

REVIEW ARTICLE

Causes and Health Issues of Iron Deficiency in Children: A Review

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ABSTRACT

Iron is a crucial micronutrient vital for child growth and development, particularly during their initial two years of life who are at an increased risk of iron deficiency anemia that can delay psychomotor development as iron binds to hemoglobin and proteins like myoglobin, transferrin, and ferritin. Iron participates in collagen synthesis, vitamin D metabolism, and dopaminergic functions too. Term infants rely on iron intake after depleting their reserves by the sixth month of life. The body efficiently recycles iron, with daily losses primarily from cell desquamation, urine, sweat, and feces. The intestinal tract plays a pivotal role in iron recycling and adjusting absorption based on body needs and age groups. Causes can be delayed introduction of complementary foods, cow's milk consumption, and dietary inhibitors like calcium and phytates. Individuals at risk of iron deficiency include preterm infants, low birth weight babies, and those with reduced gastric acidity. Prevention strategies encompass dietary modifications, iron supplementation, fortification, and biofortification. Breastfeeding, iron-containing complementary foods, and dietary diversity are recommended as preventive measures. In conclusion, this comprehensive review provides insights into the iron deficiency causes, and its profound impact on child health. Understanding these aspects is crucial for designing effective strategies to prevent and address iron deficiency globally.

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Introduction

Iron is an essential micronutrient for a child's growth and development, due to their heightened iron requirements during periods of rapid growth. Young children are a group who are very susceptible to iron deficiency and are advised by the World Health Organization to take iron supplements (1, 2). For the first six months of their lives, they have iron reserves that can last up to six months. Then,

they are mostly dependent on iron intakes to meet their high iron requirements for growth (3, 4). The body has a very effective mechanism to prevent the loss of iron as an important micronutrient. In this approach, the iron content is kept within acceptable bounds in order to suit its intended usage. Even the iron derived from red blood cells which have a half-life of 120 days, it is recycled back into the bloodstream. About 1 mg of iron is

lost per day, mostly as a result of cell desquamation. Furthermore, minute amounts are lost through perspiration, feces, and urine (5, 6).

Because absorption can vary according to body requirements and when reserves are low, absorption is significantly increased, and when they are high, absorption is inhibited in the digestive tract as an iron recycling mechanism. The rate at which iron is absorbed by the digestive tract is correlated with age. A twelve month-old child, for example, has an absorption rate that is four times higher than those of other infants in other age groups. Taking these factors into account, we can determine that the amount of iron needed each day varies depending on one's stage of life. Consequently, the Recommended Dietary Allowances (RDA) suggests a daily intake of 11 mg, 7 mg, and 10 mg of fundamental iron for infant of 7-12 months, 1-3 years, and 4-8 years, respectively (5).

For healthy physiological functions and human metabolism, iron is a necessary mineral (7). In fact, iron is required for erythropoiesis, oxidative, metabolism, and enzymatic activities, and it is a cofactor for mitochondrial respiratory chain enzymes of the citric acid cycle and DNA synthesis. It also promotes the growth of immune system cells (8-10). The bulk of the iron in the body attaches to hemoglobin; and the remaining iron is either retained in cells or binds to proteins like myoglobin, transferrin, and ferritin. Iron's complex interactions with other nutrients are demonstrated by the fact that it is essential to several enzymes involved in hydrogen peroxide reduction and helps convert beta-carotene into active vitamin A (11, 12). Iron is also necessary for the synthesis of collagen and the metabolism of vitamin D; while intracellular iron shortage may interfere with the function of osteoblasts and osteoclasts, causing abnormalities in the homeostasis of the bone and, eventually, the bone loss (13, 14). Additionally, iron exerts a complex influence on dopaminergic functions that play a crucial role in neuromodulation and regulates the quality, quantity, and timing of rapid eye movements (15).

Bioavailability of Iron from Dietary Sources

Heme iron constitutes 10–15% of the total iron intake. However, despite its lower overall presence, heme iron can contribute to over 40% of total intestinal iron absorption as it is absorbed more efficiently compared to non-heme iron, with an absorption rate ranging from 15% to 35%. The non-heme iron is found in both animal and plant sources such as grains, beans, herbs, and iron-fortified foods like cereal, differs from heme iron in its structure and absorption characteristics (16, 17).

Iron absorption relies on various factors, with the type of iron being a key determinant. Therefore, the iron content in food doesn't necessarily reflect its bioavailability. Even though plants boast high iron levels, the predominant presence of non-heme iron in plant-based sources leads to limited iron absorption due to specific molecule-iron interactions (18, 19). Because red meat contains a high concentration of highly accessible heme iron, it is the most major source of iron (20, 21). In developed nations, the iron needs of individuals are largely met by red meat, where heme iron constitutes 30–70% of the iron content. In contrast, in economically disadvantaged and underdeveloped regions, reliance on plant-based diets is more common. These diets are rich in non-heme iron and are often absorbed at a rate of less than 10%. As a result, a key determinant of the body's iron status is the consumption of foods with elevated iron content (21, 22).

Dietary Factors Affecting Iron Bioavailability

The absorption of iron is influenced by its physical states, namely ferrous and ferric. Ferrous iron is more readily incorporated into enterocytes, while non-heme iron, prevalent in the diet, is mostly present in an oxidized or ferric form (23, 24). Ferrous iron is generally soluble at a neutral pH, but ferric iron tends to precipitate in solutions with a pH greater than three. Consequently, for ferric iron to be absorbed in the less acidic proximal small intestine, it must undergo dissolution and chelation in the stomach (20, 25). Upon liberation in the intestinal lumen, iron interacts with other food components, leading to rapid chelation. These chelators can act as inhibitors or enhancers, impacting iron intake through solubility. Hence, the nature of the diet stands out as one of the key factors influencing the absorption of non-heme iron (26, 27).

Evaluation of Iron Status

A number of biochemical markers can be used to measure the various phases of iron shortage and eventually anemia. Although the activity of certain iron enzymes has not proven to be a reliable routine indicator of iron status, they are sensitive to iron deficiency (28). To accurately diagnose iron deficiency, laboratory measurements are necessary. When various iron status measurements are analyzed and assessed in light of dietary and medical history, they are extremely instructive. Some methods for calculating the amount of iron in plasma or serum include (i) Hemoglobin (Hb) as an indicator of hemoglobin in circulation, required for the transfer of oxygen entering the tissue from the alveolus. The amount of concentration per blood volume is how

the units are expressed. In most cases, the variable has a low positive predictive value with respect to iron deficiency and is not specifically related to it (29). (ii) Red cell distribution width (RDW) as this measure, which is based on automated cell counts, gives a range in the distribution of red cell sizes. It is computed by dividing the MCV unit by the MCV standard deviation. A larger RDW would indicate insufficient iron delivery to the marrow and raise the possibility of microcytic new cells entering the circulatory pool. Again, RDW is not limited to iron deficiency too (30, 31).

(iii) Mean cell volume (MCV) as a measurement of red cell volume in which the presence of tiny, microcytic red blood cells indicates inadequate iron uptake by the bone marrow. Volume is the unit of measurement. The proportional loading of hemoglobin into cells of different sizes can also be reflected by related indices like mean corpuscular hemoglobin concentration (MCHC). This cell size index may indicate a specific type of anemia, such as macrocytic anemia in cases of folate or B12 insufficiency and microcytic anemia in cases of iron deficiency. Mean cell volume is not specifically related to iron deficiency (32).

(iv) The biomarker known as soluble transferrin receptor that is found in plasma or serum. It is a transmembrane protein fragment that has been cleaved, and reticulocytes are the main source of the plasma pool. Given that the protein's expression and intracellular iron reserves are closely related, it serves as a helpful indication of both tissue iron shortage and iron deficiency erythropoiesis. Erythropoietic drive has a considerable effect on sTfR concentration, although inflammation does not seem to have any effect. There is currently no external quality control standard available, and this measure is very new. Numerous documented readings in healthy patients show that assay variability, not biological variability, is what's being suggested (30).

(v) Serum ferritin saturation and Fe concentration as a measurement of the iron carried by plasma, represented as a percentage bound for ferritin saturation and a concentration for ferritin. These measurements are vulnerable to sample contamination during analysis and have a high degree of variability within subjects (32). (vi) Body iron stores are a recently developed biomarker that logarithmically integrates ferritin and sTfR measurements. Although it provides a whole continuous range from a severe iron deficiency to an iron surplus, its current application is limited by the lack of consistency in sTfR readings. The variability within subjects has not been investigated (30).

(vii) Serum ferritin is a measurement of tissue

ferritin and the iron-storing protein. The quantity of stored iron in tissue is correlated with the amount in circulation. Iron accumulation causes cells to produce more ferritin using the same IRE pathway that was previously discovered for TfR (32). There is an inadequately explained release of tissue ferritin into the plasma pool, meaning that one microgram per liter of serum ferritin corresponds to around eight milligram of tissue pools that contain iron storage, mostly found in splenic macrophages and liver hepatocytes. Another acute phase protein, ferritin loses its ability to represent iron levels in the presence of inflammation. The clinical community has access to a defined technique and an external quality control standard (30).

Iron Deficiency

Iron insufficiency is the most prevalent deficiency state, with over two billion instances worldwide (Table 1). Anemia or iron deficiency is a common illness in both adults and children that can lead to significant morbidity and a reduced quality of life in terms of health (9, 34). A condition known as iron deficiency occurs when the body does not have enough iron to maintain normal physiological processes. It is defined by a decrease in the amount of iron in the body overall or, in some cases, by serum ferritin levels that fall below 12 mg/L in children under five years old and below 15 mg/L in individuals five years and older (35). The global prevailing nutritional challenge is still an insufficient iron intake (36). Global statistics suggest that iron deficiency anemia has affected 25% of preschool-aged children (37).

The onset of iron deficiency arises from the depletion of iron reserves, occurring when the absorption of iron fails to match the prolonged metabolic demands for sustaining growth and replenishing iron loss (28, 38). During early infancy and childhood, nutrition, including feeding practices and dietary considerations, holds significant importance as it profoundly influences the development of iron deficiency anemia (39, 40). Iron deficiency stands as the most widespread micronutrient deficit on a global scale. Compared to other life stages, infants and young children have higher iron requirements per kilogram of body weight, which puts them at risk for iron deficiency and the ensuing anemia (41). Breastfeeding exclusively for the first four to six months of life is recommended to protect infants from iron deficit and iron deficiency anemia (42).

After the sixth month of age, solid foods should be provided that are high in nutrients, including iron, zinc, phosphorus, magnesium, calcium, and vitamin B6.

Table 1: The Non-hematological Findings of Iron Deficiency (33).

General finding	Growth delay
Neurological findings	Restlessness, impaired mathematical processing and memory skills, reduced mental and motor functions, disrupted sleep patterns, diminished neurotransmitter production, restless legs syndrome, breath-holding spells
Gastrointestinal findings	Loss of appetite (anorexia), harm to epithelial tissue, manifesting as glossitis and angular cheilitis, formation of esophageal web or stricture, along with gastric atrophy, impairment of microvilli leading to enteropathy pica
Dermatological findings	Hair loss, spoon nails, Easy breakage of nails and hair

Data from the World Health Organization indicates that solid foods should provide 98% of an infant's iron requirement between the ages of six and twenty-three months (43). Children under the age of 5 months should aim for a daily dietary intake of approximately ten grams to meet metabolic demands and replenish body iron stores (44). In regions where the prevalence of anemia is equal to or exceeds 40%, as a preventive measure, the World Health Organization suggests daily iron supplementation for children between the ages of twenty- four and fifty-nine months (42). There are many main approaches to treating the population's iron deficiency. These approaches involve modifying dietary habits to enhance iron intake and bioavailability, administering iron supplements, fortifying foods with iron, and exploring innovative biofortification methods (45).

Cause of Iron Deficiency

Low iron levels occur due to the depletion of iron storage, resulting in iron deficiency. This deficiency arises when the absorption of iron is insufficient to meet the prolonged metabolic demands for iron, necessary for supporting growth and replenishing iron losses, primarily linked to blood loss (46). The main causes of iron shortage are excessive blood loss from pathologic infections like hookworm and whipworm, insufficient intake of bioavailable iron, and increased iron requirements due to rapid growth (47, 48).

When iron absorption from the diet is insufficient to meet physiological requirements, nutritional iron insufficiency results. Populations with minimal meat consumption and monotonous plant-based diets have low dietary iron bioavailability (49, 50). Iron fortification of plant-based weaning foods is unusual in many developing nations, and anemia affects more than 50% of children under the age of four months (51). The hematologic symptoms of

iron deficiency anemia manifest when hemoglobin synthesis in erythrocyte precursors is compromised due to low iron reserves, which leaves inadequate iron accessible for erythropoiesis (28). Term infants typically have ample iron stores during the initial 6-9 months of life (52).

Iron deficiency in early childhood is related by many factor such as low birth weight, prematurity, infants born to iron deficient mothers, feeding problems, late weaning, delaying the introduction of appropriate supplemental foods past the age of six months (9, 28), and excessive cow's milk more than 500 mL/day that can cause iron deficiency anemia by causing occult/overt blood loss in the gastrointestinal tract caused by the protein found in cow's milk colitis (53). On the other hand, during the second year of life, drinking unadulterated cow's milk and consuming less iron-fortified food have been associated with a higher risk of poor iron status and iron inadequacy (54). This vulnerability in the second year is exacerbated by the dietary shift that occurs at the same time as the fast growth linked to this developmental period, which involves replacing breast milk or infant formula with raw cow's milk as a major beverage (55). Both mother's milk and cow's milk contain modest amounts of iron; of these, fifty percent of the iron in breast milk is absorbed, whereas just ten percent of the iron in cow's milk is absorbed. Consuming too much cow's milk can decrease the absorption of iron-containing drugs and other nutrients (53).

In addition, the less efficient absorption of iron from vegetarian diets in comparison to diets with meat results in decreased iron reserves and a higher risk of iron deficiency in vegetarians (56). Dietary intestinal iron absorption is influenced by nutrient interactions. The main factors influencing the bioavailability of iron are dietary enhancers like proteins and ascorbic acid, as well as inhibitors like

calcium, tannins, phytates, and polyphenols (20). Iron deficiency, which is characterized by the depletion of iron reserves, can result from conditions that limit the absorption of iron such as gluten sensitivity and malabsorption disorders (Table 2). This deficiency occurs when iron absorption fails to keep pace with the extended period of metabolic demands for iron, essential for sustaining growth and replenishing iron loss primarily related to blood loss (46, 57). Early infancy and childhood are critical periods where feeding and all dietary aspects play a significant role in influencing the development of iron deficiency anemia (39).

Furthermore, iron deficiency anemia in children and adolescents may be caused by infection with *Helicobacter pylori* of the stomach mucosa. According to recent studies, infection with *H. pylori* affects iron absorption via changing iron's bioavailability rather than by decreasing stomach acid secretion or seriously impairing children's bleeding (52, 58). Unnecessarily elevated hepcidin concentrations prevent the body from absorbing iron. It has been shown that long-term low levels of systemic inflammation in young children (six to twenty three months) increased hepcidin concentrations, which hindered iron absorption and increased the prevalence of iron deficiency anemia (59).

Iron Deficiency and Child Health

Infants and young children, especially during the initial two years of life, face a heightened risk of iron deficiency (33). The easiest way to identify functional iron deficiency is by anemia, which highlights the important fact that an inadequate supply of iron affects every tissue. The functional

consequences stem from insufficient oxygen delivery as a result of lower amounts of circulating hemoglobin and decreased tissue enzyme activity that contains iron (62, 63). Iron deficiency can result in long-term and irreversible consequences, with the most significant impact in early childhood being the delay in psychomotor development and cognitive impairment (55). Evidences indicate that iron supplementation contributes to improved growth and cognitive development (64).

Children experiencing iron deficiency may struggle academically and exhibit behavioral challenges in their middle years. Additionally, iron deficiency can lead to delayed sexual development, chronic fatigue syndrome, and adverse effects on immune status (64, 65). Children, due to their high demand for growth and development, are particularly susceptible to iron-deficiency anemia. Persistent iron deprivation leads to iron depletion, subsequently resulting in low hemoglobin levels (anemia). The detrimental effects of iron deficiency on children include poor weight gain and challenges in language and behavior (66). Iron deficiency anemia emerges as a significant public health concern, adversely affecting sleep quality in childhood (67). One of the many effects of an iron lack is anemia that is a condition characterized by a decreased quantity of erythrocytes, often accompanied by a reduction in hemoglobin levels or changes in erythrocyte morphology (68).

Iron deficiency anemia occurs when there is an insufficient balance between consumption of iron, iron reserves, and the body's iron loss, leading to an inadequate assistance for the generation of red blood cells. While iron deficiency anemia seldom results in fatalities, its impact on human health is substantial

Table 2: Causes of iron deficiency in children (60, 61).

Causes	Example
Inadequate consumption of iron	<ul style="list-style-type: none"> ▪ Insufficient amount of iron in the diet ▪ Late weaning ▪ Prematurity ▪ Vegans ▪ Chronic illness ▪ Poor socio-economic state
Decreased absorption of iron in the gut	<ul style="list-style-type: none"> ▪ Ingesting iron absorption inhibitors (such as calcium, oxalate phytate and polyphenol-rich foods) ▪ Inadequate stomach acidification ▪ Use of antacids ▪ <i>Helicobacter pylori</i> infection ▪ Intestinal mucosal dysfunction (eg, coeliac disease or inflammatory bowel disease) ▪ Increased hepcidin concentrations preventing iron absorption
Increased iron requirement	<ul style="list-style-type: none"> ▪ Growth ▪ Low newborn weight
Blood loss	<ul style="list-style-type: none"> ▪ Parassitosis in the intestinal tract ▪ Cow milk protein intolerance ▪ Inflammatory bowel disease

(69). Iron deficiency anemia may arise due to factors such as insufficient iron intake, reduced absorption, heightened iron requirements, and increased iron loss caused by events like gastrointestinal bleeding or hemolysis (70).

The World Health Organization (WHO) recommends prioritizing specific age groups in the prevention and control of iron deficiency anemia. Recent guidelines advocate for enhancing nutrition through daily iron supplementation for individuals at a high risk of iron deficiency anemia (71). In accordance with the criteria set by the World Health Organization (WHO), anemia is assessed based on age and sex, utilizing average hemoglobin levels as benchmarks. For children aged 6 months to 6 years, the threshold is 11 g/dL, while for those aged 7-14 years, it is 12 g/dL (72). As of 2019, WHO data on anemia indicated a global prevalence of up to 39.8% among children under five years old, with the African region reporting an alarming 60.2% prevalence in this age group (73, 74).

The WHO estimated that approximately half of preschool children were affected by various types of anemia, primarily stemming from nutritional causes, notably iron deficiency (75, 76). Iron deficiency anemia has been shown to impact psychological and physical development in children and diminish productivity in adults (77). Iron plays a crucial role in red blood cell formation (erythropoiesis) and is an essential component of hemoglobin, serving as the oxygen-carrying molecule in red blood cells by supplying ferrous ions for heme ring formation that links four polypeptide chains in the hemoglobin structure (78, 79). The primary causes of children's iron deficient anemia include iron deficiency at birth, inadequate iron intake through food (due to exclusive breastfeeding beyond 4 months, delayed introduction of complementary foods, unbalanced nutrition, or vegetarianism), reduced iron absorption, and the pathogenesis of anemia due to a lack of iron (80). Some minerals are essential and are important for animal health as well as for human consumption (81, 82). No differences were observed when minerals were added to the food (83, 84) (Table 3).

Table 3: Iron deficiency and child's health.

Iron deficiency and child health (Reference)

Iron deficiency can result in neurodevelopmental and cognitive deficits (55, 85).

Iron deficiency can lead to delayed sexual development, chronic fatigue syndrome, and adverse effects on immune status (64, 65).

Persistent iron deprivation leads to iron depletion, subsequently resulting in low hemoglobin levels (anemia) and poor weight gain and challenges in language and behavior (66).

Iron deficiency affecting sleep quality in childhood (67).

Iron deficiency in early life is widespread and can have a severe impact on children's brain development (3).

Iron deficiency anemia was strongly related with febrile convulsion (86).

Conclusion

Iron's crucial role in various physiological functions, including erythropoiesis, oxidative metabolism, enzymatic activities, immune system cell growth, and neuromodulation, highlights its multifaceted importance in human health. The complex interactions between iron and other nutrients further emphasize the need for a balanced and varied diet to ensure optimal iron absorption and utilization. Iron deficiency, being the most prevalent deficiency globally, poses a significant health challenge, especially in infants and young children. Factors such as inadequate dietary intake, decreased absorption, increased iron requirements, and potential causes like infections contribute to iron deficiency. Early infancy and childhood represent critical periods where nutritional choices play a pivotal role in preventing iron deficiency anemia. Evaluation of iron status through biochemical markers is essential for accurate diagnosis and intervention. Hemoglobin levels, red cell distribution width, mean cell volume, and soluble transferrin receptor are among the indicators used to assess iron status. It is imperative to consider the intricate relationship between iron, its various forms, and their impact on different tissues when interpreting these markers. Iron deficiency in children can lead to a range of health issues, including growth delay, neurological disturbances, gastrointestinal problems, and skin-related symptoms. Long-term consequences may include cognitive impairment, delayed sexual development, and adverse effects on immune status. The importance of addressing iron deficiency through targeted interventions, such as iron supplementation, dietary modifications, and fortification, cannot be overstated.

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Authors' Contribution

All authors contributed equally to this work.

Conflict of Interest

The authors have no conflict of interest.

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