COMPREHENSIVE OVERVIEW OF ANEMIA: FROM CLASSIFICATION AND IRON METABOLISM TO RISK FACTORS OF IDA IN SCHOOLCHILDREN

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Abstract

Background: Anemia is one of the most important global public health issues and affects millions of people, with an especially high burden among pediatric populations. **Objectives:** The review gives a comprehensive overview of anemia, detailing its pathophysiological range, causes and clinical significance. It begins with the main types of anemia, such as megaloblastic (vitamin B12 and folate deficiencies), hemolytic, aplastic, anemia of chronic disease and hemoglobinopathies such as sickle cell disease and thalassemia. The attention then shifts to Iron Deficiency Anemia (IDA), the most prevalent subtype globally. We review the complex nature of human iron metabolism, with special emphasis on dietary interactions between heme and non-heme iron, systemic homeostasis by hepcidin and cellular pathophysiology of microcytic hypochromic erythropoiesis. Further, the review critically discusses the risk factors leading to IDA among schoolchildren in the light of a complex interaction between nutritional deficiencies, socioeconomic determinants and physiological demands of growth and risks of chronic infection. Last but not least, we underscore the profound systemic ramifications of untreated IDA in children, especially its long-term effects on neurodevelopment, cognitive performance, educational achievement and immune resilience. Sustained public health strategies such as targeted dietary intervention, community level fortification programs, early diagnostic screening and context specific health policies are needed to reverse the global trend of childhood IDA. **Conclusion:** Anemia encompasses a wide spectrum of disorders, among which Iron Deficiency Anemia (IDA) is the most prevalent, severely impairing neurocognitive development, immune function, and academic growth in schoolchildren. Combating this multifaceted condition requires a proactive, multisectoral strategy focused on targeted iron supplementation, early diagnostic screening, and improved access to adequate nutrition.

Keywords: Anemia, Classification of Anemia, Iron Deficiency Anemia, Iron Metabolism, Pathophysiology, Risk Factors, Schoolchildren.

1. Introduction

Anemia is characterized by a blood hemoglobin (Hb) concentration, hematocrit (HCT), or red blood cell (RBC) count that falls below the normal range, becoming insufficient to support

the body's physiological demands (Felner *et al.,* 2020, Turner *et al.,* 2023). According to criteria established by the World Health Organization (WHO), anemia in adults is diagnosed when hemoglobin levels are below 13.0 g/dL for men and below 12.0 g/dL for women (Patel et al., 2008, Cappellini *et al.,* 2015). It is crucial to consider that normal hemoglobin values are influenced by factors such as sex, age, altitude, smoking habits, pregnancy, and ethnic background,therefore, fixed thresholds may not accurately represent the physiological norm for every individual or population group (Pasricha *et al.,* 2018, Addo *et al.,* 2021). For children, the diagnostic thresholds are lower,for instance, the WHO defines anemia as a hemoglobin level below 11.0 g/dL in children between 6 and 59 months of age (Felner *et al.,* 2020, Braat et al., 2024). Clinically, anemia is considered a sign of an underlying pathological process rather than a standalone disease (Turner *et al.,* 2023). Common symptoms associated with this condition are fatigue, generalized weakness, and pale skin, while more severe cases can present with shortness of breath or cardiovascular complications (Turner *et al.,* 2023). A precise diagnosis typically involves measuring hemoglobin (or hematocrit/RBC count) and comparing the result to a threshold that is appropriate for the individual's specific demographic context (Cappellini et al., 2015, Braat *et al.,* 2024).

2. Types of Anemia

Anemia encompasses a range of disorders where the body has either too few red blood cells or insufficient hemoglobin, leading to a reduced capacity for oxygen transport throughout the body. These conditions are categorized according to their root cause, which could be a lack of iron, deficiencies in certain vitamins, or genetic factors. Some forms of anemia are particularly prevalent in children and women, whereas others often develop as a complication of long-term health issues. Pinpointing the specific type is a critical step for an accurate diagnosis and for choosing the most effective treatment strategy.

2.1. Vitamin B12 Deficiency Anemia (Megaloblastic Anemia)

Vitamin B12 deficiency anemia, also referred to as megaloblastic anemia, is a condition that develops when the body doesn't get enough vitamin B12, a nutrient crucial for producing healthy red blood cells (Langan& Zawistoski, 2017). This insufficiency causes the body to generate unusually large and underdeveloped red blood cells, known as megaloblasts, which leads to anemia (Stabler, 2013).

The primary reasons for a vitamin B12 deficiency are:

- **Pernicious Anemia**: This is an autoimmune disorder where the body attacks the cells that produce intrinsic factor, a protein essential for absorbing B12 (Mayo Clinic, 2025).

- **Gastrointestinal Issues**: Problems with absorption can arise from conditions like Crohn's disease or celiac disease, or from surgeries that remove parts of the stomach or small intestine (National Institutes of Health, 2024).

- **Inadequate Dietary Intake**: This is especially common among individuals following a strict vegan diet, as B12 is naturally found in animal products (Cleveland Clinic, 2025).

People with this deficiency often experience symptoms such as fatigue, pale skin, shortness of breath, dizziness, and numbness or a tingling sensation in the hands and feet. Balance issues and memory difficulties can also occur (Langan& Zawistoski, 2017). Doctors typically diagnose it through blood tests that measure B12 levels, and may also check levels of methylmalonic acid (MMA) or homocysteine for confirmation (Stabler, 2013). Treatment generally involves replenishing B12 stores through oral supplements or injections, with the method chosen based on the cause and severity of the deficiency (Mayo Clinic, 2025).

2.2 Folate Deficiency Anemia

Folate deficiency anemia is another form of megaloblastic anemia marked by large, immature red blood cells (macrocytes) circulating in the blood (Baddam, 2025). It results from an inadequate level of folate (vitamin B9), which is necessary for DNA synthesis and the proper formation of red blood cells (Green, 1999). This deficiency can stem from a diet lacking in folate, conditions that hinder its absorption, increased bodily needs, or certain medications that disrupt how the body uses folate (Baddam, 2025).

The common signs of this anemia include tiredness, paleness, breathlessness, and irritability (Swain, 1997). In more serious cases, neurological symptoms like cognitive difficulties and depression may appear, which are similar to those seen in vitamin B12 deficiency. This similarity makes it critical to tell the two deficiencies apart to ensure a correct diagnosis and the right treatment plan (Miller, 2024).

A diagnosis is confirmed by lab tests showing low folate levels in the serum or red blood cells, high Mean Corpuscular Volume (MCV), and the presence of megaloblastic cells in bone marrow samples (Green, 1999). Distinguishing it from B12 deficiency is vital because treating a B12 deficiency with just folic acid can improve the anemia but allow irreversible neurological damage to progress (Miller, 2024).

The treatment involves folic acid supplements, which are very effective at correcting the anemia. However, it's important to check a patient's vitamin B12 levels during treatment to avoid masking an underlying B12 deficiency (Swain, 1997). Public health strategies, like the mandatory fortification of flour and grains with folic acid, have successfully reduced the number of folate deficiency cases in many parts of the world (Odewoleet al., 2013).

In summary, folate deficiency anemia is a manageable condition that requires prompt diagnosis and correct treatment. Public health initiatives are fundamental in preventing this deficiency and its related health problems (Odewole et al., 2013, Baddam, 2025).

2.3 Hemolytic Anemia

Hemolytic anemia is a disorder where red blood cells are destroyed prematurely, shortening their lifespan and leading to a shortage of healthy cells to carry oxygen throughout the body (Phillips & Henderson, 2018). This destruction can happen inside the blood vessels (intravascular) or in organs like the spleen and liver (extravascular) (Tabbara, 1992).

The causes are broadly divided into two groups. Intrinsic causes are hereditary, meaning the red blood cells themselves have a defect, as seen in conditions like sickle cell disease or

hereditary spherocytosis (Phillips & Henderson, 2018). Extrinsic causes, on the other hand, come from outside the red blood cell and include autoimmune attacks, infections, or physical damage to the cells (Tabbara, 1992).

Patients often experience fatigue, paleness, jaundice (yellowing of the skin), and dark urine. Key lab tests that help confirm the diagnosis include a high reticulocyte (immature red blood cell) count, elevated lactate dehydrogenase (LDH), high levels of unconjugated bilirubin, and low haptoglobin (Tabbara, 1992). A specific test called the direct antiglobulin test (Coombs test) is crucial for identifying immune-related causes (Phillips & Henderson, 2018).

Treatment is tailored to the underlying cause. For autoimmune hemolytic anemia, corticosteroids or immunosuppressive drugs like rituximab are standard (Jäger *et al.*, 2020). For some hereditary conditions, management may involve supportive care or, in selected cases, surgical removal of the spleen (splenectomy) (Tabbara, 1992).

2.4 Aplastic Anemia

Aplastic anemia (AA) is a rare but serious disorder where the bone marrow fails to produce enough blood cells, leading to a condition known as pancytopenia (Young, 2010). In most acquired cases, the body's own immune system, particularly T-cells, mistakenly attacks the blood-forming stem cells. Inherited forms are linked to genetic mutations, such as those affecting telomerase (Shallis *et al.,* 2018). Known triggers include exposure to certain drugs, chemicals, or viral infections (Nimmana, 2025). The disease is more common in Asia than in the West, with an annual incidence of 2–6 cases per million people (Montané *et al.*, 2008).

Symptoms result from the low levels of all blood cells: fatigue from anemia, frequent infections from neutropenia, and bleeding or bruising from thrombocytopenia (Nimmana, 2025). The main treatment options are immunosuppressive therapy (often with anti-thymocyte globulin and cyclosporine) or a hematopoietic stem cell transplant, with the choice depending on the patient's age and whether a suitable donor is available (Young, 2006). With modern treatments, survival rates now exceed 80% for many patients (de Latour, 2024).

2.5 Anemia of Chronic Disease

Anemia of chronic disease (ACD), or anemia of inflammation, is the second most common anemia globally, especially among hospitalized patients and the elderly with conditions like chronic infections, cancer, autoimmune diseases, or kidney failure (Wiciński et al., 2020, de Las Cuevas Allende et al., 2021).

The root cause is ongoing inflammation. Inflammatory cytokines (such as IL-6) trigger the liver to produce more hepcidin, a hormone that blocks iron absorption in the gut and traps iron in storage cells, making it unavailable for making new red blood cells (Means, 1995, de Las Cuevas Allende *et al.,* 2021). Furthermore, these cytokines can suppress the production of erythropoietin (EPO) and make the bone marrow less responsive to it, further reducing red blood cell production (Means, 1995,Wiciński *et al.,* 2020). Inflammation can also shorten the lifespan of existing red blood cells (Means, 1995,Thomas & Thomas, 2005).

Lab tests typically show a mild to moderate, often normocytic anemia, with low serum iron, normal or low transferrin, and high ferritin levels (which acts as an acute-phase reactant) (Thomas & Thomas, 2005,Wiciński*et al.,* 2020). A key feature is "functional iron deficiency,"

where iron stores are present but inaccessible for use (Thomas & Thomas, 2005,Murawska *et al.*, 2016).

Diagnosing ACD involves ruling out other causes, particularly iron deficiency, and interpreting a combination of tests, including ferritin, transferrin saturation, and sometimes newer markers (Thomas & Thomas, 2005,de Las Cuevas Allende et al., 2021). The primary goal of treatment is to manage the underlying chronic condition. If anemia is severe, treatments may include erythropoiesis-stimulating agents (ESAs) and intravenous iron supplementation (Murawska et al., 2016, de Las Cuevas Allende *et al.*, 2021). Future therapies are exploring drugs that target hepcidin or specific inflammatory cytokines (de Las Cuevas Allende *et al.*, 2021). The outlook for patients largely depends on how well the underlying chronic disease is controlled (Wiciński et al., 2020,de Las Cuevas Allende et al., 2021).

2.6 Sickle Cell Anemia

Sickle cell anemia (SCA) is an inherited blood disorder caused by a specific genetic mutation in the beta-globin gene. This mutation leads to the production of an abnormal hemoglobin, called hemoglobin S (HbS), which causes red blood cells to become rigid and sickle-shaped, especially under conditions of low oxygen or stress (Kato et al., 2018,Elendu, 2023). These misshapen cells are fragile and prone to bursting (hemolysis), and they can block small blood vessels—a process known as vaso-occlusion. This blockage cuts off oxygen supply to tissues, leading to pain, organ damage, and a cascade of complications (Kato et al., 2018, Elendu, 2023).

The clinical picture of SCA is complex, featuring chronic anemia, episodes of severe pain known as vaso-occlusive crises, and a high risk for serious conditions like stroke, acute chest syndrome, and infections due to damage to the spleen (Brandow&Liem, 2022, Kavanagh *et al.*, 2022). The severity of the disease varies significantly from person to person, influenced by factors such as the exact genotype, the level of fetal hemoglobin, and other genetic and environmental modifiers (Kato *et al.*, 2018, Egesa *et al.*, 2022). Early detection through newborn screening is vital, as delays in diagnosis, particularly in resource-limited areas, are a major cause of early childhood mortality (Egesa *et al.*, 2022,Kavanagh *et al.*, 2022).

Treatment strategies have advanced considerably. Hydroxyurea is a foundational therapy that works by increasing fetal hemoglobin, which helps prevent sickling and reduces the frequency of pain crises (Brandow& Liem, 2022, Kavanagh *et al.*, 2022). Newer medications like L-glutamine, voxelotor, and crizanlizumab offer additional options to manage the disease. Regular blood transfusions are used to prevent stroke and treat acute complications, though they carry risks like iron overload and immune reactions (Kato et al., 2018). Currently, the only cure is a hematopoietic stem cell transplant, but its use is limited by the need for a matched donor and the associated risks (Brandow& Liem, 2022,Kavanagh *et al.*, 2022). Promising research into gene therapy and gene editing offers hope for future curative treatments (Kavanagh *et al.*, 2022, Patel *et al.*, 2024). Despite these advances, SCA still reduces life expectancy in many parts of the world and can significantly impact quality of life due to chronic pain and organ damage (Kato *et al.*, 2018,Egesa *et al.*, 2022).

2.7 Thalassemia

Thalassemias are a group of inherited disorders characterized by a defect in the production of hemoglobin's globin chains, most commonly the alpha (α) or beta (β) chains (Sanchez-Villalobos *et al.,* 2022, Bajwa& Basit, 2023). This imbalance causes the body to inefficiently produce red blood cells and leads to their premature destruction, resulting in chronic anemia.

In α-thalassemia, gene deletions reduce alpha-globin production, with severity depending on how many of the four alpha-globin genes are missing. The most severe form, involving the loss of all four genes, results in a condition called hydrops fetalis (Bajwa& Basit, 2023). In β-thalassemia, mutations in the HBB gene lead to reduced or absent beta-globin synthesis. The resulting excess alpha chains form precipitates that damage developing red blood cells in the bone marrow, a process known as ineffective erythropoiesis (Sanchez-Villalobos *et al.,* 2022).

The clinical spectrum is wide, ranging from asymptomatic carriers to a severe, transfusion-dependent form (thalassemia major) that appears in infancy (Baird *et al.,* 2022, Needs, 2023). The primary treatment for thalassemia major is regular blood transfusions, but this inevitably leads to iron overload, which must be managed with chelation therapy to prevent damage to the heart, liver, and endocrine system (Kattamis *et al.,* 2022, Needs, 2023).

Management is lifelong and involves a multidisciplinary approach, including transfusions, iron chelation, and monitoring for complications. A hematopoietic stem cell transplant can be curative for some eligible patients (Kattamis *et al.,* 2022). New therapies under investigation aim to increase fetal hemoglobin, use gene editing, or better manage iron levels (Sanchez-Villalobos et al., 2022). Access to comprehensive care dramatically influences outcomes,in many low- and middle-income countries, the disease burden remains high due to limited resources (Kattamis *et al.,* 2022). Early diagnosis through screening and consistent, specialized care are essential for improving life expectancy and quality of life (Bajwa& Basit, 2023).

2.8 Iron Deficiency Anemia

Iron deficiency anemia (IDA) is the most prevalent type of anemia globally. It develops when the body lacks sufficient iron to produce hemoglobin, which can result from inadequate dietary intake, chronic blood loss (e.g., from the gastrointestinal tract or heavy menstrual periods), or an inability to absorb iron properly (DeLoughery, 2017, Warner & Kamran, 2023).

Common symptoms include fatigue, pale skin, and shortness of breath. Laboratory tests typically reveal microcytic (small) and hypochromic (pale) red blood cells, and the diagnosis is confirmed by low levels of hemoglobin and serum ferritin, a key indicator of iron stores (Cappellini *et al.,* 2020). The treatment approach has two pillars: identifying and addressing the underlying cause of the iron deficiency, and replenishing iron stores. Oral iron supplements are the first-line treatment, while intravenous iron is reserved for cases where oral therapy is ineffective, not tolerated, or when a rapid correction is needed (DeLoughery, 2017).

3. Overview of Iron Deficiency Anemia

3.1. Definition of Iron Deficiency Anemia

Iron deficiency anemia (IDA) is a specific form of anemia where low hemoglobin levels result from inadequate iron reserves in the body, which in turn impairs the production of red blood cells (Cappellini, *et al.*, 2020, Auerbach, DeLoughery, &Tirnauer, 2025). A peripheral blood smear typically reveals microcytic (small-sized) and hypochromic (pale-staining) erythrocytes, reflecting the disruption in hemoglobin synthesis (DeLoughery, 2017, Warner & Kamran, 2024). As the most prevalent nutritional deficiency globally, IDA disproportionately impacts children, women of reproductive age, pregnant women, and the elderly (Cappellini et al., 2020, Leung *et al.*, 2024,). The manifestations extend beyond anemia itself and can include fatigue, cognitive impairment, restless legs syndrome, pica, and reduced physical work capacity, sometimes even before a significant drop in hemoglobin occurs (Auerbach et al., 2025, Leung *et al.*, 2024). The development of IDA follows a sequential pattern, beginning with the depletion of iron stores (indicated by low ferritin), progressing to a decline in transport iron (shown by low serum iron and low transferrin saturation), and finally leading to a reduction in hemoglobin production (DeLoughery, 2017,Cappellini *et al.*, 2020). Diagnostic criteria can vary,in individuals without inflammation, a serum ferritin level below 30 ng/mL or a transferrin saturation under 20% are frequently used indicators (Auerbach et al., 2025). However, in the presence of inflammation, ferritin levels can be falsely elevated, necessitating the use of adjusted thresholds or additional biomarkers for an accurate diagnosis (Cappellini *et al.*, 2020). The etiology of IDA involves several mechanisms, including insufficient dietary intake, malabsorption due to gastrointestinal disorders, increased physiological demands during growth or pregnancy, and chronic blood loss from menstrual or gastrointestinal sources (DeLoughery, 2017, Leung et al., 2024). Clinical presentation may range from no symptoms to signs such as pallor, tachycardia, exertional dyspnea, and dizziness, particularly as the anemia becomes more severe (Leung et al., 2024). Laboratory findings commonly include a low mean corpuscular volume (MCV), low mean corpuscular hemoglobin (MCH), and an elevated red cell distribution width (RDW), alongside the characteristic abnormalities in iron studies (Cappellini et al., 2020, Warner & Kamran, 2023). Management focuses on replenishing iron stores through diet and supplementation, identifying and treating the underlying cause, and considering intravenous iron therapy when oral iron is not tolerated or is ineffective (Auerbach et al., 2025). If left untreated, prolonged IDA, especially in children, can lead to developmental delays, persistent cognitive deficits, and poorer outcomes with other illnesses (Leung et al., 2024). Preventive strategies emphasize ensuring adequate dietary iron, food fortification programs, screening high-risk populations, and managing conditions that cause blood loss (DeLoughery, 2017, Cappellini et al., 2020). The red blood cells in IDA are distinctly microcytic and hypochromic, appearing smaller and paler than normal when stained (Vogelsang, 2018). They also exhibit anisopoikilocytosis, which is a variation in size (anisocytosis) and shape (poikilocytosis), with the presence of abnormal forms like elliptocytes, target cells, and dacrocytes (teardrop cells) (Armata, 2025). An increased RDW is a key laboratory feature that quantifies this red blood cell size variability and is a hallmark of iron deficiency anemia (Vogelsang, 2018).

.2. Global Burden of Anemia in Children

Anemia continues to be a major public health challenge for children under five years old worldwide, with significant negative implications for their overall health, physical growth, cognitive development, and survival rates (GBD 2019, 2022). Data from the Global Burden of Disease Study 2019 highlights the considerable impact of this condition, showing a Years Lived with Disability (YLD) rate of 1,252.88 per 100,000 children in this age group (95% UI:

831.62-1,831.34). The study further breaks down the prevalence, indicating that moderate anemia was the most common form at 985.46 per 100,000 (95% UI: 646.24-1,450.49), which was substantially higher than the rates for severe anemia (197.82 per 100,000,95% UI: 132.53-277.80) and mild anemia (69.59 per 100,000,95% UI: 24.62-152.53). The overall global prevalence was estimated at 39,517.75 cases per 100,000 population (95% UI: 38,784.81 - 40,239.62) (Y Liu, 2024).

The distribution of this burden is highly inequitable. Children in regions with a low Socio-Demographic Index (SDI), particularly in Sub-Saharan Africa and South Asia, bear the highest rates of anemia and associated years lived with disability (Y Liu, 2024). Moderate anemia was identified as the primary driver of the total YLDs globally, although severe anemia remains a significant concern in settings with limited healthcare resources (Y Liu, 2024). Analysis of trends from 1990 to 2019 reveals that while some global progress has been made, the decline in prevalence has been inconsistent, with many low-income countries showing minimal improvement (Y Liu, 2024). Research synthesizing multiple studies suggests that the worldwide prevalence of iron deficiency anemia (IDA) specifically in children under five is approximately 16.4%, with the highest concentrations found in Asia and Africa. The prevalence of iron deficiency without anemia is even greater, affecting an estimated 17.9% of young children (S Gedfie et al., 2022).

Established risk factors contributing to this high burden include being under two years of age, having a mother with anemia, low birth weight, inadequate consumption of iron-fortified foods, coming from a large family, and having a mother with a low level of education (S Gedfie et al., 2022). These factors contribute to stark regional disparities,in some areas of Sub-Saharan Africa and South Asia, more than half of all children under five are anemic, a rate far exceeding that of high-SDI regions (Y Liu, 2024). The long-term consequences of early childhood anemia are profound, linking to impaired cognitive development, poorer academic achievement, stunted physical growth, and an increased vulnerability to infectious diseases (S Gedfie et al., 2022). The situation is often worse among refugee and displaced populations, where anemia prevalence can exceed 36%, underscoring the powerful role of socioeconomic and environmental determinants (S Gedfie et al., 2022). Emerging threats, such as climate change and rising temperatures, may further intensify the problem in vulnerable areas (S Gedfie et al., 2022). Despite some progress, the absolute number of affected children remains high due to population growth and the persistence of underlying risk factors in many parts of the world (Y Liu, 2024). Proven interventions to address this issue encompass iron supplementation, enhanced maternal and child nutrition, food fortification, and malaria control. Sustained reduction of anemia prevalence globally will depend on effective monitoring, strategies focused on equity, and policies tailored to local contexts (Y Liu, 2024,S Gedfie et al., 2022).

3.3 Public Health Significance of IDA

Iron deficiency anemia is recognized as one of the most common nutritional disorders affecting children on a global scale, with a particularly heavy burden in low- and middle-income countries (Leung & Leung, 2024). It is identified as the primary cause of anemia in pediatric populations and constitutes a significant public health challenge (Stoltzfus, 2001). The condition exerts a considerable impact on neurodevelopment, leading to long-term

impairments in cognitive and motor function that can persist as deficits in learning, behavior, and academic performance, even after iron levels have been restored (Hassan et al., 2016).

Furthermore, IDA compromises the immune system, making children more susceptible to infections and increasing associated illness rates (Hassan et al., 2016). Affected children may also exhibit slower physical growth and a failure to achieve key developmental milestones, which adversely affects their overall health and quality of life (Leung & Leung, 2024). From an economic perspective, childhood anemia can diminish future productivity, as individuals who experienced it early in life may have a reduced work capacity in adulthood (Stoltzfus, 2001).

Public health strategies designed to reduce IDA include programs for iron supplementation, promotion of diverse diets, and fortification of commonly consumed foods. These approaches have demonstrated effectiveness in raising hemoglobin levels and lowering the prevalence of anemia in children (Felix et al., 2025,Kumar, 2022). Implementing early screening and intervention is considered vital, especially for groups identified as high-risk (Kumar, 2022). Consequently, addressing IDA is critical not only for improving immediate child health outcomes but also for fostering better long-term societal development and economic productivity (Stoltzfus, 2001,Leung & Leung, 2024). In essence, IDA in children represents a major public health issue with extensive consequences, necessitating the implementation of effective measures to lessen its burden and support healthy development (Felix et al., 2025).

3.4 Impact on Growth and Development

Iron deficiency anemia has a marked influence on both the physical and developmental trajectories of children. Infants and young children with IDA frequently show delays in motor development, which can endure even after receiving iron treatment (Shafir et al., 2006). Research conducted by Lozoff et al. (1991) indicated that children who had moderate anemia during infancy achieved lower scores on assessments of mental and motor function when they began school compared to children who had sufficient iron status.

The effects of IDA also encompass cognitive and socio-emotional domains. According to Lozoff (2007), infants between 6 and 24 months of age with IDA are at an increased risk for deficits in cognitive, motor, social-emotional, and neurophysiologic development. These early delays can have enduring consequences that persist after the iron deficiency has been treated (Lozoff, 2007). The impact is not confined to early childhood. Among school-aged children, iron supplementation has been associated with improvements in cognitive functions, including attention, memory, and intellectual performance (Gutema et al., 2023). However, evidence regarding its effect on broader measures of school achievement is less definitive (Gutema et al., 2023).

3.5 Educational and Cognitive Consequences

The educational and cognitive implications of iron deficiency anemia in children are profound and can influence development over the short and long term (Lozoff et al., 2000). Children who suffer from chronic iron deficiency in infancy often demonstrate lower cognitive performance later in childhood and adolescence, despite subsequent iron supplementation (Gingoyon et al., 2022). Iron plays an essential role in brain development, supporting key processes like myelination, the synthesis of neurotransmitters, and energy metabolism, all of which are fundamental to learning and memory (Lozoff, 2007).

Investigations have shown that severe or prolonged IDA early in life is linked to impairments in attention, memory, language skills, and executive function (Grantham-McGregor et al., 2001). These impairments can lead to a lack of readiness for school, lower academic accomplishment, and a higher probability of repeating grades (Lozoff et al., 2000). Even iron deficiency that has not progressed to overt anemia has been associated with lower scores on standardized tests in mathematics and reading, indicating that optimal cognitive function requires sufficient iron levels (Halterman et al., 2001).

IDA also influences socio-emotional development, leading to a higher incidence of behavioral issues such as irritability, less social interaction, and reduced motivation to learn (Lozoff, 2007). These behavioral challenges can further obstruct academic performance and relationships with peers, compounding educational difficulties. Analyses of multiple studies confirm that providing iron supplements to anemic children can enhance attention span, learning capacity, and problem-solving skills, though the degree of improvement varies with the severity and duration of the prior deficiency (Gingoyon et al., 2022).

Importantly, because iron deficiency during critical windows of brain development can lead to some irreversible cognitive deficits, early identification and preventive measures are crucial (Grantham-McGregor et al., 2001). This highlights the necessity of strategies such as iron-fortified foods, supplementation programs, and routine screening for at-risk groups (Halterman et al., 2001). Tackling IDA in early childhood is thus not just a health imperative but also an educational one, as it shapes a child's intellectual and socio-emotional growth (Lozoff et al., 2000,Gingoyon et al., 2022). In summary, iron deficiency anemia significantly undermines cognitive development, learning ability, and educational outcomes in children. Implementing effective public health strategies for prevention, early detection, and timely treatment is essential to mitigate these long-term effects and ensure children reach their full developmental potential (Lozoff, 2007).

4. Iron Metabolism and Pathophysiology

4.1 Dietary Sources of Iron (Heme and Non-Heme Iron)

Iron in the human diet is categorized into two primary types: heme iron and non-heme iron. Heme iron is derived predominantly from animal products like red meat, poultry, fish, and seafood. Non-heme iron, on the other hand, is obtained from plant-based sources such as legumes, leafy green vegetables, whole grains, nuts, and fortified food products (Carpenter & Mahoney, 1992).

A key difference between the two lies in their absorption. Heme iron is absorbed with relatively high efficiency, typically between 15% and 35%, and its absorption is minimally affected by other dietary components. Conversely, the absorption of non-heme iron is generally lower, ranging from 2% to 20%, and is highly susceptible to influence from dietary enhancers, like vitamin C, and inhibitors, such as phytates (found in grains and legumes), tannins (in tea and coffee), and calcium (Monsen& Hallberg, 1988).

While non-heme iron constitutes the larger proportion of iron consumed worldwide, its lower bioavailability presents a challenge. The inclusion of even small amounts of heme iron in a meal can enhance the total amount of iron absorbed due to its high efficiency (Pişkin et al., 2022). For instance, plant foods like legumes and leafy greens are rich in non-heme iron, but to maximize absorption, they should be consumed alongside enhancers like vitamin C-rich

foods or animal proteins (Pişkin et al., 2022). This is why diets that combine both animal and plant sources are considered most effective for maintaining optimal iron status (Vandevijvere et al., 2013).

In typical Western diets, the primary sources of heme iron are red meat and fish, while cereals, vegetables, and legumes provide most of the non-heme iron (Pipoyan et al., 2023). Populations that rely mainly on plant-based diets are at a higher risk of iron deficiency because of the lower bioavailability of non-heme iron (Kalman et al., 2025). Therefore, practical dietary approaches, such as consuming fruits rich in vitamin C with plant-based meals or including modest amounts of meat, are recommended strategies to improve the absorption of non-heme iron and help prevent iron deficiency anemia (Monsen& Hallberg, 1988).

4.2 Absorption and Transport of Iron

The process of iron absorption occurs primarily in the duodenum. For non-heme iron, which is in the ferric (Fe^{3+}) state in food, the initial step involves reduction to the ferrous (Fe^{2+}) form by enzymes known as ferrireductases (e.g., duodenal cytochrome b) located on the intestinal lining. This ferrous iron is then transported into the enterocyte (intestinal cell) by the divalent metal transporter 1 (DMT1) (Guo, Frazer, & Anderson, 2016,Okazaki, 2024). Once inside the cell, iron can be stored by binding to the protein ferritin or used for cellular functions. The iron destined for the body's systemic circulation is exported across the basolateral membrane of the enterocyte into the blood via the transporter ferroportin. This process often involves the assistance of a ferroxidase enzyme, such as hephaestin, which converts Fe^{2+} back to Fe^{3+} so it can bind to the plasma protein transferrin for transport (Gateways of Cellular & Systemic Iron Homeostasis, Knutson, 2017,Okazaki, 2024).

Heme iron, derived from animal sources, is absorbed via a separate pathway. It is taken up into the enterocyte as an intact heme molecule through specific heme transporters. Inside the cell, the enzyme heme oxygenase breaks down the heme, releasing ferrous iron (Fe^{2+}) that then joins the same intracellular pool as non-heme iron (Conrad, Umbreit, & Moore, 1999,Okazaki, 2024). The systemic regulation of iron absorption and release is critically controlled by the hormone hepcidin. When body iron stores are adequate or during inflammation, hepcidin levels rise and cause the degradation of ferroportin, thereby reducing the amount of iron released from enterocytes and other storage sites into the bloodstream (Guo et al., 2016,Okazaki, 2024).

Disruptions in this complex system, whether from genetic or acquired causes affecting proteins like DMT1, ferroportin, or the regulation of hepcidin, can lead to disorders of iron homeostasis, resulting in either iron deficiency or iron overload (Okazaki, 2024,Wessling-Resnick, 2000).

4.3 Storage forms (Ferritin, Hemosiderin)

The body's iron reserves are primarily held in two intracellular storage forms: ferritin and hemosiderin. Ferritin is a soluble and readily mobilizable protein complex that serves as the main iron storage depot, located in tissues such as the liver, spleen, bone marrow, duodenum, and skeletal muscle (Saito, 2014). Its structure consists of a protein shell that encloses a mineral core where iron is stored in the ferric (Fe^{3+}) state, enabling the safe sequestration and detoxification of free iron (Zuyderhoudt, Sindram, Marx, Jörning, & van Gool, 1983).

Hemosiderin, in contrast, is an insoluble aggregate that forms predominantly from the partial degradation of ferritin and other cellular materials. Its accumulation becomes more prominent when iron stores are elevated and ferritin's storage capacity is approached or exceeded (Saito, 2019,Zuyderhoudt et al., 1983). In states of iron overload, the proportion of iron stored as hemosiderin increases relative to ferritin. This shift occurs as the system's capacity is overwhelmed, leading to the transformation of ferritin into hemosiderin to accommodate the excess iron (Saito, 2013,Zuyderhoudt et al., 1983).

When the body requires iron, it can be mobilized from both ferritin and hemosiderin, although the iron within ferritin is more readily accessible (Saito, 2014,Saito, 2019). The dynamics of these storage pools have been modeled through "serum ferritin kinetics," which demonstrate that ferritin levels respond more quickly to changes in iron status initially, while changes in hemosiderin are slower but become more pronounced as total storage iron increases (Saito, 2013). A key point is that when total tissue ferritin iron reaches approximately 5 grams, its capacity to incorporate additional iron becomes suppressed, and any further iron is preferentially directed into hemosiderin (Saito, 2012).

Therefore, ferritin acts as the primary and dynamic iron storage reservoir under normal conditions and with mildly elevated stores. In contrast, significant hemosiderin accumulation indicates chronic or severe iron excess, functioning as an "overflow" mechanism to handle iron beyond ferritin's capacity (Saito, 2019,Zuyderhoudt et al., 1983).

4.4 Mechanisms Leading to Deficiency

The development of iron deficiency occurs when the body's iron loss, physiological demand, or impaired absorption outstrips its ability to acquire or mobilize sufficient iron. A primary mechanism is insufficient dietary intake, which is common in populations with limited access to iron-rich foods or those who consume diets with low bioavailability of iron (Auerbach et al., 2025).

Another significant pathway is an increased physiological demand for iron. This is frequently observed during life stages such as pregnancy, infancy, and periods of rapid growth in children, as well as in individuals experiencing chronic blood loss (Leung, Lam, Wong, Hon, & Li, 2024).

Chronic blood loss itself is a central mechanism. This includes loss from menstrual bleeding, gastrointestinal sources (e.g., ulcers, colon cancer, inflammatory bowel disease), parasitic infections like hookworm, or iatrogenic causes such as frequent phlebotomy (Auerbach et al., 2025,Leung et al., 2024).

Malabsorption due to gastrointestinal conditions—such as celiac disease or atrophic gastritis—or following surgeries like gastric bypass, also represents a key mechanism by reducing the uptake of dietary iron from the intestine (Auerbach et al., 2025).

Inflammation plays a crucial role through a functional mechanism. Inflammatory cytokines stimulate the production of the hormone hepcidin in the liver, which in turn suppresses the iron exporter ferroportin. This action traps iron within enterocytes and macrophages, limiting its release into the circulation and causing a functional iron deficiency despite the presence of adequate stores (Koleini et al., 2021).

Genetic predisposition can also contribute, as polymorphisms or mutations in genes that regulate iron uptake (e.g., DMT1), storage, or systemic regulation (e.g., ferroportin, hepcidin) can influence an individual's susceptibility to developing deficiency (Kotze et al., 2009).

4.5 Stages of Iron Deficiency Anemia

Iron deficiency progresses through a series of distinct stages before manifesting as overt anemia (Naigamwalla et al., 2012,Kumar et al., 2022). The initial phase is storage iron depletion, characterized by a decline in iron reserves (reflected by low ferritin), while red blood cell production and hemoglobin levels remain within normal limits. Serum ferritin is the most sensitive indicator for detecting this early stage (Naigamwalla et al., 2012,Bermejo & García-López, 2009).

The second stage, known as iron-deficient erythropoiesis or marginal iron deficiency, occurs when the iron supply to the bone marrow becomes compromised. Laboratory findings in this stage include a decrease in transferrin saturation and serum iron levels, although hemoglobin typically remains normal or near the lower end of the normal range. This stage involves functional iron deficiency that impairs red blood cell production before anemia is evident (Hanif &Anwer, 2023,Kumar et al., 2022).

The third and final stage is iron deficiency anemia (IDA) itself. At this point, iron stores are exhausted, circulating iron is insufficient, and the production of red blood cells is significantly impaired, leading to a fall in hemoglobin below the normal threshold. The red blood cells produced are often microcytic (small) and hypochromic (pale) (Naigamwalla et al., 2012,Kumar et al., 2022).

Clinical symptoms such as fatigue, pallor, and shortness of breath on exertion typically appear during this third stage. Laboratory confirmation includes low hemoglobin and hematocrit, low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), elevated total iron-binding capacity (TIBC), and very low ferritin levels (Yang et al., 2023,Naigamwalla et al., 2012). Some classification systems also include a pre-latent stage before storage depletion becomes evident, or a sub-clinical phase where iron intake is inadequate but serum ferritin remains minimally affected (Bermejo & García-López, 2009). Detecting the deficiency in stages 1 or 2 allows for intervention before the development of anemia, which is associated with more adverse outcomes if untreated (Kumar et al., 2022).

5. Factors Contributing to IDA in School Children

5.1 Nutritional Inadequacy (Low Intake of Iron-Rich Food)

Inadequate nutrition, specifically a low consumption of iron-rich foods, is a leading cause of iron deficiency anemia. Diets deficient in heme iron sources—such as meat, poultry, and fish—are especially concerning due to the lower bioavailability of non-heme iron found in plant-based foods (Prentice, 2017). In many developing countries, a heavy reliance on cereal-based diets with minimal animal products results in insufficient dietary iron, which is a major driver of anemia prevalence (Tatala et al., 1998).

Individuals following vegetarian or vegan diets face a heightened risk, as their primary source of iron is the less efficiently absorbed non-heme form (López-Moreno et al., 2025). Large-scale dietary surveys have revealed that a significant portion of certain populations fails to

meet the Estimated Average Requirement (EAR) for iron, underscoring the pervasiveness of inadequate intake (de Jong et al., 2024).

Furthermore, diets characterized by low diversity and overall energy intake further restrict iron availability, compounding the risk of deficiency. This is particularly evident in resource-limited settings where access to fortified foods and animal sources is poor, making nutritional inadequacy a pivotal factor in the development of iron deficiency anemia (Prentice, 2017,Tatala et al., 1998).

5.2 Inhibitors of Iron Absorption (Tea, Coffee, Phytates)

The absorption of non-heme iron can be significantly hindered by various dietary compounds. Phytates, which are present in whole grains, legumes, nuts, and seeds, are potent inhibitors that bind iron in the gastrointestinal tract to form insoluble complexes that cannot be absorbed (Pişkin et al., 2022). Polyphenols constitute another major group of inhibitors,this includes tannins found in tea and coffee, which can precipitate iron or obstruct its uptake across the intestinal mucosa (Zijp, Korver, &Tijburg, 2000,Hurrell, Reddy, & Cook, 1999).

Research indicates that drinking tea with a meal can reduce iron absorption by approximately 60% to 90%, depending on the tea's polyphenol content (Hurrell et al., 1999). A study by Morck, Lynch, & Cook (1983) demonstrated that a cup of coffee consumed with a hamburger meal lowered non-heme iron absorption by 39%, with tea having an even more pronounced effect. The high phytate content in staple cereals and legumes is especially problematic in populations dependent on plant-based diets, which are often simultaneously low in absorption enhancers like vitamin C or meat (Pişkin et al., 2022).

The inhibitory effect is dose-dependent, with some herbal teas having a lesser impact than black tea or strong coffee (Hurrell et al., 1999). The timing of consumption is critical,consuming tea or coffee during a meal has a much greater inhibitory effect compared to consumption an hour before or after eating (Morck et al., 1983). These inhibitors pose a particular challenge for individuals with low iron stores, as the body's inherent ability to upregulate absorption in response to deficiency cannot fully overcome the effect of strong inhibitors (Zijp et al., 2000). Dietary strategies to mitigate inhibition include combining iron-rich foods with enhancers (vitamin C, meat), avoiding tea and coffee around meal times, and using food preparation methods like soaking or fermenting to reduce phytate content in grains and legumes (Pişkin et al., 2022,Zijp et al., 2000). Awareness of these inhibitors is essential for providing effective dietary advice, particularly for at-risk groups such as pregnant women, young children, and communities with high consumption of tea, coffee, and plant-based diets.

5.3 Socioeconomic Factors (Income, Parental Education)

Socioeconomic status (SES) is a significant determinant in the prevalence of iron deficiency anemia (IDA), especially in pediatric populations. Research consistently shows an inverse relationship between family income and the risk of IDA. For example, one study of 1,245 children found that those from households with an annual income below CAD $40,000 had triple the odds of having iron deficiency and IDA compared to children from higher-income families (Bayoumi et al., 2020).

The educational attainment of parents, particularly mothers, is another critical factor. An investigation in rural Malaysia revealed that children whose mothers had lower levels of

education were significantly more likely to have IDA (Ngui et al., 2012). A similar association between maternal education and the incidence of anemia in children was observed in Morocco, emphasizing the role of maternal knowledge in preventing nutritional deficiencies (El Hioui et al., 2008).

5.4 Health Conditions (Parasitic Infections, Chronic Disease)

Underlying health issues, particularly parasitic infections and chronic diseases, are major contributors to iron deficiency anemia (IDA). Parasitic infestations, such as those caused by intestinal helminths (e.g., hookworm, Ascaris lumbricoides, Trichuris trichiura), lead to iron loss through gastrointestinal bleeding and inflammation. These infections are highly prevalent in areas with poor sanitation and are strongly linked to anemia in children (Ngui et al., 2012,Stoltzfus et al., 1997). A study in rural Malaysia, for instance, reported an anemia prevalence of 26.2% among children, with 54.9% being iron deficient and 16.9% having IDA, against a backdrop of a 76.5% prevalence of helminth infections (Ngui et al., 2012).

Chronic diseases also play a pivotal role in the pathogenesis of IDA. Conditions like chronic kidney disease, inflammatory bowel disease, and cancer can lead to anemia of chronic disease (ACD), which is characterized by a disruption in iron utilization despite the presence of adequate stores. This functional deficiency is largely driven by increased levels of hepcidin, an acute-phase reactant that inhibits both iron absorption in the gut and its release from storage sites (Moum et al., 2025,Fertrin, 2020). Patients with chronic kidney disease, for example, frequently experience a combination of absolute and functional iron deficiency, which contributes to their anemia (Gafter-Gvili et al., 2019).

The co-occurrence of IDA and ACD presents a diagnostic and therapeutic challenge, as their hematological presentations can overlap. Distinguishing between them is crucial for effective management, since IDA typically responds to iron supplementation, while treating ACD requires addressing the underlying chronic condition (Svenson et al., 2021).

5.5 Gender Differences (Girls vs. Boys)

The prevalence of iron deficiency anemia (IDA) shows notable variations between genders, particularly during childhood and adolescence. Research generally indicates that girls are more vulnerable to anemia than boys. A study conducted in Istanbul found an overall anemia prevalence of 9.4%, which broke down to 13.4% in girls compared to 5.2% in boys, though the prevalence of confirmed iron deficiency anemia itself was 3.4% without a significant gender difference (Hosceylan, 2025).

Among adolescents in Sri Lanka, a study showed that 58.1% of girls were anemic compared to 49.5% of boys, with iron deficiency identified as the cause in 47.8% of anemic girls and 30.2% of anemic boys (Hettiarachchi et al., 2006). Similarly, research in Mosul, Iraq, found iron deficiency in 20.92% of students, with a significant disparity observed between anemic and non-anemic students across genders (Al Hafidh et al., 2024).

The higher tendency for anemia in girls is often attributed to increased iron demands during menstruation, which elevates their risk of iron deficiency (Levi et al., 2019). Additionally, sociocultural factors and dietary practices in some communities may lead to preferential allocation of iron-rich foods to boys over girls, further influencing iron status (Shell-Duncan et al., 2005).

Conclusion

Anemia remains a complex health burden worldwide and spans a wide clinical spectrum from complex genetic hemoglobinopathies and bone marrow failures to severe nutritional deficiencies. IDA is the most common form of presentation, with a broad spectrum of presentations and a significant burden on the pediatric population worldwide. Recognizing human iron homeostasis, which is governed by the fine balance of dietary heme and non-heme absorption, hepcidin regulation and cellular erythropoiesis, is key to understanding the systemic shift from iron depletion to manifest microcytic hypochromic anemia.

Amidst challenges faced by school-aged children, IDA is an insidious condition that takes multiple years to manifest. It is often overlooked. Its impact goes beyond temporary fatigue to permanently affecting the neurocognitive development, immune function, and overall scholastic performance of the child. Its burden is more pronounced where there are social inequalities and micro nutrient malnutrition. An active, multisectoral approach is needed to address childhood IDA. Improving access to sufficient, safe, adequate and healthy food through socially protective measures is key in eradicating this condition. Other strategies, such as early diagnostic screening, contextual prioritization of the policy and targeted iron supplementation, should be adopted by different countries based on their contextual needs.

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