholipids (GP) including phosphatidylcholine (PC) and glycerolipids (GL) including TG, ultimately inducing depression-like behaviors through a "Firmicutes-SCFAs-lipid metabolism" mechanism. Chen et al. [46] found that in elderly depressed patients, depression severity and cognitive function positively correlated with Akkermansia, which negatively correlated with non-esterified fatty acids (FFA); mediation analysis revealed that Akkermansia affects depressive processes by mediating FFA to overactivate G protein-coupled receptors and induce neuroinflammatory responses. Additionally, some fatty acids and bile acids in lipids have antimicrobial activity; for example, $\omega$-3 PUFA, caprylic acid from medium-chain fatty acids, and cholic acid from bile acids can inhibit growth of pathogenic and putrefactive bacteria, maintaining gut microbial homeostasis [47]. This suggests dietary structure plays an important role in lipid homeostasis; the Mediterranean diet rich in $\omega$-3 PUFA, antioxidants, polyphenols, dietary fiber, and anthocyanins can create a favorable gut microbiota environment, helping maintain healthy lipid metabolism and reduce depression risk. Based on the brain-gut axis theory, the interaction between lipid metabolism abnormalities and gut microbiota dysbiosis can negatively affect mood and mental health, while healthy dietary structures aid depression recovery.

### 3.4 Lipid Metabolism and Mitochondrial Quality Control System Dysfunction

The mitochondrial quality control system, including mitochondrial biogenesis, mitophagy, and mitochondrial repair, is essential for calcium homeostasis, synaptic plasticity, cell survival, and nervous system development [48]. Studies show that mitochondrial quality control disturbances—such as reduced biogenesis, impaired mitophagy, and structural damage—lead to impaired expression of genes encoding mitochondrial proteins, damage to mitochondrial membrane proteins and lipids, electron transport chain (ETC) disruption, and increased mitochondrial oxidative damage, ultimately causing depression [6].

Mitochondrial biogenesis is the process of forming new mitochondria in cells, facilitated by nuclear and mitochondrial genomes. PGC-1$\alpha$ is known as the "master regulator of mitochondrial biogenesis," affecting mitochondrial biosynthesis

and function by regulating transcription of mitochondrial-related genes, playing an important role in depression etiology. Yang et al. [49] found that high-fat diet can induce depression-like behaviors in mice by affecting hippocampal mitochondrial biogenesis and inhibiting the cAMP response element-binding protein (CREB)/PGC-1$\alpha$ signaling pathway. Mitophagy is an early neuroprotective response that clears damaged and aged mitochondria to adapt to cellular stress [50]. The PINK1/Parkin system, induced by PTEN, is the most well-known mitophagy mechanism; after mitochondrial damage, PINK1 rapidly undergoes autophosphorylation and induces depolarized mitochondrial autophagy through a feed-forward mechanism involving Parkin activation [51]. Apolipoprotein E (ApoE) plays an important role in lipid metabolism, affecting cholesterol transport, metabolism, and clearance, while the ApoE4 allele is associated with increased depression risk. Studies show that ApoE4 mice exhibit increased p62 and Parkin1 but decreased P-AMPK$\alpha$ and LC3B II, indicating adverse effects on mitochondrial function. Additionally, ApoE4 first causes mitochondrial dysfunction, making it vulnerable to stimuli that lead to mitophagy defects and increased depression risk [52]. Mitochondrial repair refers to the process of repairing and maintaining damaged mitochondria to restore normal structure and function. However, severe lipid metabolism disorders, oxidative damage, DNA damage, or severe inner/outer membrane structural damage are difficult to repair. Chen et al. [53] found significant metabolic disturbances in fatty acyls, SL, and GP in the intestines of macaques with depression-like behaviors, closely related to mitochondrial dysfunction, along with mitochondrial structural damage due to inhibition of the phosphatidylserine decarboxylase (PSD) pathway that supplies phosphatidylethanolamine (PE) to mitochondria, resulting in decreased PE content, destroyed intestinal homeostasis, and lethal damage to mitochondrial function. Resveratrol, a natural polyphenol antioxidant, can increase PGC-1$\alpha$ levels and mtRNA expression in CUMS mice, promoting mitochondrial biogenesis and exerting antidepressant effects [54]. Cheng et al. [55] found that acupuncture at Shangxing and Fengfu points can improve depression-like behaviors in CUMS rats by mediating autophagy through the PINK1/Parkin pathway to eliminate damaged mitochondria. In summary, mitochondrial quality control system dysfunction causes lipid metabolism abnormalities and plays an important role in depression onset and development, suggesting that maintaining mitochondrial quality control stability could provide new therapeutic approaches.

### 3.5 Lipid Metabolism and Chronic Stress

Chronic stress induces depression mainly through two pathways: HPA axis overactivation and exacerbated inflammatory responses [7]. Lipid changes affect synthesis, release, and reuptake of neurotransmitters related to chronic stress, influencing HPA axis activation. Rodent studies show that long-term high-fat diet triggers neurobehavioral deficits associated with blunted mesolimbic DA function and increases HPA responses, causing metabolic dysfunction and depression-like behaviors [7]. Kim et al. [56] found that $\omega$-3 PUFA supplementa-

tion in depressed rats could regulate brain phospholipid concentrations, increase BDNF, CREB, 5-HT, and glucocorticoid receptor expression, and modulate the HPA axis, producing antidepressant effects. Conversely, lipid metabolism abnormalities can exacerbate inflammatory responses; significantly increased LDL-C, TC, and TG in mouse liver fat upregulate peripheral inflammatory factors such as IL-1$\beta$, monocyte chemoattractant protein 1 (MCP-1), and IL-17A [41]. Excessive inflammatory factors increase phospholipase A2 (PLA2) levels; enhanced PLA2 activity accelerates conversion of linoleic acid to arachidonic acid (AA), which further induces lipid peroxidation to produce pro-inflammatory mediators such as prostaglandins (PG) and leukotrienes (LT), ultimately exacerbating inflammatory responses [57]. Experimental studies show that long-term high-fat diet increases saturated fatty acids (SFA) and significantly decreases PUFA levels in the brain [58]; lower $\omega$-3 PUFA levels have been shown to stimulate neuroinflammation and increase depression risk in both humans and rodents, while $\omega$-3 PUFA supplementation can inhibit neuroinflammation and reduce behavioral indicators of mood deficits [17]. Therefore, $\omega$-3 PUFA can alleviate depressive symptoms by affecting both neurotransmitter systems and reducing neuroinflammation. Studies show that glycyrrhizin can exert antidepressant effects by regulating AA, GP, and hippocampal nerve control of the HPA axis [59]; total flavonoids from Abelmoschus manihot can inhibit inflammatory factors such as TNF-$\alpha$ through GP metabolic pathways to produce antidepressant effects [60]. Thus, lipid metabolism disorders can induce chronic stress through HPA axis overactivation and exacerbated inflammatory responses, promoting depression onset and development, while certain traditional Chinese medicine components can reverse depression progression by alleviating chronic stress through lipid metabolism pathways.

## 4. Future Directions

This article summarizes five intrinsic mechanisms linking abnormal lipid metabolism to depression progression and identifies several limitations, suggesting that future research should strengthen the following five areas: (1) Most current $\alpha$-Syn research focuses on the $\alpha$-Syn 140 isoform, while relationships between other major brain isoforms $\alpha$-Syn 112 and $\alpha$-Syn 98, as well as $\alpha$-Syn fragments $\alpha$-Syn 1-96 and $\alpha$-Syn 65-140, with different lipid categories remain in early stages and require further investigation to determine interactions between different $\alpha$-Syn forms and lipids. (2) Current research on ferroptosis inhibitors for depression treatment is limited and confined to animal studies; more animal and clinical experiments are necessary to investigate the feasibility and safety of ferroptosis inhibitors as antidepressants. (3) We found that the effect of autophagy protein expression levels in the PINK1/Parkin pathway on mitophagy remains unclear and requires in-depth study. (4) GP metabolism disturbances have been found in depressed patients, monkeys, and rodents, and total flavonoids from Abelmoschus manihot have been shown to exert antidepressant effects through GP metabolic pathways in rodents, suggesting GP metabolism may be a potential therapeutic target for depression. More

lipidomics studies are needed to clarify the antidepressant role of GP pathways. (5) Future experiments can target enzymes or lipid transporters involved in lipid metabolism to study regulatory effects on lipid levels, providing new therapeutic strategies for depressed patients.

## 5. Summary

Although lipids are central players in neurophysiology and pathology, their potential impact on depression has received limited attention. Therefore, this article first examined lipid metabolism changes in depressed patients, then elaborated on the comorbid relationships between lipid metabolism-related diseases (including overweight, obesity, and metabolic syndrome) and depression. Next, we summarized five intrinsic mechanisms linking abnormal lipid metabolism to depression progression: specifically, lipid metabolism abnormalities affect depression through SNCA gene overexpression and $\alpha$-Syn abnormal accumulation, ferroptosis, gut microbiota dysbiosis, mitochondrial quality control system dysfunction, and chronic stress. Finally, we proposed future research directions. Lipid metabolomics is a major hotspot today and a valuable tool for exploring molecular pathways in psychiatry. This article provides new feasible perspectives for depression diagnosis and treatment, offering a theoretical foundation for further exploration of the relationship between lipid metabolism and depression.

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