WYCIK, Michał, KONDRATIUK, Gabriela, KRUK, Agnieszka, ŁUPIŃSKA, Marta, STĘPIEŃ, Kamila, KUCIŃSKA, Julia, CHMIELEWSKI, Hubert, WĄDOŁOWSKI, Artur, PRZENIOSŁO, Joanna and KOMAR, Julia. Iron Deficiency in Depressive Disorders: A Review of Mechanisms, Clinical Relevance, and Treatment Perspectives. Quality in Sport. 2025;43:62357. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.43.62357
https://apcz.umk.pl/QS/article/view/62357

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 15.06.2025. Revised: 08.07.2025. Accepted: 08.07.2025. Published: 12.07.2025.

Iron Deficiency in Depressive Disorders: A Review of Mechanisms, Clinical Relevance, and Treatment Perspectives

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Abstract

Purpose of the research:

Iron deficiency (ID) is one of the most common nutritional deficiencies globally and may play a role in the development of depressive symptoms, even in the absence of anemia. This review explores the physiological links between iron status and brain function, examines current evidence on the association between iron deficiency and depression, and evaluates the impact of iron supplementation as a potential adjunctive treatment in depressive disorders.

Materials and methods:

A narrative review was conducted using articles identified from PubMed and Google Scholar. Studies included observational data, clinical trials, and systematic reviews. The analysis focused on populations with iron deficiency (with or without anemia) and assessed the effects of iron status and supplementation on mood and psychiatric symptoms.

Results:

Iron plays a crucial role in monoamine neurotransmitter synthesis, energy metabolism, and brain development. Several studies suggest that ID may contribute to depressive symptoms, including fatigue, apathy, and low mood. Supplementation with iron, both oral and intravenous, has shown potential in improving mood, reducing fatigue, and enhancing response to antidepressant therapy, particularly in populations with iron deficiency without anemia.

Conclusions:

Iron deficiency may be an underrecognized factor in the development and persistence of depression. Routine assessment of iron status and appropriate supplementation could serve as a valuable adjunct in the management of depressive disorders. Further research is needed to establish standardized diagnostic criteria and treatment protocols.

Keywords: iron deficiency anemia, iron metabolism, depression, depressive disorder, neurotransmitters, ferritin, anemia and mental health, iron supplementation and depression, anemia and mood disorders.

Introduction

Depressive disorder (DD) is among the most prevalent mental health conditions worldwide, currently affecting over 300 million people according to the World Health Organization. The etiology of DD is multifactorial, involving both non-modifiable factors such as genetic predisposition and modifiable factors including environmental and nutritional influences. Nutritional deficiencies, particularly in folic acid and vitamin B12, have been increasingly linked to both the onset and severity of depressive symptoms. Consequently, correcting these deficiencies may offer promising avenues for both prevention and treatment.

Iron deficiency anemia (IDA), the most common micronutrient deficiency globally, has also emerged as a possible contributor to depressive symptomatology. Although IDA is primarily known for its hematologic effects, its role in neurological function has attracted growing interest. Symptoms such as fatigue, irritability, and cognitive impairment are common to both IDA and DD, often leading to clinical overlap. Interestingly, several studies have observed improvements in depressive symptoms following iron supplementation, even before hemoglobin levels begin to normalize. This suggests that iron's role in the brain, particularly

in neurotransmitter synthesis and enzyme activity, may be critical to understanding its connection to mood regulation.

Advances in neuroscience have contributed to a deeper understanding of iron homeostasis and its impact on brain function. The distribution of iron within the central nervous system has been implicated in both neurodevelopment and the pathogenesis of psychiatric disorders. Despite the prevalence of both iron deficiency and depressive disorders especially among vulnerable populations such as women of reproductive age and children their interrelationship remains insufficiently explored.

This review aims to examine the evidence linking iron deficiency anemia with depressive disorder, explore the underlying biological mechanisms, and assess whether the severity of anemia correlates with depressive symptomatology. Additionally, it considers the therapeutic potential of iron supplementation in managing depressive symptoms. [21,22]

Material and Methods

A comprehensive review of the literature was conducted using PubMed, Google Scholar. The search focused on studies published in the last 10 years that explored the relationship between iron deficiency anemia (IDA) and depressive disorder (DD), including biological mechanisms, clinical correlations, and therapeutic implications. Both observational and interventional studies were included, as well as systematic reviews and meta-analyses relevant to the topic. For the bibliographic search, the following keywords and their combinations were used: iron deficiency anemia, iron metabolism, depression, depressive disorder, neurotransmitters, ferritin, anemia and mental health, iron supplementation and depression, anemia and mood disorders.

Iron Metabolism and Its Role in Brain Function

Iron is an essential element in the human body, with a daily requirement of approximately 25–30 mg, depending on factors such as age, lifestyle, and gender. Despite its critical role, iron deficiency remains one of the most widespread nutrient deficiencies globally. [1] Within the brain, which utilizes only about 2% of the body's total iron, concentrations range from 0 to 200 μg per gram of tissue in healthy adults. Lower levels are typically observed in white matter and cortical grey matter, where iron concentrations usually remain below 60 μg per gram. Approximately 90% of the brain's iron is stored in ferritin, while a minimal fraction, around 0.05%, constitutes the labile iron pool. [2], [3], [4]

Iron is involved in critical biological processes, including oxygen transport (via hemoglobin), DNA synthesis (as a cofactor for ribonucleotide reductase), and ATP production (within the citric acid cycle and electron transport chain). Maintaining balanced iron levels is vital for cellular function. However, its redox activity enables the generation of reactive oxygen species (ROS), leading to oxidative stress and influencing pathways related to cell survival and death. To manage these dual roles of iron, cells depend on a tightly regulated network of

genes controlling both intracellular and systemic iron metabolism. This regulation is mediated by key proteins, including hepcidin, ferroportin, and transferrin.

The hormone hepcidin, encoded by the HAMP gene and secreted by liver sinusoidal endothelial cells, serves as the primary regulator of systemic iron homeostasis. Hepcidin binds to ferroportin (Fpn), the primary cellular iron exporter, inducing its degradation and leading to iron retention within cells. Hepcidin expression is modulated by cellular and serum iron levels through an iron-sensing signaling pathway. Increased hepcidin levels result in the downregulation of Fpn in key iron-handling cells, such as duodenal enterocytes (responsible for dietary iron absorption), macrophages (recycling iron from erythrocytes), and hepatocytes (the body's primary iron storage site). This mechanism reduces serum iron availability. [5]

Ferroportin, expressed in various cell types, is critical for iron export. It plays a pivotal role in intestinal iron absorption, as evidenced by severe anemia and enterocyte iron accumulation in cases of intestinal ferroportin deletion. Ferroportin exports Fe2+, which must then be oxidized to Fe3+ for binding to transferrin, the plasma iron carrier. This oxidation process is facilitated by the multicopper ferroxidase hephaestin, located on the basolateral membrane of enterocytes. Impaired hephaestin function results in anemia and decreased dietary iron absorption. [6]

Transferrin, a protein carrier that binds two iron atoms (Fe3+) with high affinity, facilitates iron transport across the blood-brain barrier through the transferrin–TFR1 system, with TFR1 prominently expressed on the luminal surface of endothelial cells. Once internalized, iron enters the cytoplasmic pool of these cells and may be exported into the brain's extracellular space, where it can bind again to transferrin or form low-molecular-weight complexes with molecules like citrate, ATP, or ascorbate. Transferrin is synthesized in the brain by oligodendrocytes and the choroid plexus, although secretion occurs exclusively in the latter. Neurons predominantly acquire iron via the transferrin–TFR system and are thought to export excess iron through ferroportin, as many co-express these proteins. [7]

Iron release from duodenal enterocytes and brain microvascular endothelial cells (BMVECs) relies on ferroportin (Fpn) and is regulated by hepcidin. Unlike enterocytes, which are directly exposed to systemic circulation, BMVECs are protected by the blood-brain barrier, highlighting the existence of a unique regulatory system for iron within the central nervous system. Studies suggest that astrocytes produce hepcidin locally, which suppresses Fpn activity in BMVECs through feedback mechanisms that depend on the iron status of astrocytes. Furthermore, the brain predominantly expresses the Fpn1b isoform, which is less sensitive to intracellular iron fluctuations, emphasizing the distinct and specialized role of hepcidin in managing iron balance within the CNS. [8]

Iron turnover in the brain occurs at a slower rate compared to other organs. The process of iron uptake begins at the blood-brain barrier (BBB), where brain microvascular endothelial cells (BMVECs) are the first to interact with the transferrin-iron (Tf-iron) complex. Due to the presence of tight junctions between these cells, iron cannot pass through paracellular pathways, making the transcellular route the primary mechanism for iron entry into the brain.

The regulation is primarily mediated by transferrin receptors 1 and 2 (TFR1 and TFR2). TFR1, the major receptor for transferrin, is widely distributed in neurons, whereas TFR2, with a lower affinity for transferrin, is mainly located in dopaminergic neuron mitochondria and is not regulated by intracellular iron levels. Iron is internalized through endocytosis of the transferrin-iron complex, forming an endosome where acidic conditions facilitate the reduction of ferric iron (Fe3+) to ferrous iron (Fe2+). This reduced iron is then released into the cytoplasm via the divalent metal transporter 1 (DMT1), which also imports non-transferrin-bound iron (NTBI), likely assisted by reductases and proteins like Zip8 and Steap2. NTBI may also enter the brain via the choroid plexus epithelial cells.

Once inside the cytoplasm, iron is utilized for metabolic processes, such as the synthesis of haem groups and iron-sulfur clusters, with excess stored in ferritin or neuromelanin (NM). Ferritin, composed of H and L subunits, can store up to 4500 iron atoms, with H-subunits predominant in neurons, L-subunits in astrocytes and microglia and both forms being equally abundant in oligodendrocytes. Free iron is highly reactive, catalyzing harmful free radical reactions, but ferritin and NM mitigate these effects by storing iron in a harmless form.

Iron is exported from BMVECs through ferroportin, facilitated by the oxidizing activity of enzymes such as ceruloplasmin (CP) or hephaestin (HP). These ferroxidases, which require copper ions, convert Fe2+ to Fe3+ for binding to transferrin or ferritin. Astrocytes are a key source of CP in the brain, producing a glycosylphosphatidylinositol-linked form (GPI-Cp) crucial for brain iron metabolism. A deficiency in GPI-Cp leads to reduced iron oxidation, increased Fe2+ accumulation, and impaired transferrin binding, contributing to oxidative stress and cellular damage. Proper functioning of this system is essential for maintaining iron homeostasis and preventing neurotoxicity. [3], [9], [10]

Iron metabolism is tightly regulated to balance its essential roles, such as energy production and hemoglobin synthesis, with the potential harm of oxidative stress caused by excess iron. Regulation occurs at both cellular and systemic levels. Cellular control involves iron-regulatory proteins (IRP1 and IRP2), which modulate the translation of mRNAs encoding key iron metabolism proteins based on intracellular iron availability. Systemically, the hormone hepcidin, encoded by the HAMP gene, is the primary regulator. Hepcidin modulates iron absorption, recycling, and storage by controlling the expression and degradation of ferroportin, the sole cellular iron exporter. High hepcidin levels reduce iron availability by limiting absorption and release, while deficiency has the opposite effect. Hepcidin also plays a role in the central nervous system, affecting iron transport in astrocytes and microglia and demonstrating anti-inflammatory properties, such as attenuating β-amyloid-induced oxidative stress. Inflammatory stimuli, like lipopolysaccharides or interleukin-6, can significantly upregulate hepcidin expression, which helps mediate the body's response to infection and inflammation. [3]

Iron Deficiency Anemia and Its Neuropsychiatric Manifestations

Iron deficiency anemia (IDA), though not typically considered a life-threatening condition and often underestimated by healthcare providers, can significantly impact overall health.

Symptoms of iron deficiency commonly include fatigue and reduced physical performance, largely attributable to decreased levels of hemoglobin, myoglobin, and cytochromes, which impair oxygen transport and muscle oxygenation. Furthermore, mitochondrial oxidative capacity declines due to diminished synthesis of iron-sulfur proteins.

Given that approximately 20% of the body's oxygen consumption is utilized by the brain, the reduced oxygen delivery associated with anemia adversely affects mental health. Iron is essential for synthesizing neurotransmitters like dopamine and serotonin, as well as supporting mitochondrial function, all of which are critical for brain health. Specifically, iron is necessary for serotonin production, a neurotransmitter closely linked to the development of neuropsychiatric disorders. [11]

Iron deficiency (ID) can affect individuals of all age groups. In individuals aged 65 and older, lower hemoglobin levels and elevated serum transferrin receptor levels are linked to a greater incidence of depressive symptoms. [12] Children are also significantly affected. ID during the first 1000 days of life poses significant risks to brain development. It disrupts critical processes such as myelination, neurotransmitter signaling, and energy metabolism, which are essential for healthy neurological function. These disruptions can negatively impact the development of the visual and auditory cortex, as well as receptive language, speech production, and higher cognitive abilities. Furthermore, the long-term effects may include deficits in recognition memory, impaired motor skills during childhood, and behavioral disorders later in life. [3] Since iron deficiency is the leading cause of most anemia cases, a 2019 study revealed that anemia diagnosed before the 30th week of pregnancy was associated with a modestly increased risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in children, as well as a notably higher risk of intellectual disability. [13] A 2019 meta-analysis also found that anemia during and after pregnancy significantly raised the risk of postpartum depression. [14] These results imply that anemia occurring earlier in pregnancy could negatively affect the child's neurodevelopment.

Neuropsychiatric disorders, including depression and anxiety, are becoming increasingly prevalent, impacting approximately 30% of the global population. These conditions are associated with impairments in neurotransmitter synthesis, reduced neuroplasticity, and compromised neurodevelopment. Iron deficiency has been linked to changes in behavior and development, affecting brain regions such as the hippocampus and striatum, as well as key neurotransmitters like serotonin, norepinephrine, and dopamine. Studies suggest a relationship between insufficient iron intake and a higher occurrence of depression. [15], [16]

Iron plays a crucial part in psychiatric conditions beyond the usual neurodegenerative diseases. Low iron levels in areas such as the basal ganglia and thalamus have been associated with psychotic and schizotypal symptoms in early psychotic disorders, while reduced striatal iron levels in depression are linked to cognitive and emotional deficits. However, these observations mainly pertain to specific forms of iron, like ferritin-bound iron. Post-mortem studies have revealed higher total iron levels despite lower ferritin concentrations in the prefrontal cortex of individuals with schizophrenia, indicating complex mechanisms of iron dysregulation in mental health disorders. [17] Additionally, iron deficiency in the central nervous system is believed to contribute to the pathophysiology of restless leg syndrome

(RLS). Studies have shown that individuals with RLS exhibit significantly lower levels of CSF ferritin and elevated levels of CSF transferrin compared to healthy controls. [18] Furthermore, ID can adversely affect sleep quality, with individuals experiencing iron deficiency anemia reporting poorer sleep compared to healthy controls. This is likely linked to disruptions in neurotransmitter metabolism. As iron is essential for the functioning of neurotransmitters that regulate sleep, its deficiency can result in altered sleep patterns, including changes in REM sleep. [19]

The interplay between iron metabolism and pharmacological treatments adds another layer of complexity to the understanding of anemia, particularly in vulnerable populations such as the elderly. Polypharmacy represents a potential risk factor for various forms of anemia. Iron deficiency anemia can result from the use of commonly prescribed medications such as proton pump inhibitors, H2 receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants. Drug-induced immune hemolysis has also been reported, most frequently associated with cephalosporin antibiotics, beta-lactamase inhibitors, certain chemotherapy agents (e.g., carboplatin, oxaliplatin), and methyldopa. Additionally, some medications may contribute to macrocytic anemia due to deficiencies in vitamin B12 (e.g., proton pump inhibitors, H2 receptor antagonists, or biguanides) or folic acid (e.g., phenytoin, sulfasalazine, methotrexate, trimethoprim). Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), may elevate the risk of anemia by increasing the likelihood of bleeding. This effect is thought to be linked to platelet dysfunction and enhanced gastric acid secretion induced by these drugs. [20]

Evidence linking DD with IDA

A cohort study by Liu et al. (2023), based on data from the China Health and Retirement Longitudinal Study, investigated the relationship between depressive symptoms and anemia in individuals aged 45 and older. The analysis, which included over 10,000 participants at baseline and nearly 6,000 in follow-up, demonstrated that the prevalence of anemia increased with the severity of depressive symptoms. Individuals experiencing depressive symptoms or depressive disorder were more likely to develop anemia over time compared to those without such symptoms. The study also found that hemoglobin levels tended to be lower in participants with higher depression scores, suggesting a biological link between mood disturbances and iron metabolism. These findings support the hypothesis that depression and anemia are interconnected conditions, particularly in aging populations, and underscore the importance of recognizing and addressing comorbid depressive symptoms in patients at risk of or already affected by anemia. [23]

A comprehensive nationwide cohort study conducted by Chen et al. (2020) in Taiwan examined the association between iron deficiency anemia (IDA) and the risk of developing psychiatric disorders, including depression. Utilizing data from the Taiwan National Health Insurance Research Database spanning from 2000 to 2012, the researchers identified adults aged 20 years and older with newly diagnosed IDA. These individuals were matched with non-IDA controls at a 1:2 ratio based on age and gender. The study followed participants until the end of 2013, assessing the incidence of psychiatric disorders.

The findings revealed that individuals with IDA had a significantly higher risk of developing psychiatric disorders compared to those without IDA. Specifically, the adjusted hazard ratio (aHR) for psychiatric disorders in the IDA group was 1.52 (95% confidence interval [CI]: 1.45–1.59). Among the various psychiatric conditions, the IDA group exhibited notably higher incidences of anxiety disorders, depression, sleep disorders, and psychotic disorders.

Importantly, the study also investigated the impact of iron supplementation on the risk of psychiatric disorders among individuals with IDA. The results indicated that IDA patients who received iron supplementation had a significantly lower risk of developing psychiatric disorders compared to those who did not receive supplementation. This suggests that iron supplementation may have a protective effect against the onset of psychiatric conditions in individuals with IDA.

Overall, this study underscores the significant association between IDA and an increased risk of psychiatric disorders, highlighting the potential benefits of iron supplementation in mitigating this risk. [24]

A hospital-based case-control study conducted by Shafi et al. (2018) at Sindh Rangers Hospital, Karachi, between January and July 2017, investigated the association between iron deficiency anemia (IDA) and depressive disorder (DD). The study included 100 patients diagnosed with depressive disorder and an equal number of age- and gender-matched healthy controls, selected through purposive sampling. Diagnosis of depression was made by a consultant psychiatrist using ICD-10 criteria, and symptom severity was measured using the Hamilton Depression Rating Scale (HAM-D), with a minimum score of 8 required for inclusion. Participants were aged 18–60, and individuals with other psychiatric conditions, chronic medical illnesses, or pregnancy/postpartum status were excluded.

Data were collected using a semi-structured questionnaire documenting socio-demographic details and clinical outcomes. Blood samples were analyzed for hemoglobin levels and peripheral blood films. The median hemoglobin level among depressed patients was 11.9 g/dL (IQR=1.27), significantly lower than the 12.9 g/dL (IQR=1.3) found in the control group. This indicated a higher prevalence of anemia among those with depression.

The study concluded that there is a significant relationship between iron deficiency anemia and depressive disorder, with symptom severity appearing to increase alongside the degree of anemia. The authors recommend further research with larger sample sizes to validate these findings. [21]

A recent cross-sectional study utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2005–2010 examined the relationship between iron deficiency and depressive symptoms in nonpregnant women of reproductive age in the United States. The analysis indicated that women with iron deficiency, as measured by elevated transferrin receptor levels or low body iron stores, exhibited higher prevalence of depressive symptoms compared to those with adequate iron status. This association was particularly pronounced among women from low-income backgrounds, suggesting that socioeconomic factors may exacerbate the impact of iron deficiency on mental health. These findings underscore the importance of considering iron status in the assessment and management of depressive symptoms in women of reproductive age, especially in socioeconomically disadvantaged populations. [25]

A web-based cross-sectional study by Hidese et al. examined the relationship between iron-deficiency anemia (IDA) and depression in a large sample of 11,876 Japanese adults, including 1,000 individuals with a self-reported history of depression and 10,876 population-based controls. Psychological distress was assessed using the 6-item Kessler Scale (K6). The study found that a self-reported history of IDA was significantly more common among those with depression than among controls, in both men and women.

Participants with IDA had higher psychological distress scores and lower BMI values than those without IDA, regardless of depression history. Logistic regression analysis confirmed that self-reported depression and psychological distress were positively associated with IDA, while BMI was negatively associated. In women, IDA was also linked to physical conditions such as pregnancy, childbirth, gastric ulcers, and uterine fibroids—factors known to influence iron levels and often co-occurring with depression. However, the association between depression and IDA remained statistically significant after adjusting for these conditions in men but not in women, suggesting a stronger role of biological or nutritional factors in female participants.

Although most individuals with IDA did not report depression, the study supports a weak but meaningful link between iron deficiency and depressive symptoms. The authors note that iron is essential for neurotransmitter synthesis, including dopamine and serotonin, implying a possible biological connection. They propose that addressing IDA might benefit individuals with comorbid depression before initiating antidepressant treatment.

Despite limitations such as reliance on self-reported data and the cross-sectional design, the findings provide preliminary evidence that IDA is associated with a higher prevalence of depression and psychological distress, highlighting the need for further research with clinically validated measures. [26]

Impact of iron supplementation

There is evidence indicating that iron supplementation for iron deficiency may lead to improvements in psychiatric symptoms.

In a 2016 observational study of 412 adult psychiatric patients, Kassir et al. found that the majority (81%) had iron deficiency, defined as a transferrin saturation <30% or serum ferritin <100 ng/mL. Although these thresholds are not standard and may have overestimated the prevalence of deficiency, over half of the iron-deficient patients experienced a reduction or resolution of psychiatric symptoms following treatment with iron supplementation and/or psychotropic medications. Iron therapy appeared to reduce symptoms such as hyperemotivity, anxiety, irritability, aggressiveness, sadness, anhedonia, apathy, asthenia, sleep disorders, dysautonomia, eating disorders, restless-leg syndrome, and cognitive dysfunction—likely through its role in monoaminergic neurotransmitter synthesis. A daily intake of 50–200 mg of elemental iron seemed to enhance the efficacy of psychotropic drugs and even exert antidepressant-like effects. Fewer side effects and psychiatric hospitalizations were observed among patients receiving both iron and antidepressants. Non-responders included those who discontinued the study, were lost to follow-up, had persistent iron deficiency due to nonadherence, or had comorbid somatic conditions affecting iron metabolism. [27]

In a 2021 prospective study, 19 children and adolescents aged 6 to 15 years with serum ferritin levels below 30 ng/mL received oral iron supplementation over a 12-week period. Significant improvements were observed in sleep quality, depressive symptoms, and overall mood, as measured by the Pittsburgh Sleep Quality Index, the Center for Epidemiologic Studies Depression Scale, and the Profile of Mood States (POMS). [28,29]

Some evidence indicates that iron supplementation may improve psychiatric symptoms even in individuals with iron deficiency without anemia. In a 2018 systematic review, Houston et al. evaluated 1,170 adults with iron deficiency but no anemia, treated with oral, intramuscular, or intravenous iron. The study showed a significant improvement in fatigue, although physical capacity remained unchanged. [30]

A randomized, double-blind, placebo-controlled trial by Sheikh et al. evaluated the efficacy of early iron supplementation in non-anemic postpartum women diagnosed with depressive symptoms. Seventy mothers were enrolled one week after delivery and randomly assigned to receive either 50 mg of elemental iron daily or placebo over a six-week period. The iron-supplemented group showed significantly higher post-intervention ferritin levels and a marked reduction in Edinburgh Postnatal Depression Scale (EPDS) scores compared to placebo. Improvement in depressive symptoms was observed in 42.8% of the iron group versus 20% in the placebo group. Notably, women with persistent depressive symptoms had

significantly lower ferritin levels and a higher prevalence of iron deficiency, highlighting the potential role of early iron supplementation in improving postpartum mood disturbances even in the absence of anemia. [31]

Conclusion

Iron deficiency may play an important role in the development and persistence of depressive symptoms, even when anemia is not present. Research shows that low iron levels can affect brain function, especially through its role in producing neurotransmitters related to mood regulation. Several studies suggest that iron supplementation can help reduce symptoms of depression, improve sleep and fatigue, and support the effects of antidepressant treatment.
Although the current evidence is promising, more high-quality studies are needed to better understand this connection and to define clear guidelines for diagnosis and treatment. Recognizing and addressing iron deficiency could become a simple but effective step in supporting mental health, especially in patients with depressive symptoms.

Disclosure

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Receiving funding - no specific funding

All authors have read and agreed with the published version of the manuscript.

Funding statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

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