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AZƏRBAYCAN RESPUBLİKASI ELM və TƏHSİL NAZİRLİYİ
AKADEMİK ABDULLA QARAYEV adına FİZİOLOGİYA İNSTİTUTU

Azərbaycan Milli Elmlər Akademiyası
MƏRKƏZİ ELMİ KİTABXANA

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August 27-29, 2025 / Baku, Azerbaijan

Institute of Physiology named after Academician Abdulla Garayev

PROCEEDINGS BOOK

EDITOR
Prof. Dr. Ulduz Həşimova

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A STUDY OF THE RELATIONSHIP BETWEEN ANEMIA AND SOME PSYCHOLOGICAL PARAMETERS

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ABSTRACT

In this study, our aim is to investigate several connections between anemia and psychological parameters. Anemia is a clinically substantial and global pathology that, affecting all demographic groups, is characterized by a decline in hemoglobin (Hb) concentration threshold, and/or red blood cell (RBC) count physiologically normal threshold, weakens oxygen delivery to tissues. More than 400 anemia types exist, and three reasons for anemia are thought to be main causes of anemia which are blood loss, dysfunctional erythropoiesis, hemolysis. Anemia manifests in several ways, such as insufficient intake of essential micronutrients, for example, folate, cobalamin (B12), Vitamin C, Vitamin A, and especially iron. Formation of these nutrition deficiencies with RBCs and Hb may cause the appearance of nutritional anemia. Genetic mutations also have role in anemia's emergence, for instance, sickle cell anemia (SCA) occurs by an autosomal recessive mutation in the β-globin gene, or thalassemia, another inherited disorder, presents due to mutations in α-globin genes (alpha thalassemia) and β-globin chains (beta thalassemia). In addition to physiological manifestations of anemia, it has also been considered to influence psychological health, with growing recognition of its role in the development of mood disorders, cognitive decline, and overall mental well-being. Over the years, anemia has been associated with a wide array of psychiatric diseases including depression, and anxiety, for example, undesirable outcomes of SCA- which are pain crisis, dissatisfaction of body, sleep disorders, have been concerned to contribute development of depression in patients with SCA. Common symptoms of anemia, which are tiredness, lethargy, faint feeling, headache, or shortness of breath, are also thought to, affecting daily life, be promoters of a variety of psychological matters. Anemia, also associated with cognitive impairment, such as worsening memory, lack of attention, or decreased psychomotor speed, which were also concerned to contribute to development of depression. Role of nutritional deficiencies on mental have been repeatedly mentioned. Crucial role of iron on mood regulation affecting neurotransmitter metabolism has been consistently pointed. In addition to deficiencies, several psychological aspects may emerge due to lack of vitamin B12, such as anger, anxiety, or psychosis. One of the reasons for maternal depression, which has detrimental outcomes for mothers and infants, was also thought to be anemia. Perinatal populations show a consistent clinical signal: a systematic review and meta-analysis reports higher odds of maternal depressive symptoms when anemia is present during pregnancy or postpartum, underscoring

the need to co-manage hematologic status in obstetric mental-health pathways. Besides mood disorders, contemporary evidence supports a bi-directional model linking anemia and psychological distress. Inflammatory signaling particularly interleukin-6 riven hepcidin induction limits iron export via ferroportin, sustaining iron-restricted erythropoiesis; reciprocally, anemia-related fatigue, sleep fragmentation, and activity restriction can amplify distress and reduce self-care, maintaining a feedback loop. This physiology helps explain why psychological symptoms may persist even with mild hematologic abnormalities and motivates integrated screening. In conclusion, these days that prevalence of anemia progressively increases, it is important to have knowledge about connection between anemia and psychological parameters. Therefore, for future studies, further investigations into anemia and its psychological outcomes should be conducted.

Keywords: Anemia, Mental Health, Depression, Anxiety, Cognitive İmpairment

INTRODUCTION

Anemia is clinically substantial pathology that is characterized by a decline in hemoglobin (Hb) concentration threshold, and/or red blood cell (RBC) count physiologically normal threshold, weakens oxygen delivery to tissues (Chaparro & Suchdev, 2019; Deivita et al., 2021). A recent study in 2021 posited that 1.9 billion people suffer from anemia (GBD 2021 Anaemia Collaborators, 2023). Additionally, even though anemia is seen in any part of life span, it demonstrates higher prevalence in pregnant women and infants (Bala et al., 2024; Prasad & Singh, 2022). Several studies also suggested that rural populations are at higher risk of anemia (Mishra et al., 2021; Saxena & Singh, 2023). Chaparro & Suchdev (2019), furthermore, associated Hb concentration with sex differences which starts with puberty due to menstrual cycle and continue throughout reproductive ages (Prochaska et al., 2021; Turner et al., 2023; Yıldız et al., 2021). More than 400 anemia types exist, and, moreover, it occurs due to three main reasons: blood loss, dysfunctional erythropoiesis which is impaired red blood cell production, and hemolysis which is destruction of red blood cells (Chaparro & Suchdev, 2019; Izere, 2025; Sankar & Oviya, 2024). Additionally, anemia can be also manifested in numerous ways (GBD 2021 Anaemia Collaborators, 2023), such as insufficient intake of essential micronutrients, for instance, folate, cobalamin (B12), vitamin C, vitamin A, and especially iron, or genetic mutations, such as sickle cell anemia (Baker et al., 2021; Correa-Agudelo et al., 2021; Deivita et al., 2021; Hakami et al., 2024; Warner & Kamran, 2023). Common symptoms of anemia can be defined as tiredness, lethargy, faint feeling, headache, shortness of breath, and pallor (Manish, 2025; Turner et al., 2023). Anemia manifests in a diverse array of types, and each type can be categorized through distinct factors (Suprapti et al., 2025). It may be classified by morphology of red blood cells (Baldwin et al., 2023): microcytic anemia exhibits a feature that means corpuscular volume is lower than normal (MCV < 80 fL); macrocytic anemia presents with larger red blood cells (MCV > 100 fL); and normocytic anemia is characterized by normal red blood size (MCV = 82-100 fL) (Al-Attar et al., 2020). In addition, it can be present in a way of inheriting, such as sickle cell anemia (SCA) which is a condition is caused by an autosomal recessive mutation in the β-globin gene. SCA is a hereditary blood disorder, affecting millions of individuals worldwide, that is characterized by abnormal hemoglobin which causes red blood cells to occur sickle shape (Essien et al., 2023; Obeagu & Obeagu, 2023; Obeagu et al., 2024; Sankar & Oviya, 2024). The pathogenic feature of SCA is the abnormal sickling and loss of RBCs inducing hemolytic crises, vaso-occlusive crises- occur when RBCs become sickle shape and block small vessels (Zaidi et al., 2021; Zolaly et al., 2019), and severe pain episodes (Bhattacharya et al., 2021; Essien et al., 2023; Mangla et al., 2023; Obeagu, 2024) Thalassemia is another inherited disorder which is a reason of a reduction in the synthesis of α or β chains of hemoglobin (Agastiniotis & Lobitz, 2019; Baldwin et al., 2023;

Gluba-Brzózka et al., 2021; Huang et al., 2020; Kattamis et al., 2021). In an individual without sickness, six globin chains are present (α, β, γ, δ, ε, ζ). Alfa and beta globin chains, within the six globin chains, have crucial role in the ability of hemoglobin to release and bind the oxygen (Bajwa & Basit, 2023; Sankar & Oviya, 2024). The deficient globin chain is defining characteristics of the disease, leading hemolysis or ineffective erythropoiesis (Kattamis et al., 2022; Musallam et al., 2023). Thalassemias can be differentiated according to mutated genes; alpha thalassemia occurs due to mutation in α-globin genes which are located on chromosome 16, and beta thalassemia occurs due to mutation in β-globin chains which are located on chromosome 11 (Ali et al., 2021; Kattamis et al., 2020; Nithichanon et al., 2020; Sadiq et al., 2024). Furthermore, there might be various deficiencies in individuals' body, such as iron, vitamin B12, and other vitamins and minerals that cause nutritional anemia with a formation with red blood cells (RBCs) and hemoglobin (Hb) (Andres et al., 2019; Dhobe & Singh, 2021; Wang et al., 2025). Nutritional anemia represents a significant global health matter across all demographics with particularly elevated susceptibility evident in pediatric populations, women of reproductive age, and geriatric populations, and, also it seems, mostly, in developing countries (Hakami et al., 2023)

ANEMIA SYMPTOMS AND PSYCHOLOGICAL CONSEQUENCES

Psychological facts of anemia have been demonstrated by numerous studies; Hisam et al. (2018) posited several aspects of anemia that profoundly affect individual's mental well-being, such as recurrent therapeutic interventions, reduced life expectancy, and anticipated disease- or treatment-related complications; Ahmed et al. (2023) demonstrated an association between anemia and depression, and untreated cases elevate the likelihood of depression threefold relative to those without anemia. Over the years, anemia has been repeatedly connected with psychological conditions through several aspects that anemia causes. One of them is cognitive impairment. Recent studies revealed that anemia, due to several reasons, such as brain hypoxia, or nutritional deficiencies, may lead to cognitive impairment (Kung et al.,2021; Owais et al., 2021; Tadesse et al., 2019). The construction of cognitive functioning integrates multiple neurocognitive domains, including sustained attention, episodic and working memory systems, perceptual processing speed, executive functions, and metacognitive decision-making abilities (Morozova et al., 2022). In a study Bahrami et al. conducted (2020) with adolescent girls, they found that anemic girls had lowers scores in cognitive ability tasks than non-anemic girls which were memory, inhibitory control and selective attention, decision-making, and planning. Result of the study was a positive correlation between Hb levels and cognitive ability scores. Furthermore, anemia was linked with poorer working memory and diminished processing speed (Kim et al., 2019). Winchester et al. (2018) also mentioned the link between mean corpuscular volume, red blood cell distribution width, and hemoglobin concentration with cognitive functions. Furthermore, Hammar et al., (2022) mentioned a contribution of cognitive deficit to the development of depression. Recent studies indicated that cognitive impairment attenuates individual's mental well-being in the timeline, from earliest cognitive complaints to mild cognitive impairment, or to beginning of dementia; quality of life may decrease, depression or anxiety symptoms may be started to develop (Brain et al., 2025; Gopalakrishnan et al., 2024; Lyu et al., 2024). Complementary to this, decreased cognitive abilities, for instance, worsening memory, lack of attention, decreased psychomotor speed, diminished learning abilities and many more have been demonstrated as obstacles against a good quality of life, such as work problems, or troubles in academic life which may contribute to presentation of depression (Huang et al., 2022; Moir et al., 2018). Stites et al. (2018) found that there is an important negative association between three cognitive complaints- which were cognitive difficulties, distress, and memory- and quality of life, and they also mentioned the relation between

cognitive complaints and several psychological consequences, such as anxiety, depression, stress, and mental well-being in geriatric population. In addition, Kułak-Bejda et al. (2021) also explained suicide risk in geriatric population as a consequence of cognitive impairment due to deficits in executive function, cognitive control, and problem-solving capacity hinder their important abilities to cope with life problems. There is growing evidence that symptoms of anemia which may be fatigue, feelings of weakness, forenamed cognitive impairment, cachexia, or eating disorders that affect individual's mental well-being causing anxiety, depression, loneliness, social isolation (Ahmed & Vasiliadis, 2021; Midilli et al.,2019; Wang et al., 2023). Fatigue and feelings of weakness that are stemmed from anemia restrict people's lives significantly. Recent studies revealed that, low hemoglobin levels were connected with lack of concentration, drop-off in productivity in work, and struggling for pursuing daily activities (Weckmann et al., 2023; Wouters et al., 2019). Likewise, systematic reviews suggested that anemia affects labor productivity from physical and psychological perspective negatively, and with the proper treatment, these negative outcomes of anemia can be regained partially (Marcus et al., 2021). Beyond these limits of physical limitations, fatigue and weakness may affect patients' mental well-being. Persistent low energy levels and fatigue may increase depressive mood, cause a decline in motivation, and confine social life (Moya et al., 2022). Especially postpartum anemia increases depressive symptoms in mothers and effects mother-infant relationship (Bombač Tavčar et al., 2024). Similarly, in geriatric populations, anemia was linked with more fatigue scores, lower muscle power, and loss of psychosocial independence (Neidlein et al., 2021). In addition to contributions of anemia symptoms to development of psychiatric manifestations, sickle cell anemia (SCA) is one of the mentally threatening anemia types due to its common symptoms among patients, such as painful episodes, or sleep distributions can lead mental disorders, for example depression, anxiety (Essien et al., 2023; Obeagu, 2023; Pecker & Darbari, 2019). Essien et al., (2023) also pointed out that stigma which is faced by SCA patients also causes several psychological issues- disturbed sexuality, increased levels of pain and psychological stress, and self-inefficacy. In the other hand, some studies indicated that relationship between SCA and cognitive impairment that affect patients' life quality, others pointed that this relation may be emerged due to low hemoglobin levels (Choi et al., 2019; Stotesbury et al., 2018). Even though the negative correlation between Hb levels and broad range of mental disorders have been indicated (Hosseini et al., 2018; Korkmaz et al., 2015), on the other hand, psychiatric disorders may be present due to lack vitamins, such as iron, vitamin B6, omega 3 fatty-acids, folate, vitamin B12, selenium, and zinc that are crucial for hemoglobin production, formation of red blood cells and may lead nutritional anemia (Andrès et al., 2019; Behera & Balakrishnamony, 2022; Deivita et al., 2021; Salehi-Abargouei et al., 2019). Besides nutritional anemia is common and its prevalence high in developing countries, it affects individuals in all demographic groups, but it was reported that older adults, young children, and women are more prone to nutritional anemia in other patients (Behera, & Balakrishnamony, 2022; Bhadra & Deb, 2020; Hakami et al., 2024). In childhood population, nutritional anemia is concerned to be a determinant factor for reduced physical, cognitive, and emotional capacity, and, moreover, among adults, it is thought to be a negative factor for low productivity, reduced cognitive abilities, and having vulnerable immune system (Dhobe, 2021; Wang et al., 2025). Globally, iron deficiency anemia (IDA) is a disorder which has the highest prevalence among all anemia types (Mishra et al., 2021). Iron is crucial nutrient for human body; it has a significant role several main biological functions, for instance, hemoglobin synthesis, energy metabolism, oxygen transport, immunological modulation, and; it is also important for development and functioning of the brain, myelin production, neurotransmitter metabolism, and synthesis of neurotransmitters (Bhadra & Deb, 2020; Kedir et al., 2024; Qiu et al., 2022; Wu et al., 2023;). Iron deficiency anemia or iron deficiency have been linked with psychiatric manifestations of psychological symptoms over the years by researchers, for

instance, pica- especially pagophagia which is an impulse to eat ice- was strongly connected with iron deficiency anemia, and in most cases, days or weeks after the iron treatment, regression has been seen (Ganesan & Vasauskas, 2023). In a similar manner, link between IDA and restless leg syndrome (RLS) in adults is remarkable; RLS is approved to have a connection in disruption in brain hemostasis and dopaminergic function, the emergence of IDA significantly enhances the prevalence of RLS, and iron treatment has showed considerable healings of symptoms (Short et al., 2024). A decline in sleep quality due to RLS may contribute depression and anxiety symptoms and decrease quality of life; recent studies pointed out that individuals with RLS had higher levels of depression and anxiety comparing to control groups (An, Sun, Yuan, Wu, & Lu, 2024). In a study conducted in Turkey revealed that women with IDA showed significant drop-off comparing to control group in energy/fatigue, physical function, and general health perspective (Yıldırım Baş, 2019). Similarly, to explain IDA effects on mental well-being, recent studies indicated a relationship between role of iron in brain development, dopaminergic neurotransmission, and myelination of white matter, and so, carries several risks for mental health (Pino et al., 2017; Reid & Georgieff, 2023; Uçar et al., 2020). A cohort study conducted with adults demonstrated an increased risk of anxiety, depression, psychotic disorder, and sleep disorders in individuals with IDA, and also showed that iron therapy may decrease the risk of psychiatric manifestations (Lee et al., 2020). This relationship between IDA and psychiatric manifestations can be acceptable biologically; iron is a crucial nutrient for dopamine synthesis; ID or IDA can disrupt mood and sleep affecting myelination and dopaminergic transmission (Kulaszyńska et al., 2024). Anemia also can lead to serious cognitive problems, especially during the brain's most sensitive developmental periods. During adolescence, when the prefrontal cortex matures rapidly and academic skills reach their peak, iron deficiency anemia can permanently impair higher-order mental functions such as planning and abstract thinking. Research shows that low hemoglobin and iron levels negatively impact both cognitive performance and white matter integrity in young people (Larsen et al., 2023). Indeed, even in non-anemic young women, depleted iron stores have been linked to slower planning and poorer executive skills (Scott & Murray-Kolb, 2016).

From a therapeutic perspective, iron supplementation is not just about improving blood counts; it is also a critical intervention for maintaining brain health. This is because iron plays a direct role in the production of neurotransmitters like dopamine and serotonin, which play a crucial role in mood regulation (Lozoff & Georgieff, 2018). Meta-analysis demonstrates that iron supplement may have a significant effect on depression patients with ID (Pakzad et al., 2024). It was also shown that iron treatment has a meaningful curative effect for quality of life and daily functioning, besides hematologic regulations (Mo et al., 2023). Collectively, IDA or ID has been associated with a wide array of psychiatric manifestations such as anxiety disorders, depression, psychotic disorders, and sleep disorders (Lee et al., 2020; Levin & Gattari, 2023).

VITAMIN B12 DEFICIENCY AND PSYCHOLOGICAL OUTCOMES

The other aspect to be a reason for development of mental problems in individuals with anemia may be B12 deficiency. The B vitamins are crucial for the synthesis of neurotransmitters, functioning of the neurological system, methylation, red blood cell production, DNA synthesis, development and maturation of neurological system and brain (Al Mansoori et al., 2021; Kazanci et al., 2016; Kennedy et al., 2024). Cognitive impairment, mood disorders, or idiopathic fatigue have high prevalence in general populations, vitamin B6, vitamin B9, and vitamin B12 are crucial nutrients for myelin and neurotransmitter synthesis, and their deficiencies carry risks for cognitive decline and mental health problems (Markun et al., 2021). Recent studies indicated an association between deficiency of vitamin B12 and a wide array of health issues, which may be anemia, metabolic disorders or several mental problems, such as

cognitive decline- which we mentioned before its role on development of several psychological symptoms-, depression, anxiety, psychotic symptoms, mania, delirium (Hakami et al., 2024; Nichols et al., 2021; Sahoo & Sahu, 2024). Moreover, Kennedy et al. (2024) suggest that neuropsychiatric symptoms that are emerged by the contributions of B12 deficiency necessitate cobalamin treatment, comprising cognitive impairment. Likewise, Yamomoto et al. (2020) reported a case about 57-year-old male with no mental history. His symptoms have started with numbness in his right hand, and developed to some symptoms such as dysstasia, incontinence, and visual hallucinations. They mentioned that all his tests were clear but eventually his blood tests revealed anemia and renal dysfunction, and his B12 levels were low at 190 pg/mL (reference range, 233-914 pg/mL). Yamomoto et al. (2020) also mentioned that in the same case report, after cobalamin treatment his symptoms regressed, however, 41 days after his admission to the university hospital, his cognitive decline symptoms persisted. Neurodevelopmental impacts of B12 are also well-studied; B12 serves as an important coenzyme in chemical pathways that are crucial for neurological health, for example synthesis of monoamine to sustain neurological health, therefore, deficiency of B12 may lead several neurological symptoms, and can lead disruptions in mental well-being (Sangle et al., 2020; Silva, 2024; Taj et al., 2024). Additionally, deficiency of vitamin B12 has been connected with raised plasma homocysteine- which have been also associated with psychiatric manifestations, such as schizophrenia, autism, and mood disorders-. (Esnafoğlu & Yaman, 2017; Tan et al., 2023). Saraswathy et al. (2019) found that there was no relationship between vitamin B12 and depression and generalized anxiety disorder, however, they also reported that patients with hyperhomocysteinemia were linked with anxiety. In addition to homocysteine levels due to B12 deficiency, studies also indicated the emergency of obsessive-compulsive disorder relating homocysteine levels (Yan et al., 2022). Folate and vitamin B12 are essential for converting homocysteine back into methionine. Methionine then produces S-adenosylmethionine (SAMe), which is the main provider of methyl groups in the brain (Elstgeest et al., 2017). SAMe is required for the production of key neurotransmitters such as serotonin, dopamine, and norepinephrine. When this cycle is disrupted, homocysteine levels rise and the balance of neurotransmitters is affected. Over the past decade, research has shown that these changes are linked to depressive symptoms and other mental health problems (Moradi et al., 2021; Liwiński et al., 2023). Clinical studies also suggest that adding L-methylfolate to antidepressant treatment can provide modest benefits, while S-adenosylmethionine supplementation shows supportive but still limited evidence (Cuomo et al., 2020; Gao et al., 2024a). In addition to effects of vitamin B12 deficiency to all demographic groups, it has been repeatedly revealed that vitamin B12 deficiency in pregnancy or throughout childhood negatively impacts neurodevelopment; insufficient levels of vitamin B12 in children was linked with manifestation of depression; anxiety, schizophrenia, obsessive-compulsive disorder were also associated with vitamin B12 in children and adults (Esnafoglu & Ozturan, 2020; Hope et al., 2020; Tan et al., 2023). Psychotic symptoms related to vitamin B12 deficiency are rare but well-documented, and they have been connected to multiple neuropsychiatric conditions such as dementia, delirium, various psychotic disorders, schizoaffective disorder, bipolar disorder, depression, and catatonia. (Blom, 2024; Sahoo & Sahu, 2024). Gboluaje et al. (2018) reported, likewise, a case about 54-old-female who was admitted with hypothermia and cataplexy. Within six months, her symptoms developed to visual hallucinations and social withdrawal. She was misdiagnosed as catatonic schizophrenia, as she did not respond to lorazepam treatment. Eventually, her vitamin B12 deficiency and macrocytic anemia was detected.

VITAMIN D DEFICIENCY AND PSYCHOLOGICAL OUTCOMES

Another aspect of anemia has a role in mental well-being is Vitamin D, which plays a significant role in human body in calcium absorption and homeostasis- affecting bone health and metabolism-, development of brain and its functioning, antioxidant defense system, anti-inflammatory process, and immune modulation (Hill & Aspray, 2017; Lerner et al., 2018; Sassi et al., 2018). Due to role of vitamin D in brain, as vitamin D receptors existence in various brain parts, such as hippocampus, hypothalamus, substantia nigra, and thalamus, its deficiency may lead several neurological diseases; and additionally, due to its part in regulating synthesis of neurotrophins, as well as crucial for biosynthesis of neurotransmitters including acetylcholine, dopamine, and gamma-aminobutyric acid (Máčová et al., 2017; Moretti et al., 2018; Zmijewski, 2019). There is growing evidence that demonstrates the association between vitamin D deficiency and psychiatric manifestations depending on vitamin D role in human body; vitamin D serves as a regulator in serotonin and melatonin regulation which has a crucial contribution for human mental health in sleep, such as restless leg syndrome, sleep apnea, and mood continuation (Huiberts et al., 2021; Singh et al., 2024). Vitamin D has been associated with psychological symptoms repeatedly, for instance, several neuropsychiatric disorders, such as schizophrenia, Alzheimer's disease, and autism (Föcker et al., 2017; Staal., 2016). Furthermore, vitamin D is also thought to be a related factor with the development of depression (Menon et al., 2020; Ronaldson et al., 2022). Cheng et al. (2020) found that vitamin D may change people's negative emotions. In addition to its important role in sleep control and neurotransmitter production, which are linked to some psychiatric problems, vitamin D is also connected with psychological distress and overall quality of life (Alghamdi et al., 2020; Eid et al., 2019; Koduah et al., 2017; Singh et al., 2024). Studies also show that taking vitamin D supplements can help improve life quality and reduce symptoms of depression (Głąbska et al., 2021; Vellekkatt & Menon, 2017).

IRON AND FOLATE: BIOLOGICAL, PSYCHOLOGICAL, AND SOCIAL DIMENSIONS OF ANEMIA

As highlighted earlier, anemia needs to be understood not only as a biological condition but also as a psychological challenge, and these two perspectives should be addressed together. Still, looking only at biology and psychology does not fully capture the complexity of the problem. Recent studies show that social factors—such as community norms and shared perceptions—also play a decisive role. The RANI project in India is a good example: by engaging social expectations and collective understanding, it encouraged greater use of iron–folic acid (IFA) tablets. This approach showed that when medical treatment is supported by social strategies, the outcomes can be much stronger (Kang et al., 2025; Talegawkar et al., 2021; Yilma et al., 2020). These findings revealed that psychosocial interventions and community-based perception management play a critical role in reducing anemia prevalence. However, the effects of iron and folate deficiencies on brain development and cognitive processes cannot be ignored. While iron plays a critical role in dopaminergic neurotransmission, myelination, and oxygen transport; folate is indispensable for DNA synthesis, methylation processes, and neurotransmitter production. The interaction between these two micronutrients becomes pronounced, particularly during the brain's sensitive developmental periods (Cohen Cadosh et al., 2021). When folate and iron deficiencies co-occur, impairments in white matter integrity, weakening of executive functions, and susceptibility to mood disorders may increase (Kaya et al., 2023). Indeed, Kułak-Bejda et al. (2021) reported that impairments in executive functions (planning, cognitive flexibility, inhibitory control, working memory) reduce the capacity of elderly individuals to cope with daily stress and that these deficiencies can increase suicide risk by reinforcing feelings of helplessness, hopelessness, and impulsivity. Therefore, the

psychosocial and cognitive dimensions of anemia, as well as its hematological aspects, must be taken into account. Shaping social norms in the community, when addressed together with biomedical interventions, can offer a holistic approach that strengthens both psychological well-being and brain health and improves long-term health outcomes (Kang et al., 2025; Pickett & Wilkinson, 2015). After discussing iron, the next important nutrient to consider is to be folate. Like iron, folate is closely connected with mental health, and recent systematic evidence indicates that L-methylfolate augmentation can significantly improve depressive symptoms (Al Maruf, Poweleit, Brown, Strawn, & Bousman, 2021). Iron works through dopamine, myelination, and oxygen transport, while folate acts as the main fuel for one-carbon metabolism, often called the brain's "biochemical editing" system. Beyond blood production, folate also affects mood and thinking. It does so through the 5-MTHF → SAMe pathway, meaning the active form of folate helps produce substances like serotonin, dopamine, and norepinephrine, which are linked to happiness and energy. When folate levels are low, homocysteine increases, blood vessel and brain connections weaken, white matter becomes less healthy, and processing speed can slow down (Reynolds, 2014; Shulpekova et al., 2021).Neuroimaging and cohort data have shown that low folate may be associated with reduced hippocampal volume (Scott et al., 2004), changes in prefrontal volume/physiology (Roussotte et al., 2017), and impaired white matter integrity (Beydoun et al., 2020; Kaya et al., 2023); and, in young adults, low circulating folate increases the risk of peripheral neuropathy—it is likely that neuropathic pain and functional loss secondarily pull down quality of life and mood (Taverner et al., 2019). In the clinical picture, concentration difficulty, memory complaints, and anxious-depressive mood are observed in addition to fatigue/pallor/shortness of breath; in diagnosis, serum (short-term) and RBC folate (long-term) should be considered together, B12 must definitely be ruled out and, if necessary, completed with MMA–homocysteine—otherwise, high-dose folic acid can mask the neurological damage of B12 deficiency (Johns Hopkins Medicine, 2025; Reynolds, 2014). In treatment, while oral folic acid is sufficient in most cases with confirmed deficiency, folic acid treatment can provide a modest but significant additional benefit to SSRIs in cases of partial/non-response to depression treatment; this contribution is more visible in subgroups with inflammation/metabolic risk or folate pathway variants and is positioned alongside, not instead of, the antidepressant (Maletic, et al., 2023; Papakostas et al., 2012). From a holistic perspective, iron and folate are two fundamental elements that complement each other in brain health: anxiety, depression, psychotic symptoms, and sleep problems are more frequently seen in individuals with iron deficiency anemia, and these risks can be reduced with appropriate iron treatment (Lee et al., 2020); folate deficiency similarly erodes mood and cognitive skills such as thinking and memory (Ding et al., 2025; Gao et al., 2024b). When the two deficiencies coexist, a "double burden" is created, particularly on "executive functions" like planning, attention, and cognitive flexibility, and on the health of the protective sheath surrounding nerve fibers. Therefore, the treatment approach should aim to correct iron and folate together, not only to restore blood values but also to improve mood, sleep, and general quality of life. At the community level, social norm-focused programs aimed at increasing iron-folic acid use provide broader and more lasting benefits by strengthening the effect of clinical treatments (Kang et al., 2025; Mo et al., 2023; Pakzad et al., 2024; Reid & Georgieff, 2023; Talegawkar et al., 2021).

SLEEP DEPRIVATIONS OF ANEMIA AND MENTAL WELL-BEING

Recent studies indicated the association between anemia and sleep quality due to several reasons, such as pain crisis of SCA, vitamin D, or iron deficiency. When sleep is disrupted, not only does fatigue increase; the risk of experiencing depression, anxiety, and psychotic experiences also rises. Longitudinal data show that the risk of developing depression in

subsequent years is approximately twofold in individuals with insomnia (Baglioni et al., 2011), and other meta-analyses have shown that insomnia predicts the onset of depression (Li et al., 2016). A clue to causality comes from digital Cognitive Behavioral Therapy for insomnia (CBT-I) studies: when sleep is enhanced, not only sleep but symptoms such as paranoia and hallucinations also decrease significantly (Freeman et al., 2017). At the biological mechanism level, sleep deprivation overstimulates the amygdala and weakens the prefrontal cortex's "braking" capacity, increasing emotional fluctuations (Yoo et al., 2007); additionally, there is an increase in inflammation markers (e.g., CRP, IL-6) and disruptions in the brain's glymphatic cleansing system, which accelerates during sleep (Irwin et al., 2015; Xie et al., 2013). At the mechanism level, recent fMRI and behavioral studies show that one night or partial sleep deprivation disrupts the balance in amygdala–prefrontal/anterior cingulate circuits; weakens emotional conflict resolution; and leads to significant changes in broad network connectivity (Ben Simon & Walker, 2020; Lam et al., 2024; Peng et al., 2024). However, some experiments have also reported a temporary increase in amygdala–anterior cingulate connectivity after insomnia, which can be positively correlated with mood; these findings indicate that insomnia can sometimes engage compensatory circuits (Chai et al., 2023). This line connects with the previous section: in a large Chinese cohort, short or very long nighttime sleep was associated with the development of new anemia at follow-up (Liu et al., 2018); in another aspect, adults with anemia have a higher probability of developing insomnia (Neumann et al., 2021), and in iron deficiency anemia, both sleep quality and quality of life may be significantly worse (Sincan et al., 2022). Recent studies reviews also recommend the systematic assessment of iron status (especially ferritin; with CRP if necessary) in individuals with sleep complaints and carefully considering the treatment threshold even if levels are in the low-normal range and symptoms are present (McWilliams et al., 2024). Thus, an approach that simultaneously targets the anemia ↔ sleep ↔ mental health cycle—correcting iron/folate + evidence-based sleep interventions—can accelerate both biological (blood values) and psychological (mood, anxiety, cognition) improvement together (Baglioni et al., 2011; Freeman et al., 2017; Irwin et al., 2015; Liu et al., 2018; Neumann et al., 2021; Sincan et al., 2022; Xie et al., 2013).

CONCULUSION

In conclusion, anemia’s biological consequences are often discussed; however, its psychological side is also far more profound. Among several negative outcomes of anemia, most of them cause such psychological symptoms, for example, in general, depression, anxiety, obsessive-compulsive disorder, bipolar disorder, mania, delirium, sleep disorders, restless leg syndrome, schizophrenia, schizoaffective disorder. Its impact extends from the cellular level—where oxygen delivery, neurotransmitter synthesis, and myelin formation are disrupted—to the broader psychosocial sphere, where fatigue, feeling of weakness, reduced resilience, and social withdrawal interfere with overall well-being. Reduced labor productivity, low academic performance, or low energy to perform daily routines are several consequences of them. Inherited forms such as sickle cell anemia and thalassemia further complicate the picture, as they combine biological fragility with chronic pain, stigma, and emotional burden. Furthermore, several nutritional deficiencies, such as iron, folic acid, vitamin B12, or vitamin D, which are important for mental health in many ways, for example, regulating neurotransmitter metabolism, or contributing development and growth neurological system may also be determinant factors in the emergence of psychiatric disorders. Equally important aspect is the recognition that anemia disproportionately affects vulnerable groups, including women of reproductive age, children, and the elderly, who are already at higher risk for both physical and psychological stressors. Due to anemia often functions as both a symptom and a contributing factor within broader pathological processes. For instance, nutritional anemias

may emerge as secondary consequences of chronic illnesses, while at the same time, deficiencies such as iron, folate, or vitamin B12 may trigger neurological and psychiatric complications of their own. Individuals living in developing countries are at risk of iron, folate and vitamin B12 deficiency due to difficulty in accessing adequate and balanced nutrition individual and societal level, socioeconomic status, education level and dietary habits directly affect the prevalence and severity of anemia.

SUGGESTIONS

These days that anemia shows a progressive increase, it is crucial to have a knowledge about its psychological side also to improve effectiveness of treatment and protect patients' mental well-being. Regarding the existed association between anemia and psychology, it is clear that negative outcomes of anemia which disrupt individuals' mental health are essential to interfere. These consequences require not the only standard hematological correction of anemia but also the compulsory integration of psychological screening for aforementioned diseases into routine patient assessment. individuals needs to be more careful about eating habits and be aware that diseases shall be treated before they get chronical. Clinical management should involve collaboration between hematologists, psychiatrists, psychologists, and nutritionists, ensuring that biological treatment is supported by dietary counseling and psychosocial support. Early diagnosis is important for preventing disease progression and minimizing the psychological complications that are associated with anemia. Moreover, future researches should be conducted to investigate mental wellbeing of anemia patients, therefore, to reduce or cure the emerged mental diseases.

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