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IRON DEFICIENCY IN EARLY LIFE AND LATER BEHAVIORAL OUTCOMES: A SYSTEMATIC REVIEW

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Abstract

Background: Iron deficiency during early life is the most common micronutrient deficiency worldwide and may have lasting effects on neurodevelopment and behavior. This systematic review aimed to explore the relationship between iron deficiency in infancy (0–24 months) and behavioral outcomes beyond two years of age. **Methods:** This study was a systematic literature review of twenty-three articles. These articles were sourced from scientific journal articles on ScienceDirect, covering studies published between 2005 and 2025. Inclusion criteria were longitudinal cohort or randomized controlled trials assessing behavioral outcomes such as attention, hyperactivity, and socio-emotional regulation. **Results:** Early-life iron deficiency was consistently associated with increased internalizing and externalizing behaviors, attention deficits, and symptoms of ADHD and Sluggish Cognitive Tempo persisting into adolescence. Timing and severity of deficiency influenced outcomes, with prenatal deficiency affecting recognition memory and executive function, while infant deficiency predicted behavioral dysregulation and academic difficulties. Targeted iron supplementation reduced behavioral problems, whereas excessive or non-individualized supplementation showed limited benefits. **Conclusions:** Iron deficiency in early life has long-term behavioral consequences. Early detection and individualized interventions are crucial for preventing neurobehavioral impairments and optimizing child development.

Keywords: Iron deficiency, infancy, behavior, neurodevelopment, supplementation

Introduction

The global nutrition landscape has shifted substantially in recent decades, with many countries simultaneously facing undernutrition, micronutrient deficiencies, and overnutrition, which is a phenomenon often described as the triple burden of malnutrition.[1] Among micronutrient deficiencies, iron deficiency remains the most prevalent worldwide, particularly affecting infants and young children during critical periods of growth and neurodevelopment.[2] Iron deficiency anemia (IDA) continues to be recognized as a significant public health concern, especially in low- and middle-income countries, where its prevalence frequently exceeds the World Health Organization (WHO) threshold for public health significance.[3] In Indonesia, 26,8% of children 5-14 years old found to be anemic.[4] Nearly 40% of young women in Indonesia (aged 15–24), based on the Indonesian Family Life Survey (IFLS-5), are anemic[5], increasing the risk of maternal anemia during pregnancy and the likelihood of infants being born with anemia.[6]

Iron plays a fundamental role in early brain development through its involvement in myelination, neurotransmitter synthesis, and energy metabolism.[7] During infancy and early childhood, the brain undergoes rapid structural and functional maturation, making it particularly vulnerable to nutritional insults.[8] Deficiency of iron during this sensitive developmental window may lead to alterations in neural circuitry that persist beyond the period of deficiency itself.[9] Consequently, early-life iron deficiency has been consistently associated with impaired cognitive development, delayed motor skills, and reduced academic performance later in childhood.[10]

Beyond its established effects on cognition, emerging evidence suggests that iron deficiency in early life may also influence behavioral and socio-emotional outcomes.

Observational and longitudinal studies have reported associations between early iron deficiency and behavioral manifestations such as inattention, increased internalizing and externalizing problems, reduced social engagement, and altered emotional regulation in later childhood and adolescence.[11–13] These behavioral alterations are hypothesized to be linked to iron-dependent neurotransmitter systems, particularly dopaminergic and serotonergic pathways, which are critical for attention, motivation, and emotional control.[14–16]

However, findings across studies remain heterogeneous. Differences in study design, timing and severity of iron deficiency exposure, outcome measurement tools, and follow-up duration complicate interpretation. Moreover, behavioral outcomes are often treated as secondary endpoints, leading to inconsistent reporting and limited synthesis across the literature. While several narrative reviews have discussed the neurodevelopmental consequences of iron deficiency, a comprehensive synthesis specifically focusing on long-term behavioral outcomes remains limited.

Given the potential implications for lifelong mental health, educational attainment, and social functioning, a clearer understanding of the association between early-life iron deficiency and later behavioral outcomes is critically needed. Therefore, this systematic review aims to exploring existing evidence on the relationship between iron deficiency during early life and behavioral outcomes in later childhood and beyond, with particular attention to the timing of exposure, persistence of effects, and methodological quality of the available studies.

Method

This paper was a systematic review that adhered to the PRISMA declaration and checklist, which provide recommended reporting elements for systematic reviews and meta-analyses. The question of the study was: "*Does iron deficiency in infants aged 0–24 months influence long-term behavioral outcomes beyond the age of two years?*" Literature searches were conducted using databases from ScienceDirect. The keywords used included ""Iron deficiency," "Iron deficiency anemia," "Infants," "Baby," "Toddler," "Behavior," "Attention," "Hyperactivity," "ADHD," "Socioemotional," "Behavioral Problem," Long-term," "Follow-up," "Later Childhood," and "Adolescence." combined using Boolean operators (AND, OR).

Studies were selected based on the following inclusion criteria: The population consisted of infants aged 0 to 24 months at the time of iron status assessment. The exposure being investigated was iron deficiency (with or without anemia), as determined by biochemical markers such as hemoglobin, serum ferritin, or transferrin saturation. The comparator group included infants who were iron-sufficient or non-deficient. The outcomes focused on long-term behavioral results measured beyond the age of two years, including attention, hyperactivity, socio-emotional behavior, and other related behavioral domains. The study design included longitudinal cohort or follow-up studies that were published in peer-reviewed journals. All studies had to be published in the English language.

The exclusion criteria for this study included cross-sectional studies without follow-up, short-term intervention trials lasting less than one year, case reports, reviews, conference abstracts, animal studies, and studies that did not report behavioral outcomes. The selection process adhered to the PRISMA flow diagram (see Figure 1). The initial search retrieved articles from five different databases. After removing duplicates and applying the inclusion and exclusion criteria, we screened the titles and abstracts, followed by a full-text assessment for eligibility. Two reviewers independently evaluated the eligibility of the studies, and any disagreements were resolved through discussion. This systematic review has been submitted for registration in PROSPERO.

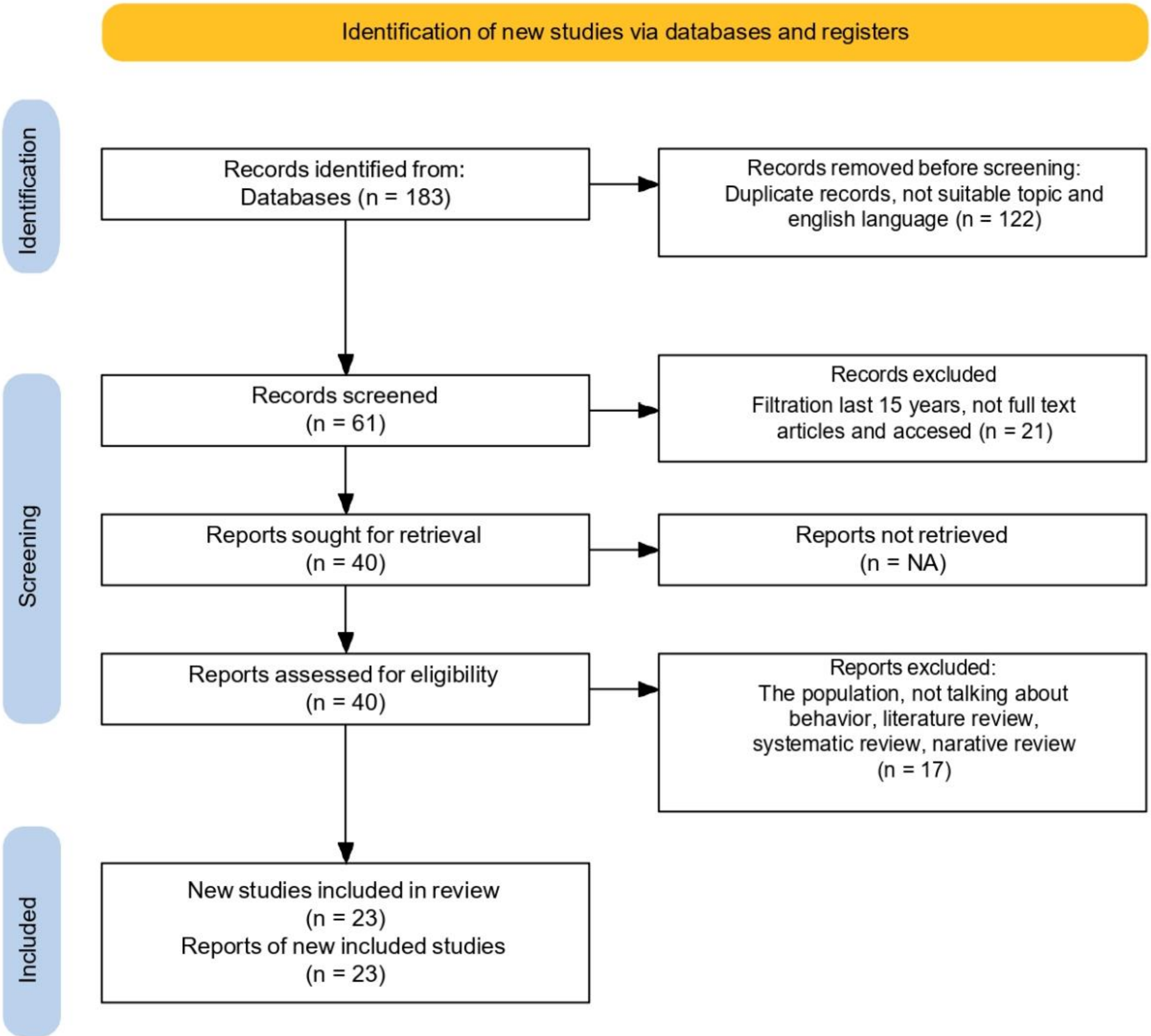

Figure 1. PRISMA Flowchart of Literature Search and Study Selection

Results and Discussion

Based on the data summarized in the systematic review, Table 1 highlights the effects of iron deficiency and iron supplementation on cognitive, behavioral, and neurodevelopmental outcomes across early life stages. Overall, multiple studies consistently indicate that iron status during the prenatal period, infancy, and early childhood plays a crucial role in long-term neurobehavioral development.

FIGURES AND TABLES

Table 1. Summary of the included studies.

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Iglesias–vázquez, L.; Canals-Sans, J.; Hernández-Martínez, C.; Voltas, N.; Arija, V.	Prenatal iron supplementation adjusted to maternal iron stores reduces behavioural problems in 4-year-old children	Maternal and Child Nutrition	2024	RCT	Tarragona, Spain.	230 non-anaemic pregnant women and their children (4-year follow-up)	Prenatal iron supplementation (20, 40, 80 mg/day) tailored by maternal Hb and serum ferritin levels	Child behavioural problems and executive function (CBCL, BRIEF-P, TRF) at 4 years	High-dose iron supplementation (80 mg/day) improved behavioural outcomes and executive function in children of mothers with low iron stores (SF < 15 µg/L), but worsened behavioural outcomes in children of mothers with normal–high iron stores (SF > 65 µg/L), except for depressive and attention/hyperactivity problems. Low-dose iron supplementation (20 mg/day) improved behaviour only in children whose mothers had normal–high iron stores	Individualized prenatal iron supplementation based on maternal iron status reduces behavioural problems, whereas excessive iron may adversely affect child behaviour

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Hua, M.; Shi, D.; Xu, W.; Zhu, L.; Hao, X.; Zhu, B.; Shu, Q.; Lozoff, B.; Geng, F.; Shao, J.	Differentiation between fetal and postnatal iron deficiency in altering brain substrates of cognitive control in pre-adolescence	BMC Medicine	2023	Longitudinal cohort study with neuroimaging (fMRI)	Southeastern China	71 children aged 8–11 years from a birth cohort	Fetal iron deficiency vs postnatal iron deficiency (9 months) vs iron-sufficient	Proactive and reactive cognitive control; behavioural performance and fMRI brain activation	All groups demonstrated the ability to use proactive and reactive cognitive control. The fetal ID group showed lower overall accuracy compared with postnatal ID and iron-sufficient groups. The iron-sufficient group exhibited greater brain activation in proactive versus reactive conditions, while this pattern was reversed in the postnatal ID group. No condition-related activation differences were observed in the fetal ID group, which instead showed increased activation in reward-related brain regions during proactive conditions	Timing of iron deficiency differentially alters long-term brain function supporting cognitive control
East, P.L.; Doom, J.R.; Blanco, E.; Burrows, R.; Lozoff, B.; Gahagan, S.	Iron Deficiency in Infancy and Sluggish Cognitive Tempo and ADHD Symptoms in Childhood and Adolescence	Journal of Clinical Child and Adolescent Psychology	2023	Longitudinal cohort	Santiago, Chile	N = 959 children (followed from infancy to 16 years)	Infant iron status at 12–18 months (iron sufficient, ID without anemia, ID anemia)	Sluggish cognitive tempo, ADHD symptoms, verbal and math abilitie	Greater severity of iron deficiency in infancy was associated with higher levels of sluggish cognitive tempo (SCT) and inattentive–hyperactive–impulsive (AD-HI) symptoms at ages 5, 10, and 16. Infant iron deficiency was not directly associated with math skills, but was indirectly associated with poorer verbal and math performance through increased AD-HI symptoms	Iron Deficiency in Infancy and Sluggish Cognitive Tempo and ADHD Symptoms in Childhood and Adolescence

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Geng, F.; Mai, X.; Zhan, J.; Xu, L.; Georgieff, M.K.; Shao, J.; Lozoff, B.	Timing of iron deficiency and recognition memory in infancy	Nutritional Neuroscience	2022	Longitudinal cohort study with neurophysiological assessment (ERP study)	Zhejiang Province, China	87 infants at 9 months; 112 infants at 18 months	Fetal–neonatal iron deficiency vs postnatal iron deficiency vs iron-sufficient	Recognition memory assessed using ERP components (Nc, LSW)	At 9 months, all groups showed attention differences (Nc) between mother and stranger faces, but only ID groups showed differences in memory-updating processes (LSW). At 18 months, iron-sufficient and postnatal ID groups showed condition-related differences in attention (Nc), whereas the fetal-neonatal ID group did not. No group showed LSW differences at 18 months. Brain regions involved differed by timing of iron deficiency.	Timing of iron deficiency and recognition memory in infancy
Nygren, G.; Linnsand, P.; Hermansson, J.; Dinkler, L.; Johansson, M.; Gillberg, C.	Feeding Problems Including Avoidant Restrictive Food Intake Disorder in Young Children With Autism Spectrum Disorder in a Multiethnic Population	Frontiers in Pediatrics	2021	Prospective longitudinal study with retrospective data analysis	Gothenburg, Sweden	46 preschool children with ASD	Presence of feeding problems and ARFID; nutritional deficiencies including iron deficiency	Feeding behaviour, BMI, nutritional status, persistence over time	Feeding problems were identified in 76% of children with ASD. Feeding disorders were present in 54%, including ARFID in 28% and other feeding disorders in 26%. Children with feeding problems more often had ASD level 2 severity and lower birth weight. ARFID was associated with very early onset feeding problems, low BMI, nutritional deficiencies (including iron deficiency), and persistent symptoms at 2-year follow-up.	Feeding problems including ARFID in young children with autism spectrum disorder

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
McCarthy, E.K.; Murray, D.M.; Hourihane, J.O.B.; Kenny, L.C.; Irvine, A.D.; Kiely, M.E.	Behavioral consequences at 5 y of neonatal iron deficiency in a low-risk maternal-infant cohort	American Journal of Clinical Nutrition	2021	Prospective longitudinal birth cohort study (observational)	Cork, Ireland	697 maternal–infant pairs (high-risk subgroup n=306)	Neonatal iron deficiency (cord ferritin <76 μg/L) vs iron-sufficient	Behavioural problems and cognitive outcomes at 5 years	Neonatal iron deficiency was not associated with cognitive outcomes at 2 or 5 years. Behavioral outcomes were largely similar after adjustment. In the high-risk subgroup, neonatal iron deficiency was associated with significantly higher internalizing and total problem behavior scores at 5 years, even after multivariable adjustment. Cognitive and IQ outcomes remained unaffected.	Behavioural consequences at 5 years of neonatal iron deficiency in a low-risk cohort
Doom, J.R.; Gahagan, S.; Caballero, G.; Encina, P.; Lozoff, B.	Infant iron deficiency, iron supplementation, and psychosocial stress as predictors of neurocognitive development in Chilean adolescents	Nutritional Neuroscience	2021	Prospective cohort follow-up	Santiago, Chile	796 adolescents (mean age 14.4 year	Infant iron status, iron supplementation, psychosocial stress	Executive function, processing speed, motor function, risk-taking	Infant psychosocial stress predicted poorer adolescent neurocognitive outcomes, including reduced risk-taking, poorer planning ability, and slower processing speed. Infant iron-deficiency anemia predicted lower risk-taking behavior. Iron supplementation in infancy showed limited long-term benefits and high-dose iron was associated with poorer motor and processing speed outcomes. No significant interactions were found between infant iron deficiency and psychosocial stress.	Infant iron deficiency, iron supplementation, and psychosocial stress as predictors of adolescent neurocognitive development

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Reid, B.M.; Doom, J.R.; Argote, R.B.; Correa-Burrows, P.; Lozoff, B.; Blanco, E.; Gahagan, S.	Pathways to inflammation in adolescence through early adversity, childhood depressive symptoms, and body mass index: A prospective longitudinal study of Chilean infants	Brain, Behavior, and Immunity	2020	Prospective longitudinal	Santiago, Chile	600 adolescents	Early-life adversity, BMI trajectory	Inflammation (hsCRP) in adolescence	Interpersonal conflict stress in infancy was indirectly associated with higher hsCRP levels in adolescence through higher childhood BMI intercept and steeper BMI growth trajectory. Childhood BMI (both early level and growth over time) was the strongest predictor of adolescent inflammation. Financial stress and maternal depressive symptoms in infancy were not directly associated with hsCRP. Depressive symptoms across childhood were not associated with inflammation.	Pathways to inflammation in adolescence through early adversity and BMI
Doom, J.R.; Richards, B.; Caballero, G.; Delva, J.; Gahagan, S.; Lozoff, B.	Infant Iron Deficiency and Iron Supplementation Predict Adolescent Internalizing, Externalizing, and Social Problems	Journal of Pediatrics	2018	Longitudinal follow-up study	Santiago, Chile	1018 adolescents; 893 parents	Infant iron deficiency and preventive iron supplementation	Internalizing, externalizing, and social problem	Adolescents with iron deficiency (with or without anemia) in infancy showed significantly higher internalizing, externalizing, and social problems in adolescence compared with iron-sufficient peers. Parent reports indicated higher social, ADHD, oppositional defiant, conduct, aggressive, rule-breaking, and PTSD problems, while adolescent self-reports showed higher anxiety and social problems. Iron supplementation in infancy was associated with lower parent-reported conduct problems but higher adolescent-reported ADHD symptoms.	Infant iron deficiency and iron supplementation predict adolescent behavioural problems

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
East, P.L.; Delker, E.; Lozoff, B.; Delva, J.; Castillo, M.; Gahagan, S.	Associations Among Infant Iron Deficiency, Childhood Emotion and Attention Regulation, and Adolescent Problem Behaviors	Child Development	2018	Longitudinal cohort study	Santiago, Chile	1,116 adolescents (original preventive trial cohort).	Severity of infant iron deficiency	Behavioural and socioemotional outcomes	Iron deficiency during infancy was associated with higher levels of internalizing (e.g., anxiety, depression), externalizing (e.g., aggression, rule-breaking), and social problems in adolescence. Associations persisted after adjustment for socioeconomic and perinatal factors. Severity of iron deficiency predicted magnitude of behavioral problems.	Long-term behavioural effects of infant iron deficiency
Berglund, S.K.; Chmielewska, A.; Starnberg, J.; Westrup, B.; Hägglöf, B.; Norman, M.; Domellöf, M.	Effects of iron supplementation of low-birth-weight infants on cognition and behavior at 7 years: A randomized controlled trial	Pediatric Research	2018	RCT	Sweden	285 marginally low-birth-weight infants (205 followed at 7 years)	Iron supplementation (1–2 mg/kg/day) vs placebo	Cognitive performance (IQ), behavioral problems (CBCL)	No significant differences in IQ scores across groups. However, iron-supplemented children had lower externalizing behavior scores (aggressive and rule-breaking) than placebo group. No differences in internalizing behavior or cognitive impairment.	Early iron supplementation reduces long-term behavioral problems but does not significantly affect cognitive outcomes
Algarín, C.; Karunakaran, K.D.; Reyes, S.; Morales, C.; Lozoff, B.; Peirano, P.; Biswal, B.	Differences on brain connectivity in adulthood are present in subjects with iron deficiency anemia in infancy	Frontiers in Aging Neuroscience	2017	Longitudinal cohort	Chile	31 young adults (14 former IDA; 17 controls).	History of infant IDA vs iron sufficient	Resting-state brain functional connectivity (DMN)	FIDA adults showed altered brain connectivity: decreased connectivity in posterior DMN regions (cuneus, PCC, parahippocampal gyrus) and increased connectivity in anterior DMN and dorsal attention networks (medial frontal gyrus, intraparietal lobule).	Infant IDA is associated with persistent alterations in brain network organization detectable in adulthood

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Moore, S.S.; Watemberg, N.	Syncope is a frequently under-diagnosed condition in infants and toddlers and has similar features to those seen in adolescents and adults	Acta Paediatrica, International Journal of Paediatrics	2016	Prospective longitudinal cohort study	Israel	37 children aged 0–6 years	Vasovagal syncope vs misdiagnosed conditions (e.g. epilepsy)	Clinical features, diagnostic procedures, recurrence	Individuals with iron deficiency anemia during infancy demonstrated significantly poorer executive function, lower educational attainment, and more symptoms related to inattention and behavioral regulation difficulties in adulthood compared with controls. These associations persisted after adjustment for socioeconomic and perinatal factors.	Vasovagal syncope in infants and toddlers has similar features to older children and is frequently misdiagnosed, leading to unnecessary investigations
Warthon-Medina, M.; Qualter, P.; Zavaleta, N.; Dillon, S.; Lazarte, F.; Lowe, N.M.	The long term impact of micronutrient supplementation during infancy on cognition and executive function performance in pre-school children	Nutrients	2015	RCT	Peru	902 infants initially; 182 children aged 36–48 months at follow-up	Multiple micronutrient supplementation vs iron alone during infancy	Intelligence (WPPSI), executive function, working memory, inhibition, social-emotional behavior	No significant differences between MMN and iron groups in IQ, working memory, inhibition, or social-emotional scores; gender differences observed (girls higher in verbal IQ and social competence; boys higher in problem behavior).	Multiple micronutrient supplementation during infancy did not confer additional long-term cognitive benefits compared with iron supplementation alone
Abdullah, K.; Thorpe, K.E.; Mamak, E.; Maguire, J.L.; Birken, C.S.; Fehlings, D.; Hanley, A.J.; MacArthur, C.; Zlotkin, S.H.; Parkin, P.C.	Optimizing early child development for young children with non-anemic iron deficiency in the primary care practice setting (OptEC): Study protocol for a randomized controlled trial	Trials	2015	RCT	Toronto, Ontario, Canada	150 children aged 12–40 months with non-anemic iron deficiency (NAID) (75 intervention, 75 placebo)	Oral iron supplementation plus dietary advice vs placebo plus dietary advice	Primary: Early child development (Early Learning Composite score); Secondary: hemoglobin, serum ferritin, child behavior	As a study protocol, no final results are reported. Primary outcome is change in child development (Early Learning Composite score) after 4 months. Secondary outcomes include hemoglobin, serum ferritin levels, and child behavior measures.	The trial is designed to determine whether 4 months of oral iron supplementation plus dietary advice improve developmental outcomes compared with placebo plus dietary advice in young children with NAID. The study aims to address gaps in evidence regarding early treatment of NAID.

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Surkan, P.J.; Charles, M.K.; Katz, J.; Siegel, E.H.; Khatry, S.K.; LeClerq, S.C.; Stoltzfus, R.J.; Tielsch, J.M.	The role of zinc and iron-folic acid supplementation on early child temperament and eating behaviors in rural Nepal: A randomized controlled trial	PLOS ONE	2015	Community-based cluster randomized controlled trial (2×2 factorial design)	Nepal	569 infants aged 4–17 months randomized into four groups (placebo, zinc, iron–folic acid, zinc + iron–folic acid)	Zinc supplementation vs no zinc; Iron–folic acid supplementation vs no iron–folic acid	Child temperament scores; child eating behavior scores	No significant effect of zinc or iron-folic acid on temperament or eating behaviors overall; only zinc improved eating behaviors among children with baseline iron-deficiency anemia (β = −0.3, 95% CI −0.6, −0.01).	Micronutrient supplementation showed no general behavioral benefits, but zinc supplementation may improve eating behaviors in iron-deficient anemic children
Molteno, C.D.; Jacobson, J.L.; Carter, R.C.; Dodge, N.C.; Jacobson, S.W.	Infant Emotional Withdrawal: A Precursor of Affective and Cognitive Disturbance in Fetal Alcohol Spectrum Disorders	Alcoholism: Clinical and Experimental Research	2014	Prospective longitudinal cohort study	Cape Town, South Africa	144 infants (subsamples: withdrawal n=85; interaction n=127; temperament n=119); longitudinal follow-up to 9 years	Exposure: Prenatal alcohol exposure (measured during pregnancy using timeline follow-back). Comparison: Non-exposed or minimally exposed infants	Infant emotional withdrawal (ADBB scale); mother–infant interaction; infant temperament; cognitive outcomes (IQ at 5 and 9 years); affective outcomes (Draw-A-Person test)	Prenatal alcohol exposure was associated with increased infant emotional withdrawal and reduced activity. Infant emotional withdrawal predicted poorer cognitive (IQ) and affective outcomes at ages 5 and 9 years. Emotional withdrawal was more pronounced in children later diagnosed with FAS or PFAS. These associations were independent of mother–infant interaction, infant temperament, maternal depression, and postpartum alcohol use.	Infant emotional withdrawal is an early, specific marker of prenatal alcohol exposure. It precedes formal FAS/PFAS diagnosis and independently predicts long-term cognitive and affective impairment, indicating that socioemotional disturbances in FASD originate early in neurodevelopment rather than as secondary effects of later cognitive deficits.

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Lozoff, B.; Smith, J.B.; Kaciroti, N.; Clark, K.M.; Guevara, S.; Jimenéz, E.	Functional significance of early-life iron deficiency: Outcomes at 25 years	Journal of Pediatrics	2013	Prospective longitudinal cohort study	San José, Costa Rica	122 young adults (33 chronic iron-deficient in infancy; 89 iron-sufficient)	Chronic severe iron deficiency in infancy vs iron-sufficient before/after therapy	Educational attainment, employment, marital status, emotional & mental health	Adults with chronic iron deficiency in infancy were less likely to complete secondary school (58% vs 20%), more likely to be single (84% vs 24%), and reported poorer emotional health and more negative emotions; No significant differences were found in employment or physical health outcomes. Associations persisted after adjustment for sex and socioeconomic status.	Chronic iron deficiency in infancy is associated with persistent adverse functional and psychosocial outcomes into adulthood, suggesting long-term loss of human potentia
Fuglestad, A.J.; Georgieff, M.K.; Iverson, S.L.; Miller, B.S.; Petryk, A.; Johnson, D.E.; Kroupina, M.	Iron deficiency after arrival is associated with general cognitive and behavioral impairment in post-institutionalized children adopted from eastern europe	Maternal and Child Health Journal	2013	Prospective longitudinal cohort study	United States	57 children	Iron-deficient vs iron-sufficient children post-adoption	Cognitive development (Mullen Scales), behavior (TBAQ-R), attention, hyperactivity	At baseline, 26% were iron deficient; at follow-up, 18% were iron deficient. Iron deficiency at follow-up was associated with significantly lower Mullen Early Learning Composite scores, poorer expressive language, and higher rates of inattention and hyperactivity. Eighty percent of iron-deficient children scored below average on cognitive testing compared with 32% of iron-sufficient children. Behavioral problems (inattention/hyperactivity) mediated the association between iron deficiency and cognitive performance.	Iron deficiency after adoption is linked to cognitive and behavioral impairment, highlighting the need for monitoring iron status during early post-adoption period

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Congdon, E.L.; Westerlund, A.; Algarín, C.; Peirano, P.; Gregas, M.; Lozoff, B.; Nelson, C.A.	Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years	Journal of Pediatrics	2012	Prospective longitudinal cohort study	Santiago, Chile	209 children (116 formerly iron-deficient anemic; 93 controls) followed to age 10 years	Former iron-deficiency anemia vs non-anemic controls	Event-related potentials (FN400, P300), recognition memory task	Behavioral accuracy on recognition memory tasks was comparable between groups. However, children with former iron-deficiency anemia showed slower reaction times, delayed FN400 latency, absence of the typical FN400 new/old effect, and reduced P300 amplitudes compared with controls, indicating altered neural processing of recognition memory despite normalized iron status.	Early-life iron deficiency causes long-lasting neurophysiological alterations in memory processing, persisting despite iron treatment
Bénéfice, E.; Lévi, P.; Banouvong, P.	Progressive growth deterioration in a context of nutritional transition: A case study from Vientiane (Lao PDR)	Annals of Human Biology	2012	Prospective longitudinal cohort study	Vientiane, Lao PDR	157 mother–infant pairs followed for 2 years; mothers (mean age 28.2 years) and their children from birth to early childhood	Level of urbanization (central zone vs. first and second urbanized belts); maternal nutritional intake and maternal anthropometric status	Maternal dietary intake (energy and micronutrients); child anthropometric indicators (HAZ, WAZ, WHZ); prevalence of stunting and wasting; birth weight	Maternal energy intake averaged ~83% of recommended requirements with deficiencies in calcium, vitamin A, folate, and iron. Child stunting prevalence was ~14%, with progressive decline in height-for-age over time, more pronounced among boys. Birth weight and maternal stature were significant predictors of child linear growth.	Urbanization level influences dietary patterns and the pace of nutritional transition. Despite relatively lower stunting prevalence compared to national data, children exhibited progressive growth deterioration over time. Maternal nutritional status and birth weight play a critical role in child linear growth, indicating intergenerational effects of malnutrition during early nutritional transition.

Author	Title Article	Journal	Publication Year	Study Design	Region	Population / Sample Size	Exposure / Comparison	Outcomes Assessed	Results	Summary of Findings
Turner, C.A.; Xie, D.; Zimmerman, B.M.; Calarge, C.A.	Iron Status in Toddlerhood Predicts Sensitivity to Psychostimulants in Children	Journal of Attention Disorders	2012	Retrospective observational study	USA	29 children (93% male; mostly ADHD)	Hematological indices in toddlerhood (Hb, MCV, RDW) vs sensitivity to psychostimulant dose	Psychostimulant sensitivity (weight-adjusted MPH dose)	Mean corpuscular volume (MCV) in toddlerhood significantly predicted sensitivity to psychostimulants years later; higher MCV linked to higher sensitivity (lower required dose); other indices showed trends but not significant	Early iron status may influence later dopaminergic response and treatment sensitivity in children with ADHD
Lukowski, A.F.; Koss, M.; Burden, M.J.; Jonides, J.; Nelson, C.A.; Kaciroti, N.; Jimenéz, E.; Lozoff, B.	Iron deficiency in infancy and neurocognitive functioning at 19 years: Evidence of long-term deficits in executive function and recognition memory	Nutritional Neuroscience	2010	Longitudinal cohort	Costa Rica	114 young adults (33 chronic iron-deficient; 81 iron-sufficient)	Chronic severe iron deficiency in infancy vs good iron status	Executive function, recognition memory, frontostriatal & hippocampal tasks	Formerly iron-deficient group showed more switching errors (set-shifting) on Trail Making; less initial planning time and more moves on difficult planning tasks; marginal deficits on extradimensional reversal; poorer pattern recognition memory at longer response latencies—reflecting frontostriatal and hippocampal vulnerabilities.	Chronic severe iron deficiency in infancy leads to long-term neurocognitive deficits, likely due to persistent alterations in dopamine systems and hippocampal function

Iron is an essential micronutrient that plays a critical role in brain development from gestation through early life, primarily through its involvement in myelination, neurotransmitter synthesis, and neuronal energy metabolism.[2] Maternal iron levels are directly linked to child neurodevelopment, as recent evidence from Iglesias-Vázquez et al (2024) highlights the importance of tailoring iron supplementation during pregnancy[6] according to maternal iron stores, which high doses benefit children's executive function when maternal iron reserves are low but may be detrimental when reserves are normal or high.[17] Similarly, Arija et al (2019) reported that maternal ferritin levels within the normal range and appropriate iron intake during pregnancy were associated with better working memory and executive function scores in children at 7 years of age. These findings strengthen the evidence for a link between prenatal iron status and long-term cognitive outcomes in children.[18]

Iron deficiency during critical periods such as the prenatal stage and early infancy can disrupt myelination and neuronal function, thereby increasing the risk of long-term impairments in cognition, attention, and learning ability.[19] Hua et al (2023) reported that early-life iron deficiency exerts differential effects on the activation of brain regions involved in cognitive control in preadolescent children. It implies that iron adequacy depends not only on quantity but also on timing of exposure, and suggests that iron supplementation alone may be insufficient to prevent alterations in brain function resulting from deficiency during sensitive periods of brain growth.[20] Consistent with this evidence, systematic reviews of randomized controlled trials and observational studies indicate that both iron deficiency and excess during pregnancy can harm children's mental and psychomotor development.[21] Mechanistically, iron deficiency impairs iron-dependent enzymatic activity, slows synapse formation, and affects the metabolism of dopamine and other neurotransmitters, ultimately influencing behavioral development and overall brain function.[19]

The timing of iron deficiency is a critical factor determining its impact on brain development and child behavior. Geng et al (2022) demonstrated that fetal-neonatal iron deficiency disrupts recognition memory as early as 9 months of age through alterations in ERP components associated with attention and memory updating.[22] In contrast, Doom et al (2021) and East et al (2023) reported that iron deficiency during infancy increases the risk of impaired executive function, attention deficits, and symptoms of ADHD and sluggish cognitive tempo (SCT) persisting into adolescence.[23,24] These findings are consistent with longitudinal research in Chile, which links iron deficiency between 6 and 18 months to poorer executive control, inattention, and SCT symptoms at age 10, as well as lower educational attainment in young adulthood.[25] Meanwhile, McCarthy et al (2021) found that neonatal iron deficiency did not significantly affect cognition at the age of five, but was associated with increased internalizing problems in high-risk groups.[26] Prenatal iron deficiency, associated with reduced brain iron accumulation, may increase the risk of delayed recognition memory, slower neural processing, and impairments in motor function. [27,28] Furthermore, Fuglestad et al (2013) reinforce the evidence that post-adoption iron deficiency also affects cognitive and behavioral development, including increased symptoms of inattention and hyperactivity. These findings strengthen the essential role of iron in central nervous system maturation, particularly during critical periods of brain development.[29]

During infancy and early childhood, iron deficiency is consistently linked to persistent impairments in attention regulation and executive function, which persist into adolescence.

East et al (2023) provided further evidence that iron deficiency between 12 and 18 months of age is linked to increased symptoms of SCT and ADHD, which may in turn exacerbate difficulties in emotional regulation, social interaction, and long-term academic performance.[23] Similarly, Doom et al (2021) demonstrated that early-life iron deficiency predicts deficits in executive function and processing speed during adolescence.[24] Iron deficiency reduces neuronal mitochondrial capacity for energy production, particularly in regions such as the hippocampus, thereby hindering neuronal maturation and brain plasticity, which effects may persist even after iron status is corrected.[30,31] Studied by Lozoff et al (2013) and Lukowski et al (2010), which showed that severe iron deficiency in infancy is associated with lower educational attainment, impaired planning, and memory deficits, highlighting the potential for long-lasting and difficult-to-reverse consequences.[32,33]

Besides cognitive outcomes, iron deficiency during infancy is closely associated with increased internalizing and externalizing behavioral problems, as well as difficulties in social and emotional regulation that persist into adolescence. A longitudinal study by Reid et al (2020) demonstrated that interpersonal stress in infancy is linked to heightened inflammation during adolescence through pathways mediated by body mass index (BMI), highlighting the importance of BMI and nutritional status as key mediators in neuroimmunological development.[34] Reid & Georgieff (2023) reported that early-life stress and iron deficiency synergistically elevate pro-inflammatory cytokines, such as IL-6, and activate the hypothalamic–pituitary–adrenocortical (HPA) axis. Through hepcidin regulation, these processes disrupt iron homeostasis and sustain chronic inflammation, thereby exacerbating adverse neurocognitive outcomes in children.[35] Similarly, Campbell et al (2020) reported that maternal prenatal stress and elevated pre-pregnancy BMI contribute to reduced fetal iron status, increasing the risk of infant iron deficiency and aggravating neuroimmunological dysfunction throughout childhood growth.[36]

Furthermore, Doom et al (2018) and East et al (2018) found that iron deficiency during infancy correlates with internalizing problems (anxiety and depression), externalizing behaviors (aggression and rule-breaking), and social difficulties during adolescence. It suggests that iron status is an independent predictor of behavioral development.[11,37] In addition, neuroimaging evidence from Algarín et al (2017) demonstrated long-term alterations in brain connectivity, particularly within the default mode network (DMN), among individuals with a history of iron-deficiency anemia in infancy, supporting the persistence of effects on executive function and memory.[38] Moreover, fMRI studies in young adults revealed reduced connectivity in networks involved in cognitive inhibitory control and attention, accompanied by increased posterior connectivity, which is thought to reflect compensatory mechanisms to maintain mental performance.[39]

Intervention through iron supplementation in low-birth-weight infants, as reported by Berglund et al (2018), was shown to reduce externalizing behavior scores such as aggression and rule-breaking, although it did not significantly affect IQ. Iron supplementation may have a greater impact on behavioral regulation than on cognitive function.[40] In contrast, multiple micronutrient supplementation (MMS) during infancy has not been shown to provide additional cognitive benefits compared to iron alone, as reported by Warthon-Medina et al (2015).[41] Similarly, Surkan et al (2015) reported that combined iron and zinc supplementation did not yield significant behavioral improvements overall. However, zinc appeared to improve eating behavior in children with iron-deficiency anemia.[42] These findings are further supported by a recent study by Lu et al (2024), which demonstrated that MMS did not significantly improve cognitive, language, or motor development, IQ, or the incidence of developmental disorders compared with placebo. This evidence indicates that the addition of micronutrients beyond iron does not provide substantial developmental advantages.[43]

In clinical practice, the OptEC protocol proposed by Abdullah et al (2015) emphasizes the importance of early intervention for non-anemic iron deficiency (NAID) through supplementation and dietary education, given the potential neurocognitive impact of subclinical iron deficiency.[44] Supporting this, addressing iron deficiency anemia more broadly requires integrated interventions across all life stages, with experts highlighting that health education and nutritional measures, including dietary education, should begin as early as adolescence to mitigate its intergenerational effects.[45]

Infants and preschool children with low iron status are at higher risk for attention problems, delayed language development, and emotional regulation difficulties compared to those with adequate iron status.[46] Additionally, Turner et al (2012) demonstrated that iron status in early childhood is associated with later responsiveness to psychostimulants, suggesting a role of iron in dopaminergic regulation.[47] Research on preterm infants further indicates that iron deficiency at 3 months is associated with reduced cerebellum–thalamus connectivity and lower motor scores, which improve following six months of iron supplementation.[48]

Furthermore, longitudinal studies by Congdon et al (2012) and Moore et al (2016) indicate that, even after iron status is normalized, neurophysiological alterations such as delayed FN400 latency and reduced P300 amplitude can persist up to 10 years of age, suggesting long-term impairments in memory processing.[49,50] These findings are supported by Molteno et al (2014), who identified early emotional disturbances, such as withdrawal, as predictors of later affective and cognitive dysfunction, particularly among children with prenatal alcohol exposure.[51] Iron deficiency disrupts brain energy metabolism, neurotransmitter synthesis (including dopamine and serotonin), and myelination, thereby inducing mitochondrial dysfunction and oxidative stress in the hippocampus, which ultimately contributes to impairments in memory and emotion regulation.[52,53]

Feeding disorders such as Avoidant Restrictive Food Intake Disorder (ARFID) in children with Autism Spectrum Disorder (ASD) have also become a concern. Nygren et al (2021) reported a prevalence of eating disorders of 76% among preschool children with ASD, with ARFID accounting for 28%. These disorders are associated with low BMI, nutrient deficiencies (including iron), and persistent symptoms that exacerbate the risk of developmental impairments.[54–56] In term of nutrient deficiencies in Indonesia, a study reported that anemia risk among children aged 6–36 months was significantly associated with the lack of cow's milk formula consumption and inadequate intake of essential nutrients, including fats, protein, calcium, vitamin D, iron, zinc, and vitamins A, C, B6, and B12[57], while clinical case studies report that children with ASD and ARFID face serious nutrition-related complications, such as vitamin and mineral deficiencies, which can affect bone health and growth, including conditions such as osteopenia and rickets.[58]

Environmental factors also play a critical role. A study in Laos by Bénéfice et al (2012) highlighted the influence of nutritional transition and maternal nutritional status on children's linear growth, emphasizing that dietary interventions must be multigenerational, including improvements in maternal nutrition before and during pregnancy.[59] It is supported by systematic reviews and pooled analyses across diverse low- and middle-income country settings, indicating that poor maternal nutrition which particularly characterized by low BMI or limited dietary diversity during pregnancy is associated with an increased risk of stunting and low birth weight in children.[60] Furthermore, evidence from multiple studies shows that children with iron deficiency anemia have a significantly higher risk of stunting (OR = 2.27; 95% CI: 1.30–3.95), suggesting a synergistic relationship between anemia and impaired linear growth despite the low certainty of evidence.[61]

Conclusion

Based on this systematic review, iron deficiency during the prenatal period and early infancy is associated with adverse behavioral and neurodevelopmental outcomes later in childhood and adolescence, particularly in areas such as attention, executive function, and emotional regulation. Evidence suggests that targeted, timing-specific iron supplementation can support optimal behavioral development, whereas non-targeted or excessive supplementation may provide limited benefits. Therefore, early detection and individualized iron interventions for pregnant women and infants are necessary to prevent long-term behavioral consequences. Strengthening maternal–infant nutrition programs and increasing awareness of early-life iron needs are crucial to mitigating the long-term effects of iron deficiency.

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Conflict of Interest

There are no conflict interest of this publication.

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