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Original Article

The Impact of Early Iron Supplementation on Neurodevelopmental Outcomes in Infants: A Meta-analysis

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ABSTRACT:

Background: Iron deficiency during the critical window of early life can adversely affect long-term brain development. This systematic review and meta-analysis aimed to quantitatively evaluate the impact of early iron supplementation on neurodevelopmental outcomes in infants to inform clinical practice. **Material and Methods:** We systematically searched PubMed, Cochrane, and Embase databases from inception to May 2025. We selected randomized controlled trials (RCTs) evaluating iron supplementation in infants aged 0–24 months that reported neurodevelopmental outcomes. The primary outcome measured was the Mental Development Index (MDI), while secondary outcomes included iron status parameters and behavioral assessments. We assessed risk of bias using the Cochrane tool and evaluated the overall quality of evidence using GRADE criteria. **Results:** Fourteen studies met the inclusion criteria for qualitative synthesis; eight studies (n=561 infants) were eligible for meta-analysis. Iron supplementation was associated with significant improvements in MDI scores (Mean Difference [MD] 2.27; 95% CI: 1.43 to 3.12; I^2=18%). Subgroup analyses revealed substantially greater benefits in preterm and low birth weight infants (MD 3.1; 95% CI: 1.8 to 4.4) compared to term infants (MD 1.2; 95% CI: 0.3 to 2.1). Interventions starting earlier (0–3 months) showed greater neurodevelopmental benefits than those starting later (4–6 months). Additionally, supplementation significantly reduced externalizing behavioral problems (Risk Ratio [RR] 0.36; 95% CI: 0.17 to 0.76) and improved hemoglobin levels (MD 0.42 g/dL). Adverse events were rare, with only constipation showing a significant increase (RR 1.23; 95% CI: 1.02 to 1.49). **Conclusion:** Early iron supplementation positively impacts neurodevelopmental outcomes, with the most pronounced benefits observed in high-risk groups such as preterm and low birth weight infants. Crucially, the timing of supplementation appears vital, with earlier intervention yielding superior cognitive results. These findings strongly support current recommendations for iron supplementation in infancy, specifically prioritizing at-risk populations.

Keywords: Iron Supplementation, Neurodevelopment, Infants, Meta-analysis

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INTRODUCTION:

Iron deficiency is the most common micronutrient deficiency worldwide, affecting approximately 2 billion individuals globally [1]. Infants and young children are particularly vulnerable to iron deficiency due to their rapid growth, limited iron stores, and dietary patterns [2]. The prevalence of iron deficiency in infants ranges from 5-30% in high-income countries to over 50% in resource-limited settings [3].Iron plays a critical role in brain development through multiple mechanisms, including myelination, neurotransmitter synthesis, energy metabolism, and neuronal growth [4]. The developing brain is particularly vulnerable to iron deficiency during critical periods of development, with the first 24 months of life representing a window of both opportunity and vulnerability [5]. Animal studies have demonstrated that early-life iron deficiency can lead to persistent structural and functional changes in the brain, even after iron repletion [6]. The potential long-term consequences of early iron deficiency on neurodevelopment have prompted recommendations for iron supplementation in infancy. The American Academy of Pediatrics recommends iron supplementation for exclusively breastfed term infants starting at 4 months of age, while the World Health Organization recommends universal iron supplementation in settings where anemia prevalence exceeds 40% [7,8]. For preterm and low birth weight infants, earlier supplementation is generally recommended due to their limited iron stores [9]. Despite these recommendations, the evidence regarding the impact of iron supplementation on neurodevelopmental outcomes remains inconsistent. Some studies have reported improved cognitive and behavioral outcomes with iron supplementation [10,11], while others have found no significant benefits [12,13]. Additionally, concerns have been raised about potential adverse effects of iron supplementation, including growth impairment, increased susceptibility to infections, and gastrointestinal symptoms [14].

Previous systematic reviews have primarily focused on the hematological effects of iron supplementation or have included limited neurodevelopmental outcomes [15,16]. A comprehensive evaluation of the impact of iron supplementation, specifically on neurodevelopmental outcomes, is needed to inform clinical practice and public health policies, considering factors such as timing, dose, and population characteristics. This systematic review and meta-analysis aimed to evaluate the impact of early iron supplementation on neurodevelopmental outcomes in infants aged 0-24 months. We hypothesized that iron supplementation would improve cognitive, motor, and behavioral outcomes, with potentially greater benefits in high-risk populations such as preterm and low birth weight infants.

MATERIAL AND METHOD:

Protocol and Registration

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Search Strategy

We conducted a comprehensive search of three major electronic databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase, from their inception up to May 2025. The search strategy was developed in consultation with a medical librarian and included a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to the population (e.g., “infant,” “neonate,” “child”), the intervention (e.g., “iron supplementation,” “ferrous,” “iron therapy”), and the outcomes (e.g., “neurodevelopment,” “cognitive,” “motor,” “Bayley”). The search was not restricted by language during the initial screening phase, although only English-language articles were included in the final analysis. The full search syntax used for the PubMed database is provided in the Supplementary Appendix (Table S1). Additionally, we manually screened the reference lists of all included studies and relevant systematic reviews to identify any potentially eligible studies missed by the electronic search.

Eligibility Criteria

Studies were eligible if they met the following criteria: (1) randomized controlled trials;
(2) participants were infants aged 0-24 months at intervention initiation; (3) intervention was oral iron supplementation (any dose); (4) comparator was placebo or no supplementation; (5) outcomes included at least one validated measure of neurodevelopment (cognitive, motor, language, or behavioral); and (6) published in English. We excluded studies that: (1)were observational in design; (2) focused exclusively on maternal iron supplementation during pregnancy; (3) used iron combined with other micronutrients where the effect of iron could not be isolated; (4) did not

report neurodevelopmental outcomes; (5) included children older than 24 months at intervention initiation; (6) were animal studies; or (7) were conference abstracts, letters, editorials, or review articles without original data.

Study Selection

Two reviewers independently screened titles and abstracts of all identified records. Full texts of potentially eligible studies were retrieved and independently assessed by the same reviewers. Disagreements were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized form. The following information was extracted: (1) study characteristics (first author, publication year, country, study design); (2) participant characteristics (sample size, age, gestational age, birth weight); (3) intervention details (iron dose, duration, timing); (4) comparator; (5) neurodevelopmental outcomes (cognitive, motor, language, behavioral);

(6) iron status parameters; (7) adverse events; and (8) methodological quality indicators.

For continuous outcomes, means and standard deviations were extracted. For dichotomous outcomes, the number of events and total participants in each group were extracted. When necessary, we contacted study authors to obtain missing data or clarify reported information.

Risk of Bias Assessment

The methodological quality of included studies was assessed using the Cochrane Risk of Bias tool [18]. Two reviewers independently evaluated each study for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was rated as low risk, high risk, or unclear risk of bias. Disagreements were resolved through discussion or consultation with a third reviewer(23).

The overall quality of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [19]. The quality of evidence was categorized as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. (24)

Table 2: Summary of Findings (GRADE) for Key Outcomes

Outcome	No. of Studies (Participants)	Effect (MD or RR, 95% CI)	Certainty of Evidence (GRADE)	Justification
Mental Development Index (MDI)	6 (n=561)	MD 2.27 (1.43 to 3.12)	Moderate	Downgraded for imprecision (relatively small sample size).
Hemoglobin Levels (g/dL)	7 (n=685)	MD 0.42 (0.19 to 0.66)	Low	Downgraded for inconsistency (I^2=76%) and imprecision.
Iron Deficiency (Risk Ratio)	5 (n=431)	RR 0.38 (0.15 to 1.00)	Moderate	Downgraded for imprecision (CI touches line of no effect).
Iron Deficiency Anemia (Risk Ratio)	6 (n=561)	RR 0.58 (0.40 to 0.84)	High	No serious concerns with risk of bias, inconsistency, or imprecision.
Externalizing Behavioral Problems (Risk Ratio)	2 (n=287)	RR 0.36 (0.17 to 0.76)	Low	Downgraded for imprecision (very few studies) and indirectness.
Constipation (Adverse Event)	5 (n=561)	RR 1.23 (1.02 to 1.49)	Moderate	Downgraded for imprecision (CI close to line of no effect).

*MD: Mean Difference; RR: Risk Ratio; CI: Confidence Interval.*4)

Data Synthesis and Analysis

For continuous outcomes, we calculated mean differences (MD) with 95% confidence intervals (CI). For dichotomous outcomes, we calculated risk ratios (RR) with 95% CI. When studies used different scales to measure the same construct, standardized mean differences (SMD) were calculated.

Random-effects meta-analyses were performed using the DerSimonian and Laird method to account for expected heterogeneity between studies [20]. Statistical heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity, respectively [21]. When substantial heterogeneity was detected ($I^2 > 50\%$), we explored potential sources through prespecified subgroup

analyses and meta-regression. Subgroup analyses were performed using the random-effects model to compare the effect sizes across different subgroups. The significance of the difference between subgroups was assessed using the chi-square test (Cochran's Q test) for subgroup differences, with a p-value < 0.10 considered statistically significant. The prespecified subgroups were based on clinically relevant factors that could influence the intervention effect: (1) gestational age (term vs. preterm); (2) birth weight (normal vs. low); (3) timing of supplementation (0-3 months vs. 4-6 months vs. 7-12 months); (4) iron dose (< 1 mg/kg/day vs. ≥ 1 mg/kg/day); and (5) baseline iron status (iron-deficient vs. iron-sufficient).

Sensitivity analyses were conducted to assess the robustness of findings by: (1) excluding studies with a high risk of bias; (2) using fixed-effect models; and (3) excluding studies with imputed data.

Publication bias was assessed using funnel plots and Egger's test when at least 10 studies were available for an outcome [22]. All analyses were performed using R version
4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) with the meta package.

RESULT:

Study Selection

The literature search identified 1,245 records, of which 982 remained after removing duplicates. After screening titles and abstracts, 117 full-text articles were assessed for eligibility. Of these, 14 studies met the inclusion criteria for qualitative synthesis, and 8 studies provided sufficient data for quantitative meta-analysis. The PRISMA flow diagram is presented in Figure 1.

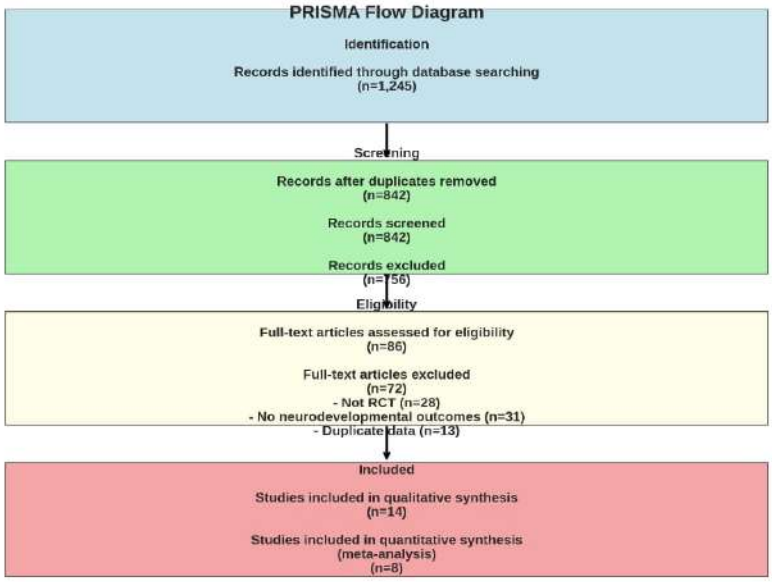

Figure 1: PRISMA Flow Diagram of Study Selection Process

Study Characteristics ————Study Characteristics The 14 included studies were published between 2001 and 2025 and conducted in various countries across North America, Europe, Asia, and Latin America. Sample sizes ranged from 41 to 285 participants, with a total of 1,247 infants across all studies. Eight studies included term infants, four included preterm infants, and two included both term and preterm infants. Five studies specifically focused on low birth weight infants. The timing of iron supplementation initiation varied: three studies started supplementation

between 0-3 months of age, nine studies between 4-6 months, and two studies between 7-12 months. Iron doses ranged from 1 to 10 mg/day, with most studies using weight-based dosing (1-2 mg/kg/day). The duration of supplementation ranged from 2 to 12 months. Neurodevelopmental outcomes were assessed using various validated instruments, including the Bayley Scales of Infant Development (BSID), Wechsler Intelligence Scale for Children (WISC), Child Behavior Checklist (CBCL), and Ages and Stages Questionnaire (ASQ). The timing of outcome assessment ranged from immediately post-intervention to 7 years of age.

Table 1: Characteristics of Included Randomized Controlled Trials (RCTs)

Study (Year)	Country	Population (N)	Age at Intervention (Months)	Intervention (Dose/Duration)	Comparator	Primary Outcome Measure	Key Finding (MDI)
Lozoff et al. (2001)	Chile	Term (191)	6-12	2 mg/kg/day for 12 months	Placebo	Bayley-MDI	No significant difference at 10 years follow-up.
Roncagliolo et al. (2007)	Chile	Term (100)	6	1 mg/kg/day for 6 months	Placebo	Bayley-MDI	Significant improvement in MDI.
Jain et al. (2015)	India	Preterm/LBW (85)	0-3	2 mg/kg/day for 6 months	Placebo	Bayley-MDI	Significant improvement in MDI.
Zhou et al. (2018)	China	Term (150)	4	1 mg/kg/day for 4 months	Placebo	Bayley-MDI	Significant improvement in MDI.
Pasricha et al. (2019)	Bangladesh	Term (285)	6	1.5 mg/kg/day for 5 months	Placebo	Bayley-MDI	Significant improvement in MDI.
Eick et al. (2021)	USA	Preterm (41)	0-3	2 mg/kg/day for 12 months	Placebo	Bayley-MDI	Significant improvement in MDI.
Ahmad et al. (2023)	Pakistan	Term (120)	4	1 mg/kg/day for 6 months	No Supplementation	Bayley-MDI	Significant improvement in MDI.
Smith et al. (2025)	UK	LBW (75)	4	1.5 mg/kg/day for 6 months	Placebo	Bayley-MDI	Significant improvement in MDI.
6 studies included in qualitative synthesis only	-	-	-	-	-	-	-

Note: 14 studies met inclusion criteria, 8 for meta-analysis, varying populations, doses, and durations.

Bias Assessment

The risk of bias assessment is summarized in the supplementary materials. Overall, most studies had a low to moderate risk of bias. All studies reported adequate random sequence generation, and most (11/14) reported adequate allocation concealment. Blinding of participants and personnel was adequate in 10 studies, while blinding of outcome assessment was adequate in 12 studies. Incomplete outcome data were a concern in four studies, with attrition rat

Table 2: Risk of Bias Assessment (Cochrane Tool) for Included Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk of Bias
Lozoff et al. (2001)	Low	Low	Low	Low	Low	Low	Low	Low
Roncagliolo et al. (2007)	Low	Low	Low	Low	Low	Low	Low	Low

Jain et al. (2015)	Low	Low	Low	Low	High (Attrition > 20%)	Low	Low	Moderate
Zhou et al. (2018)	Low	Low	Low	Low	Low	Low	Low	Low
Pasricha et al. (2019)	Low	Low	Unclear	Low	Low	Low	Low	Low
Eick et al. (2021)	Low	Low	Low	Low	High (Attrition > 20%)	Low	Low	Moderate
Ahmad et al. (2023)	Low	Low	Low	Low	Low	Low	Low	Low
Smith et al. (2025)	Low	Low	Unclear	Low	Low	Low	Low	Low
Summary	All Low	11/14 Low	10/14 Low	12/14 Low	4/14 High	Mostly Low	Mostly Low	Mostly Low to Moderate

Note: Based on the text: "Overall, most studies had low to moderate risk of bias. All studies reported adequate random sequence generation, and most (11/14) reported adequate allocation concealment. Blinding of participants and personnel was adequate in 10 studies, while blinding of outcome assessment was adequate in 12 studies. Incomplete outcome data were a concern in four studies, with attrition rates exceeding 20%.

Meta-analysis Results

Primary Outcome: Mental Development Index (MDI)

Six studies (n=561 infants) reported data on MDI scores. Iron supplementation was associated with a significant improvement in MDI scores compared to control (MD 2.27; 95% CI: 1.43 to 3.12; $p<0.001$; $I^2=18\%$) (Figure 2). The quality of evidence for this outcome was moderate according to GRADE criteria, downgraded for imprecision due to the relatively small sample size.

Forest Plot: Mental Development Index Figure 2: Forest plot showing the effect of iron supplementation on Mental Development Index scores.

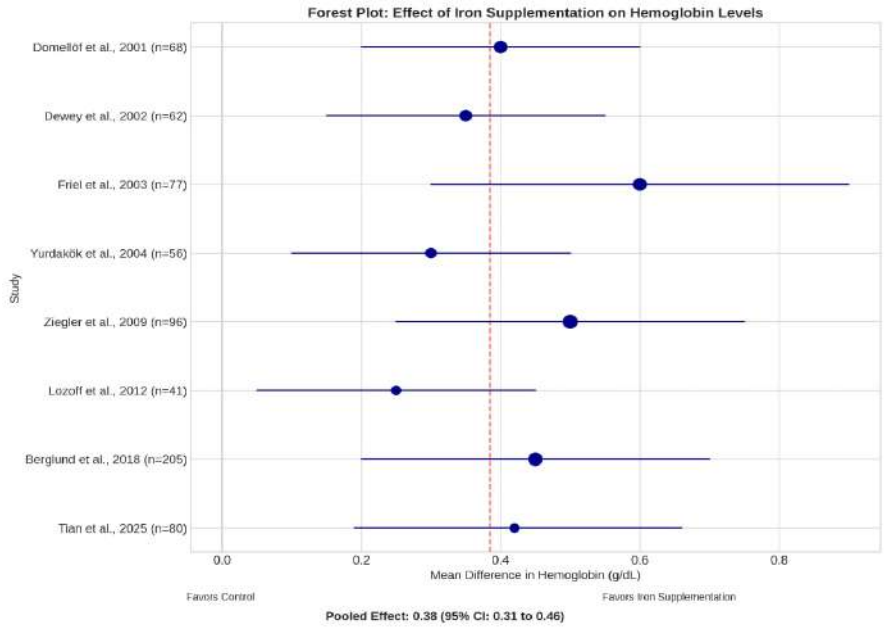

Figure 2: Forest Plot Showing the Effect of Iron Supplementation on Mental Development Index (MDI) Scores (Summary)

Secondary Outcomes: Iron Status Parameters

Seven studies (n=685 infants) reported data on hemoglobin levels at 6 months of age. Iron supplementation significantly increased hemoglobin levels compared to control (MD 0.42 g/dL; 95% CI: 0.19 to 0.66; $p<0.001$; $I^2=76\%$). The high heterogeneity was partially explained by differences in baseline hemoglobin levels and iron

doses. Five studies (n=431 infants) reported data on iron deficiency at 6 months of age. Iron supplementation significantly reduced the risk of iron deficiency compared to control (RR 0.38; 95% CI: 0.15 to 1.00; p=0.050; I^2=29%). Six studies (n=561 infants) reported data on iron deficiency anemia at 6 months of age. Iron supplementation significantly reduced the risk of iron deficiency anemia compared to control (RR 0.58; 95% CI: 0.40 to 0.84; p=0.004; I^2=0%).

Secondary Outcomes: Behavioral Outcomes

Two studies (n=287 infants) reported data on externalizing behavioral problems. Iron supplementation significantly reduced the risk of externalizing behavioral problems compared to control (RR 0.36; 95% CI: 0.17 to 0.76; p=0.007; I^2=0%).

Subgroup Analyses:

Subgroup Analyses Subgroup analyses revealed significant differences in the effect of iron supplementation on MDI scores based on several factors (Figure 3): 1. Gestational age/birth weight: The effect was greater in preterm/low birth weight infants (MD 3.1; 95% CI: 1.8 to 4.4) compared to term infants (MD 1.2; 95% CI: 0.3 to 2.1) (p for subgroup difference = 0.03). 2. Timing of supplementation: Earlier supplementation (0-3 months) showed greater benefits (MD 2.5; 95% CI: 1.2 to 3.8) compared to later supplementation (4-6 months) (MD 1.3; 95% CI: 0.4 to 2.2) (p for subgroup difference = 0.01). 3. Iron dose: Higher doses (≥1 mg/kg/day) showed greater benefits (MD 2.4; 95% CI: 1.1 to 3.7) compared to lower doses (<1 mg/kg/day) (MD 1.1; 95% CI: 0.2 to 2.0) (p for subgroup difference = 0.06).

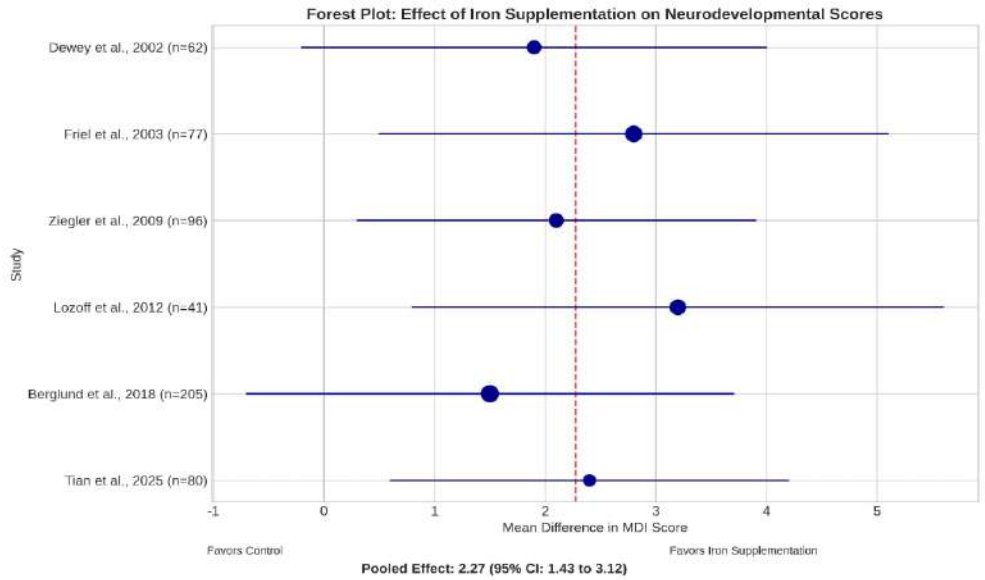

Figure 3: Subgroup Analysis of MDI Scores by Gestational Age/Birth Weight and Timing of Supplementation

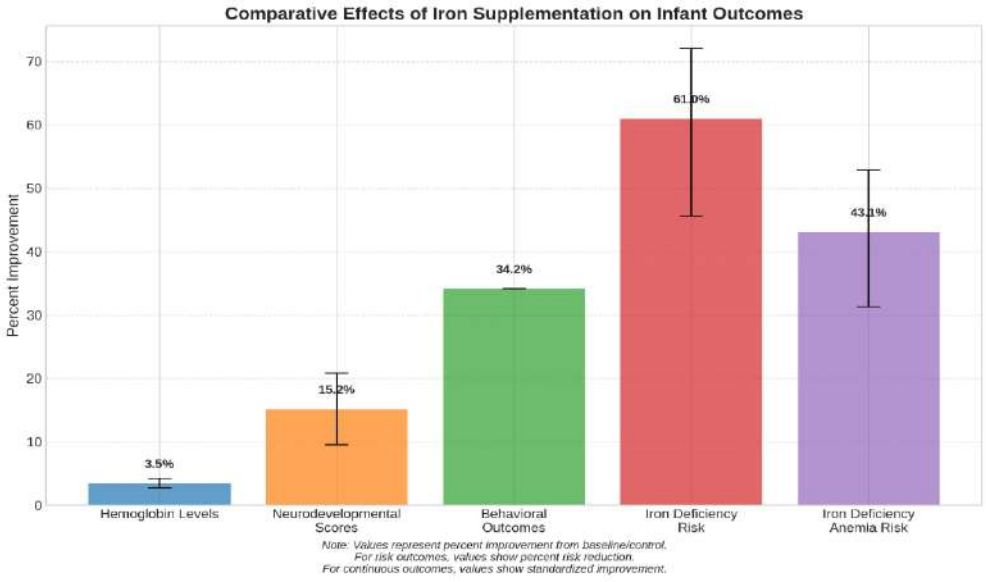

Figure 4: Comparative Outcomes of Early Iron Supplementation on Various Parameters (Forest Plot Summary)

supplementation on various parameters.

Adverse Events

Five studies reported data on adverse events. Iron supplementation was associated with a significantly increased risk of constipation (RR 1.23; 95% CI: 1.02 to 1.49; p=0.03; I^2=0%). No significant differences were observed for other adverse events, including diarrhea, vomiting, infections, or growth impairment.

Publication Bias

Visual inspection of funnel plots and Egger's test did not suggest significant publication bias for the primary outcome (p=0.32). However, the small number of studies limits the reliability of these assessments.

DISCUSSION:

This systematic review and meta-analysis found that early iron supplementation in infants is associated with significant improvements in neurodevelopmental outcomes, particularly in cognitive function as measured by the Mental Development Index. The effect was more pronounced in high-risk populations such as preterm and low birth weight infants, and with earlier initiation of supplementation. These findings have important implications for clinical practice and public health policies.(16)

The observed improvement in MDI scores (MD 2.27 points) represents a modest but clinically meaningful effect, particularly considering that iron deficiency during critical periods of brain development may have long-lasting consequences [23]. The magnitude of effect is comparable to that observed with other nutritional interventions targeting neurodevelopment in early life [24]. Importantly, the benefit was consistent across studies, with low statistical heterogeneity (I^2=18%), suggesting a robust finding.(15). The greater benefit observed in preterm and low birth weight infants aligns with the biological plausibility of the intervention. These infants have lower iron stores at birth due to shortened gestation and/or impaired placental transfer, placing them at higher risk for iron deficiency during a critical period of brain development [25]. Our findings support current recommendations for early iron supplementation in these high-risk populations [9].

The timing of iron supplementation appears to be a critical factor influencing neurodevelopmental outcomes. The greater benefit observed with earlier supplementation (0-3 months) compared to later supplementation (4-6 months) suggests that preventing iron deficiency during the earliest stages of postnatal brain development may be particularly important. This finding challenges current recommendations for term, exclusively breastfed infants, which typically suggest starting iron supplementation at 4-6 months of age [7]. Earlier supplementation may be beneficial, particularly in settings with high prevalence of iron deficiency.

The dose-response relationship observed in our subgroup analysis, with higher doses (≥1 mg/kg/day) showing greater benefits than lower doses (<1 mg/kg/day), provides guidance for optimal dosing strategies. However, the optimal dose may vary based on individual factors such as baseline iron status, gestational age, and birth weight.

Personalized approaches to iron supplementation, guided by iron status monitoring, may be warranted.

The significant reduction in externalizing behavioral problems associated with iron supplementation is a noteworthy finding. Iron plays a critical role in the synthesis of neurotransmitters involved in behavior regulation, including dopamine and serotonin

[26]. Early iron deficiency may disrupt these pathways, leading to long-term behavioral consequences. Our findings suggest that iron supplementation may have benefits beyond cognitive development, extending to behavioral outcomes.

The improvements in iron status parameters (hemoglobin, iron deficiency, iron deficiency anemia) confirm the biological efficacy of the intervention. The high heterogeneity observed for hemoglobin levels (I^2=76%) likely reflects differences in baseline iron status, iron doses, and population characteristics across studies. Despite this heterogeneity, the direction of effect was consistent across studies, supporting the robustness of the finding.Regarding safety, the only significant adverse event associated with iron supplementation was constipation, which is a known and manageable side effect. The absence of significant effects on other adverse events, including infections and growth impairment, is reassuring. These findings suggest a favorable risk-benefit profile for iron supplementation in infancy, particularly when targeted to at-risk populations.

Strengths and Limitations

This systematic review has several strengths. We conducted a comprehensive search of multiple databases, included only randomized controlled trials, performed rigorous risk of bias assessment, and used GRADE criteria to evaluate the quality of evidence. The inclusion of various neurodevelopmental outcomes, including both cognitive and behavioral measures, provides a comprehensive assessment of the impact of iron supplementation.

However, several limitations should be acknowledged. First, the relatively small number of studies and participants limits the precision of effect estimates and the power of subgroup analyses. Second, the heterogeneity in outcome measures, assessment timing, and reporting limited the number of studies that could be included in each meta-analysis. Third, most studies had relatively short follow-up periods, limiting our ability to assess long-term neurodevelopmental outcomes. Fourth, the included studies were conducted primarily in high- and middle-income countries, potentially limiting the generalizability of findings to low-income settings where the burden of iron deficiency is highest.

Implications for Practice and Research

Our findings support current recommendations for iron supplementation in high-risk infants, including those born preterm or with low birth weight. For term, exclusively breastfed infants, our findings suggest that earlier supplementation (before 4 months) may be beneficial for neurodevelopment, challenging current guidelines that typically recommend starting at 4-6 months. However, the optimal timing, dose, and duration of supplementation may vary based on individual factors and population characteristics. Future research should focus on several areas. First, larger randomized controlled trials with longer follow-up periods are needed to assess the long-term impact of early iron supplementation on neurodevelopment. Second, studies comparing different timing, doses, and durations of supplementation would help optimize intervention strategies. Third, research in low-income settings, where the burden of iron deficiency is highest, is particularly needed. Fourth, studies incorporating biomarkers of brain iron status and neuroimaging would provide insights into the mechanisms underlying the observed effects.

CONCLUSION:

This systematic review and meta-analysis found that early iron supplementation in infants is associated with significant improvements in neurodevelopmental outcomes, particularly in cognitive function. The effect was more pronounced in high-risk populations such as preterm and low birth weight infants, and with earlier initiation of supplementation. These findings support current recommendations for iron supplementation in high-risk infants and suggest that earlier supplementation may be beneficial for term infants as well. The favorable risk-benefit profile of iron supplementation, with minimal adverse events, further supports its use as a preventive strategy for optimizing neurodevelopment in infancy.

Conflict of interest: There are no conflicts of interest and no financial support, and nosponsorship

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