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Iron Supplementation in Children, Ferroptosis, and Neurodegenerative Diseases in Adulthood

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Iron Requirements and Epidemiological Data

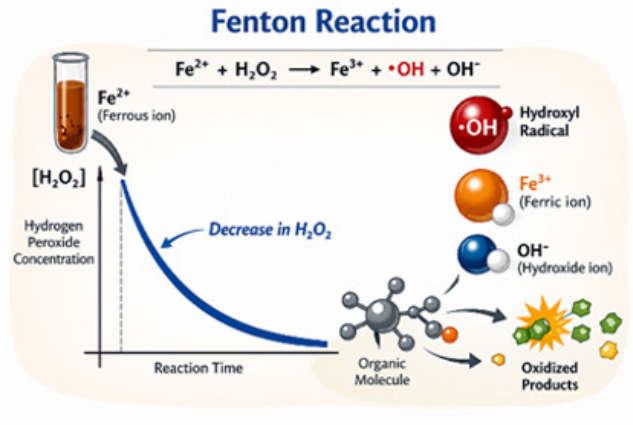
During the transition from physiological neonatal polycythemia to the so-called physiological anemia of infancy, iron released from the breakdown of excess erythrocytes contributes substantially to body iron stores during the first months of life. A healthy term infant has approximately 250 mg of total body iron at birth, increasing to about 500 mg by 6 months of age. During this period, endogenous iron stores generally provide sufficient iron to support growth and erythropoiesis in healthy term infants. From approximately 6 months of age, however, rapid growth progressively increases dietary iron requirements. The absorbed iron requirement is approximately 1 mg/day, and because only a fraction of dietary iron is absorbed, an intake of around 10 mg/day may be required to meet physiological needs. This requirement is particularly relevant in exclusively breastfed infants, as human milk contains relatively low concentrations of iron (approximately 0.2–0.4 mg/L). Consequently, prolonged exclusive breastfeeding beyond 6 months without an adequate source of complementary dietary iron may increase the risk of iron deficiency. Iron deficiency remains the most common nutritional deficiency worldwide and is a major cause of anemia. Global estimates indicate that approximately 2 billion people are affected by anemia, with iron deficiency accounting for a substantial proportion of cases. In 2016, anemia affected an estimated 41.7% of children under 5 years of age, 40.1% of pregnant women, and 32.5% of non-pregnant women worldwide. The World Health Organization has estimated that approximately 42% of anemia cases in children and 50% in women may be attributable to iron deficiency and could therefore potentially benefit from interventions aimed at improving iron status. However, meta-analyses of population-based studies have suggested lower attributable fractions, approximately 25% in children and 37% in women, highlighting the heterogeneous and multifactorial etiology of anemia across populations. Despite these differences in epidemiological estimates, iron deficiency is widely recognized as the most prevalent nutritional deficiency in childhood. Its relevance extends beyond hematological abnormalities because iron availability is closely linked to brain maturation. Iron deficiency during critical periods of development has been associated with alterations in cognitive, language, motor, and behavioral development, raising particular concern about the consequences of inadequate iron availability during infancy and early childhood.

The biological Paradox of Iron and early Neurodevelopment

Iron metabolism illustrates a fundamental biological paradox. Iron is an essential trace element and an indispensable cofactor in numerous processes required for normal brain development, including mitochondrial energy metabolism, axonal function, monoamine neurotransmitter synthesis, and myelination. The developing brain is therefore particularly dependent on adequate iron availability. At the same time, the redox activity that makes

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iron biologically useful also accounts for its potential toxicity when cellular iron homeostasis is disrupted. Excess intracellular labile iron can promote the generation of reactive oxygen species through Fenton chemistry (Figure 1), increasing oxidative stress and favoring lipid peroxidation and oxidative damage to cellular macromolecules. Under specific conditions, iron-dependent lipid peroxidation can trigger ferroptosis, a regulated form of cell death mechanistically and morphologically distinct from apoptosis and necrosis. Ferroptosis is characterized by iron-dependent accumulation of lipid peroxides and is associated with characteristic mitochondrial alterations, including reduced mitochondrial volume, loss or reduction of cristae, and increased membrane density, while nuclear morphology and plasma membrane integrity may initially remain relatively preserved. This dual role of iron is particularly relevant during infancy. The first year of life is characterized by rapid changes in brain architecture, including intense synaptogenesis, myelination, and maturation of neuronal networks. These processes create a period of increased vulnerability in which disturbances in iron availability may interfere with normal neurodevelopment. Iron deficiency, with or without anemia, during infancy has been associated with poorer cognitive, language, motor, and behavioral outcomes. Electrophysiological studies provide additional evidence that the neurological effects of early iron deficiency may extend beyond the period of hematological deficiency. Infants with iron deficiency anemia have shown delayed central nervous system conduction, particularly in brainstem auditory and visual pathways, as assessed by evoked potentials. Importantly, abnormalities in conduction velocity have been reported to persist from infancy into early childhood despite iron treatment and normalization of conventional hematological parameters. Such findings suggest that iron deficiency occurring during critical developmental windows may produce neural alterations that are not necessarily reversed by subsequent correction of systemic iron status. This observation is particularly important when considering iron supplementation during early life. Both insufficient iron availability and excessive or poorly regulated iron accumulation may have biological consequences in the developing nervous system. The narrow balance between the developmental requirement for iron and its capacity to promote oxidative injury provides a mechanistic basis for examining whether early-life iron exposure could influence ferroptotic pathways and, potentially, neurological vulnerability later in life.



This reaction promotes the generation of hydroxyl radicals (•OH), which can initiate the oxidation of membrane phospholipids containing polyunsaturated fatty acids (PUFAs). The resulting accumulation of lipid peroxides, together with characteristic mitochondrial alterations, including reduced mitochondrial volume and loss of mitochondrial cristae, is a hallmark of ferroptotic cell death.
Figure 1: The Fenton Reaction and the Molecular Induction of Ferroptosis.

Fragility of Neuronal Connectivity and Windows of Opportunity

Neuroimaging studies provide further evidence that iron availability during early development is associated with the maturation of neural connectivity. In a prospective longitudinal study of preterm infants using diffusion tensor imaging (DTI), Li et al. (2021) reported alterations in white matter microstructure associated with iron deficiency, including impaired cerebellar–thalamic structural connectivity. These abnormalities were consistent with disrupted myelination and were associated with poorer subsequent motor performance, as assessed using the INFANIB and PDMS-2 scales. Importantly, the study also suggested that early correction of iron deficiency may improve developmental trajectories. Iron supplementation at 2 mg/kg/day, initiated at 40 weeks of corrected gestational age, was associated with improved structural connectivity and motor outcomes at 6 months. Although these findings should not be interpreted as evidence that all early neural alterations caused by iron deficiency are fully reversible, they support the existence of developmental windows during which adequate iron availability is particularly important. Thus, the timing of iron deficiency, its duration, baseline iron status, and the timing and dose of supplementation should all be considered when evaluating its effects on neurodevelopment.

The U-shaped Risk Curve and the Danger of Overexposure

The high global prevalence of iron deficiency and iron deficiency anemia has historically supported preventive strategies based on iron supplementation and food fortification, particularly in populations with a high prevalence of deficiency. However, increasing evidence suggests that the relationship between iron exposure and neurodevelopment is not linear. The systematic review by Torralba Fit et al. (2026), which included data from 7,840 infants, supports a model in which both insufficient and excessive iron exposure may be associated with unfavorable developmental outcomes. This concept is consistent with a U-shaped relationship, although the position and width of the optimal range are likely to depend on baseline iron status, gestational age, birth weight, diet, inflammatory status, and other individual and population-level factors. The benefits of supplementation are most consistently observed among infants at increased biological risk of iron deficiency, including preterm and low-birth-weight infants and children with documented low iron status. In these populations, early iron supplementation has been associated with improvements in developmental outcomes. For example, Tiwari and Kukreja (2026) reported differences of up to 6.5 points in Bayley-III cognitive and language scores at 24 months in supplemented high-risk infants. The situation is less clear in healthy term infants with adequate baseline iron status. In the randomized SIBDI trial conducted in Poland and Sweden, Svensson et al. (2024) found that supplementation with 1 mg/kg/day of iron did not significantly improve psychomotor, cognitive, or language development during the first three years of life. These findings indicate that additional iron does not necessarily confer neurodevelopmental benefit when iron availability is already sufficient. Long-term observations from the Chilean cohort raise a different concern. Infants randomized to receive high-iron formula (12.7 mg/L) who had relatively high baseline hemoglobin concentrations (>125 g/L) subsequently showed poorer performance in selected neurodevelopmental domains than comparable children receiving lower iron exposure (East et al., 2019; East et al., 2023). Reported differences included visuomotor integration, spatial memory, matrix reasoning, emotional awareness, and educational attainment, although the magnitude and consistency of these associations varied across outcomes and follow-up periods. These observations do not establish that early iron supplementation causes later neurodegeneration. They do, however, challenge the assumption that iron exposure above physiological requirements is necessarily harmless. Excess iron may increase the labile iron pool, promote oxidative stress and lipid peroxidation, interfere with the metabolism of other trace elements, and modify the intestinal microbiota. These mechanisms provide biological plausibility for investigating whether excessive iron exposure during sensitive developmental periods could influence long-term neurological vulnerability, including pathways involving ferroptosis.

Hematologic-Cerebral Dissociation and Hemoglobin Deficiency

A major limitation of conventional screening is the reliance on hemoglobin concentration as the primary indicator of iron deficiency. Hemoglobin is primarily a marker of anemia rather than a sensitive indicator of early iron depletion. During progressive iron deficiency, available iron is preferentially directed toward erythropoiesis, while iron delivery to other tissues, including the developing brain, may become insufficient before hemoglobin concentrations fall below the diagnostic threshold for anemia. This hematological–cerebral dissociation is particularly relevant during infancy, when iron-dependent processes such as myelination, mitochondrial metabolism, and neurotransmitter synthesis are highly active. Consequently, a normal hemoglobin concentration does not necessarily indicate adequate iron availability for neurodevelopment. Neuroimaging studies support this concept, showing alterations in brain microstructure and structural connectivity associated with iron deficiency during early development (Li et al., 2021). Assessment of iron status should therefore not rely exclusively on hemoglobin. Combining hemoglobin with biomarkers of iron stores, particularly serum ferritin, provides a more informative assessment of iron status. Because ferritin is an acute-phase reactant and may increase during inflammation, its interpretation should be accompanied by an inflammatory marker such as C-reactive protein. Approaches integrating hematological and biochemical markers may improve the identification of children at risk of iron deficiency before overt anemia develops (Parkin et al., 2021; Gingoyon et al., 2022). Such an approach may help address two opposing clinical problems: failure to identify iron deficiency before anemia develops and unnecessary supplementation of children who already have adequate iron stores. However, the optimal timing of screening, combination of biomarkers, and diagnostic thresholds remain subjects of investigation and may need to be adapted to the prevalence of iron deficiency and the clinical and nutritional characteristics of each population.

The Pathophysiological Bridge: From Weaning to Adult Neurodegeneration

An important unresolved question is whether disturbances in iron homeostasis during early development can influence susceptibility to neurological disease later in life. Brain iron concentrations and their regional distribution change throughout the lifespan and are tightly controlled by mechanisms governing iron uptake, transport, storage, utilization, and export. During infancy and weaning, when dietary iron exposure changes substantially and the brain is undergoing rapid maturation, disruption of these regulatory processes could theoretically have consequences extending beyond the immediate developmental period. A mechanistic link between iron dysregulation and neurodegeneration is biologically plausible. An increase in redox-active iron promotes the generation of reactive oxygen species, oxidation of polyunsaturated membrane lipids, mitochondrial dysfunction, and cellular damage. When antioxidant defenses, particularly those controlling phospholipid hydroperoxides, are insufficient to counteract this process, iron-dependent lipid peroxidation can progress toward ferroptotic cell death. Ferroptosis has increasingly been implicated in the pathophysiology of several neurodegenerative disorders. Abnormal iron accumulation, oxidative stress, lipid peroxidation,

and impaired antioxidant defenses have been described in Alzheimer's disease, Parkinson's disease, and Huntington's disease, although their relative contribution and causal position within each disease process remain under investigation. In Parkinson's disease, for example, iron accumulation in the substantia nigra occurs in a region characterized by progressive loss of dopaminergic neurons. Alzheimer's disease is also associated with alterations in iron handling, lipid metabolism, and oxidative homeostasis, whereas Huntington's disease involves mitochondrial dysfunction and disturbances in cellular iron metabolism. These observations provide a mechanistic framework linking iron homeostasis, lipid peroxidation, and neuronal vulnerability. Nevertheless, direct evidence demonstrating that iron supplementation during infancy increases the risk of neurodegenerative disease decades later is currently lacking. The proposed connection should therefore be regarded as a biologically plausible hypothesis rather than an established causal pathway. Determining whether early-life iron status modifies long-term susceptibility to ferroptosis represents an important area for future longitudinal and mechanistic research.

Implications for Public Health and the Need for Population-Adapted Consensus

Current recommendations for iron supplementation during infancy differ substantially among professional organizations, reflecting differences in the interpretation of available evidence and in the populations for which the recommendations were developed. The American Academy of Pediatrics has recommended iron supplementation at 1 mg/kg/day from 4 months of age for exclusively or predominantly breastfed term infants until adequate iron-containing complementary foods are introduced. In contrast, European recommendations have generally not supported routine iron supplementation in healthy term infants of normal birth weight when adequate dietary iron intake can be ensured. These differences illustrate an unresolved clinical problem: prevention of iron deficiency must be balanced against unnecessary exposure in infants who already have adequate iron stores. This issue also extends to the iron content of infant formulas. Historically, formulas containing relatively high iron concentrations have been used in some countries to reduce the risk of iron deficiency anemia. However, long-term observations from the Chilean cohort suggest that high iron exposure may not be optimal for infants with high baseline iron status. These findings should be interpreted cautiously but support the broader principle that the appropriate iron intake may depend on the initial iron status of the child rather than on a single supplementation strategy applied to the entire population. Evidence from clinical studies conducted in populations with markedly different nutritional and socioeconomic characteristics further supports this distinction. Trials in settings with a high prevalence of nutritional iron deficiency cannot necessarily be extrapolated directly to healthy infants living in populations with low rates of deficiency. Similarly, findings from SIBDI indicate that routine supplementation of healthy term infants may provide little or no measurable neurodevelopmental advantage, whereas evidence from preterm, low-birth-weight, and iron-deficient infants supports supplementation when the biological risk of deficiency is substantial. The available evidence therefore favors a risk-adapted approach to iron prevention. Gestational age, birth weight, feeding pattern, maternal iron status, dietary iron intake, growth, inflammatory conditions, and biochemical indicators of iron status may all contribute to identifying infants most likely to benefit from supplementation. When screening is performed, hemoglobin should not be considered in isolation; markers of iron stores and inflammation can provide additional information before anemia becomes established. Interest in this approach is reinforced by increasing evidence linking disturbances in iron metabolism and ferroptosis-related mechanisms to neurological disorders across the lifespan. Associations have been reported in neurodevelopmental conditions, including attention-deficit/hyperactivity disorder, as well as in neurodegenerative diseases such as Parkinson's and Alzheimer's disease. These associations do not demonstrate that early iron exposure causes these disorders, but they emphasize the importance of understanding how cerebral iron homeostasis is established during infancy and how it changes during critical transitions such as weaning. Overall, iron supplementation provides clear benefits when iron requirements cannot be met through endogenous stores and diet, particularly in infants at increased risk of deficiency. Conversely, the available evidence does not demonstrate a neurodevelopmental benefit from systematically increasing iron exposure in all healthy term infants with adequate iron status, and some long-term observations raise concern about excessive exposure in iron-replete children. Preventive strategies should therefore aim to maintain iron availability within an appropriate physiological range rather than simply maximizing iron intake. Population-adapted screening, identification of biological risk, and appropriate use of biomarkers may provide a more rational basis for supplementation while minimizing the consequences of both iron deficiency and unnecessary iron exposure during critical periods of brain development.

References

1. Torralbas Fitz SJ, Sanchez VJ, Hoyos AM, Pena DEM (2026) Iron Supplementation and Neurodevelopmental Outcomes in Infancy and Early Childhood: A Review. Children 13(9): 1274.
2. Li M, Ji C, Xuan W, et al. (2021) Effects of Daily Iron Supplementation on Motor Development and Brain Connectivity in Preterm Infants: A Diffusion Magnetic Resonance Study. Front Neurosci 15: 769558.
3. Wang Y, Wu Y, Li T, et al. (2019) Iron metabolism and brain development in premature infants. Front Physiol 10: 463.
4. East PL, Reid B, Blanco E, Burrows R, Lozoff B, (2023) Iron supplementation given to nonanemic infants: neurocognitive functioning at 16 years. Nutr Neurosci 26(1): 40-49.
5. East P, Doom J, Blanco E, et al. (2022) Young adult outcomes associated with lower cognitive functioning in childhood related to iron-fortified formula in infancy. Nutr Neurosci 25(4): 709-718.
6. Svensson L, Chmielewski G, Czyżewska E, et al. (2024) Effect of Low-Dose Iron Supplementation on Early Development in Breastfed Infants: A Randomized Clinical Trial. JAMA Pediatr 178(7): 649.
7. Tiwari SA, Kukreja I (2026) Impact of Early Iron Supplementation on Cognitive Outcomes in Infants Born to Anemic Mothers: A Longitudinal Birth Cohort Analysis. Indian J Pediatr 93(4): 376-381.
8. Reichert CO, de Freitas FA, Sampaio-Silva J, et al. (2020) Ferroptosis Mechanisms Involved in Neurodegenerative Diseases. Int J Mol Sci 21(22): 8765.

9. WHO (2020) guideline on use of ferritin concentrations to assess iron status in individuals and populations. World Health Organization.

10. (2015) WHO. The global prevalence of anaemia in 2011. 40

11. Gao Q, Zhou Y, Chen Y, Hu W, Jin W, et al. (2025) Role of iron in brain development, aging, and neurodegenerative diseases. Ann Med 57(1): 2472871.

12. Parkin PC, Borkhoff CM, Macarthur C, Abdullah K, Birken CS, et al. (2021) Randomized Trial of Oral Iron and Diet Advice versus Diet Advice Alone in Young Children with Nonanemic Iron Deficiency. J Pediatr 233: 233-240.

13. Gingoyon A, Borkhoff CM, Koroshegyi C, Mamak E, Birken CS, et al. (2022) Chronic Iron Deficiency and Cognitive Function in Early Childhood. Pediatrics 150(6): 2021055926.

14. Collard KJ (2009) Iron homeostasis in the neonate. Pediatrics 123: 1208-1216.

15. Petry N, Olofin I, Hurrell RF, et al. (2016) The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: a systematic analysis of national surveys. Nutrients 8: E693.

16. Camaschella C (2019) Iron deficiency. Blood 133(1): 30-39.