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Post-Motor Development Outcome in Pediatric Population Receiving Iron Supplementation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Iron's vital role in early neurodevelopment, especially in motor skill acquisition, underscores its importance for pediatric health professionals and researchers, emphasizing the need to understand how supplementation impacts outcomes.
Methods: This study was conducted following PRISMA guidelines. We conducted a systematic search of PubMed, DOAJ, and Scopus for studies assessing motor development measured with the Bayley Scales of Infant Development among children receiving iron supplementation. A random-effects meta-analysis was performed to evaluate the pooled mean motor score. The pooled post-supplementation ferritin levels varied widely, with a mean of 76.62 (95% CI: −30.86; 184.10), highlighting the complexity and importance of personalized approaches in iron management for clinicians and researchers.
Conclusion: While current evidence suggests iron supplementation supports normal motor development, the variability in ferritin levels and unclear dose-response relationships should motivate healthcare professionals to pursue further research to optimize strategies for neurodevelopmental benefits.

Keywords: *Iron Supplementation, Ferritin, Motor Development, Pediatric.*
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INTRODUCTION

Iron is critically important for early neurodevelopment, especially in relation to the acquisition of motor skills, but the effect of iron supplementation on motor outcomes is not clear. Acute iron deficiency is among the commonest forms of micronutrient malnutrition globally, with infants and early childhood being high-risk periods. In several low- and middle-income countries, the range of anemic children younger than four years was 46-66%, about half of which is attributable to iron deficiency.[1,2] Iron deficiency during early life has been linked to structural and metabolic abnormalities of the central nervous system (CNS), as well as long term cognitive and behavioral deficits, retardation of growth, impaired immunity, and altered psychosocial development. These conditions interfere with motor development during critical periods of brain maturation.[3,4]

Multiple risk factors drive pediatric iron deficiency. Insufficient dietary intake and low iron bioavailability, impaired intestinal absorption from protein-energy malnutrition, and rapid growth periods markedly increase iron accumulation. Preterm and low-birthweight infants are at especially high risk because they have smaller iron stores at birth, as shortened gestation limits third-trimester iron accretion, while often experiencing accelerated postnatal growth.[3,4]

Iron is ubiquitous, performing numerous essential functions in addition to its role as a constituent of hemoglobin. Iron derived from these molecules is transported on transferrin and stored predominantly as ferritin, or in the less soluble polymeric form named hemosiderin. Assessment of the serum ferritin concentration is a well-established surrogate for total body iron stores, and therefore, it acts as both a diagnostic biomarker of iron status.[5] Iron is necessary for processes that are integral to visceral synaptic transmission and motor pathway maturation. Energy metabolism, myelination, and dopaminergic signaling deficits provide a coherent mechanism with which early-life iron insufficiency disrupts the development of motor skills.[3-7]

While routine iron supplementation is broadly recommended to that it may limit deficiency, population recommendations for group intake differ from those proposed for therapeutic dosing used in treatment and from requirements in specific groups, including preterm and low-birthweight infants. National policy guidelines by the Indonesian Pediatric Society or *Ikatan Dokter Anak Indonesia* (IDAI) recommend routine iron supplementation in all infants and children aged less than two years with a high prevalence of iron deficiency living at risk or not consuming iron-fortified foods. But these population targets vary from therapeutic regimens as well as from requirements in unique cohorts.[8]

Clinical trials and programmatic protocols differ considerably in dosing, frequency, formulation, duration of treatment, and timing with respect to both infancy and periods of rapid growth. This heterogeneity likely contributes to inconsistent findings on neurodevelopmental outcomes despite consistent hematologic improvements.[3,7,9]

Standardized neurodevelopmental measures such as the Bayley Scales allow domain-specific comparisons, including fine/gross motor subscales. Therefore, this scoring is suitable for claiming evidence across studies.[10,11] Despite strong biological plausibility and routine use of iron supplementation, uncertainty remains about the dose-response relationship between iron parameters, supplementation dosing, and motor development outcomes. Therefore, this systematic review and meta-analysis aim to evaluate whether and how iron status, such as ferritin and iron supplementation dose, relates to motor development in pediatric populations, using standardized motor outcomes as the primary outcome measure.

METHODS

This study was conducted according to PRISMA guidelines. We searched PubMed, DOAJ, and Scopus via Publish or Perish version 8.6.4198.8332 for studies reporting motor development measured using the Bayley Scales in children receiving iron supplementation. A random-effects meta-analysis was used to pool outcomes. We searched online databases for studies reporting iron supplementation doses that affect motor development outcomes in pediatric populations. Although we do not restrict studies based on their year of publication, we exclude articles based on reasons such as 1). The study was duplicated or is a previous version of a follow-up study derived fully/partially from the same set of patients; 2). The study is irretrievable; 3). The study is not a peer-reviewed journal article; 4). The study was not written in English; 5). The study reported fewer than 5 subjects; 6). The study did not report on pediatric patients; and 7). The study did not report on the effect of iron on motor development measured by Bayley's Scales of Infant and Toddler Development.

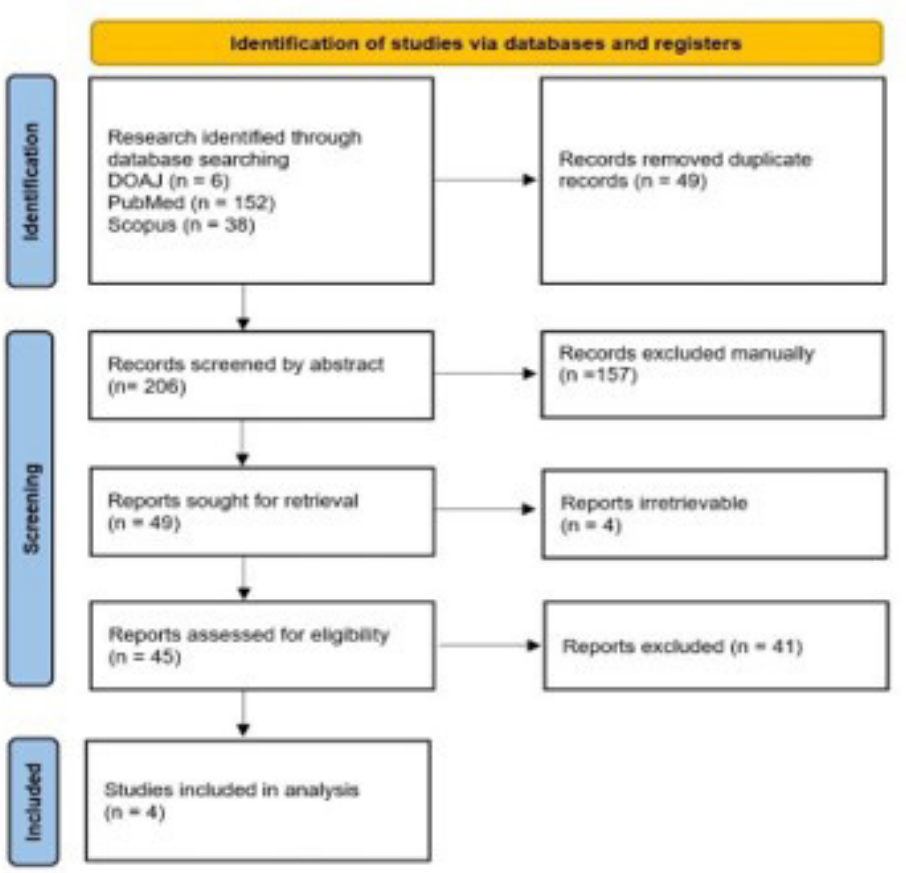


Figure 1. PRISMA Diagram Flow Chart

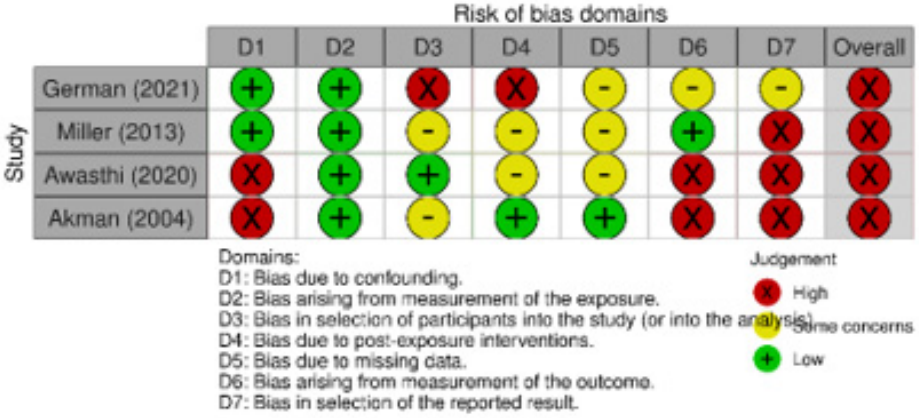


Figure 2. Risk of Bias using ROBINS-E

Data gathered in the standardized sheets were as follows: 1) Study profile: first author and year of publication; 2) Study design: number of subjects; 3) Subject profile, which includes the following: 3a) Age and 3b) Sex; 4) Primary outcome: motor development scores assessed via Bayley Scales of Infant Development-III, and 5). Secondary outcome: moderating factors such as age at supplementation, baseline iron status, duration of intervention, and co-interventions. A random-effects model was employed alongside Knapp-Hartung adjustments to measure confidence intervals and a restricted maximum likelihood estimator (REML) to calculate heterogeneity variance. The effect of iron supplementation dose on motor development outcomes, as measured by standardized developmentalassessment

Table 1. **Iron Supplementation Dose and Motor Development; IDA: Iron Deficiency Anemia, NAID: Non-Anemic Iron Deficiency, GA: Gestational Age, SD: Standard Deviation**

Study (year)	Total Sample (n)	Subjects (% male)	Age	Iron Supplementation Dose	Bayley scales pre-supplementation	Bayley scales post-supplementation	Serum iron (ng/mL)	Duration given (weeks)
German KR (2021)	62	59.7% (37/62)	28.1 weeks GA at birth (± 2.6 weeks)	6.1 mg/kg/day (at 30 days) 7.6 mg/kg/day (at 60 days) 7.8 mg/kg/day (at 90 days)	Not available	Motor: 89.1 (SD 10.7) Bayley was only assessed at 24 months	Not directly measured Median ferritin per infant: 75.9 (± 69.4) Median ZnPP/H per infant: 165.1 (± 64.6)	12 to 13
Miller SM (2013)	41	49% (20/41)	28.8 weeks GA at birth	10.4 mg/kg/day	Not available	Motor: 100 (SD 11) (treatment)	Treatment: Start 187±131 → End 176±118	3
Awasthi S (2020)	80	46,30%	6 months	0.5 mg/kg/day	Not available	Motor: 103.9 (SD 8.11)	Ferritin at 12 months: 27.0	26
M. Akman (2004)	IDA 37 NAID 40	60.9% IDA: 25 (59.5%) NAID: 25 (62.5%)	Mean age: 17.0 ± 7.0 months; IDA: 14.6 ± 6.5 NAID: 18.5 ± 6.1	6 mg/kg/day	IDA: Motor 87.45 ± 12.25 NAID: Motor 93.77 ± 11.52	IDA: 12.00; Motor 93.78 ± 11.10 NAID: Motor 97.82 ± 10.67	Ferritin levels: Pre-treatment: IDA 5.57 ± 3.77 NAID 7.23 ± 3.39 Post-treatment (after 3 months): IDA 28.06 ± 16.48 NAID Tr+ 33.49 ± 20.05	12

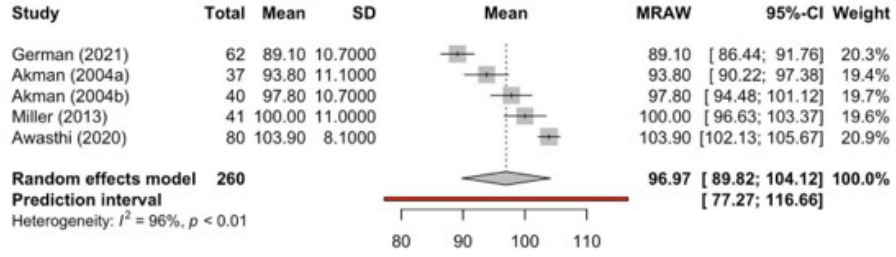


Figure 3. Forest Plot of Bayley Scores Across Studies

tools (Bayley Scales of Infant Development-III), commonly reported in composite scores or percentiles, will be summarized with a forest plot. Heterogeneity (I2) was categorized as low (75%). Statistical analyses were performed with R version 2023.6.2+561.

The process of screening is displayed in the PRISMA diagram (Figure 1). Risk of bias was assessed using the ROBINS-E (Risk of Bias in Non-Randomized Studies of Exposures), and it was visualized using the Robvis tool (Figure 2).

RESULTS

Out of the studies included for review, one was published in 2004, another in 2013, a study in 2020, and the last one in 2021. The studies are as follows from four countries: Akman et al., which was carried out in Turkey, Miller et al. in Canada, German et al., which was also done in Canada, and Awasthi et al., which was completed in India. In total, the four studies contributed 1094 subjects to our synthesis. Akman et al., and Miller et al., in a cohort study, they included 94 children. Included 64 patients, German et al. reported data from 920 children and adolescents, whereas Awasthi et al. included 16 pediatric subjects. Complete demographic data are shown in Table 1.

Four studies (n=260) were included. The pooled Bayley motor score after supplementation was 96.97 (95% CI 89.82 to 104.12). Pooled ferritin response was heterogeneous (mean 76.62; 95% CI −30.86 to 184.10), and there was substantial between-study heterogeneity. There was considerable heterogeneity across included studies, with large variability in participant characteristics, baseline iron status, and supplementation regimens. The small number of included studies and relatively small sample sizes also limit the interpretation of these findings, which may affect the applicability and generalizability of pooled estimates. The Bayley motor score forest plot includes five studies that show individual study post-supplementation means ranging from 89.1 to 103.9 (Figure 3). The pooled Bayley motor score was 96.97 (95% CI 89.82-104.12) with a prediction interval of 77.27-116.66, indicating that the overall motor development score was within the normal range. (Figure 3). Statistical heterogeneity showed that the variability of this study is very high ($I^2 = 96\%$, $p < 0.01$).

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The serum ferritin forest plot includes four studies and was dominated by high variability, ranging from 28.1 to 176.0. The pooled ferritin estimate was 76.62 µg/L (95% CI -30.86 to 184.10) with an extremely wide prediction interval -240.82 to 394.06, and heterogeneity $I^2 = 97\%$, $p < 0.01$. The ferritin estimate showed a very wide confidence interval that crossed zero along with a broad prediction interval, indicating substantial between-study variability and limited precision of the pooled result (Figure 4).

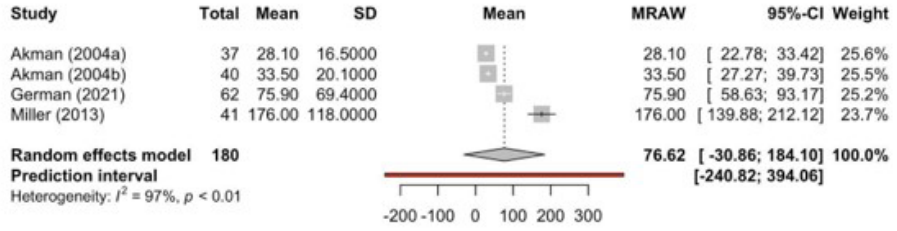


Figure 4. Forest Plot of Ferritin Levels Across Studies

DISCUSSION

This study investigated the association between iron supplementation, iron status biomarkers, and motor development outcomes in the pediatric population. Our pooled results suggest that iron supplementation was associated with motor development scores within normal developmental ranges based on Bayley motor testing. However, we did not find strong evidence that ferritin response or post-treatment iron status directly predicted motor score outcomes. These results indicate a potential supportive role for iron supplementation but also highlight uncertainty regarding the benefit of giving iron supplementation to the pediatric population.

Our primary analysis demonstrated that the pooled post-intervention Bayley motor score was 96.97, which is within the normal range developmentally. While this outcome indicates that iron supplementation may be sufficient to sustain motor development, it does not necessarily validate improvement beyond neurodevelopmental expectations. In contrast, the pooled ferritin response was markedly heterogeneous (estimated mean 76.62 µg/L in the supplemental group), indicating that supplementary iron does not lead to a consistent increase in stores over and above other populations, as suggested by this biomarker report directly related to neurodevelopmental function during early childhood. The combination of normal motor development and variable biochemical response raises the possibility that motor trajectories may depend on factors beyond iron status alone. Although the pooled motor scores after iron supplementation were within the normal range, the results should be interpreted cautiously.

During fetal development, iron supply depends entirely on maternal-placental transfer. About 80% of fetal iron stores accrete in the third trimester. Thus, fetal body iron content rises to ~75 mg/kg towards the end of gestation, with 75-80% incorporated into hemoglobin in red blood cells, 10% into iron-containing proteins, and 10-15 % stored as ferritin. These preliminary stages of progressive iron deficiency are characterized by reduced iron delivery to and redistribution of iron within the organs, followed by a decrease in the body's iron stores, tissue iron deficiency, and finally anemia characterized by decreased erythropoiesis with insufficient use of body available iron. Its most common biomarker is the serum ferritin. Low levels have great specificity for iron deficiency, and lower values have been correlated with negative neurodevelopmental outcomes. An index of iron status that is also useful for detecting marginal deficiency is the erythrocyte ratio of zinc protoporphyrin to heme (ZnPP/H), which increases because Zn replaces iron in the protoporphyrin ring during heme synthesis when the availability of the metal is low. Thus, increased ZnPP/H indicates iron-restricted erythropoiesis and may identify the early stages of iron deficiency before the onset of anemia.[12,13]

Iron is essential for the synthesis of dopamine and dopaminergic neurotransmission. Neuromodulation is altered with the disruption of dopaminergic pathways, such as impairment in motor function.[14] An experimental study by Erikson et al. showed that iron-deficient rats displayed decreased reuptake of dopamine in the striatum associated with reduced density of the dopamine transporter. Moreover, the authors showed that dopamine transporter function was impaired, as evidenced by diminished efficiency of dopamine uptake.[15] In a separate study, Erikson et al. showed that rats develop systemic iron deficiency, which is associated with increased striatal dopamine D1 and D2 receptor deficits, suggesting disrupted

dopaminergic receptor signaling within basal ganglia–related pathways.[13,16] This suggests that iron deficiency can reduce motor function through disrupting several levels of dopaminergic signaling, from the reuptake of dopamine to receptor-mediated transmission. Iron is needed for myelination in early neurodevelopment. In infants, observational data link poorer motor development with iron deficiency in the absence of anemia. These are domains implicated in myelination and basal ganglia function.[4,13,17]

Iron plays a role in CNS development because numerous neurodevelopmental processes rely on iron-dependent enzymes and proteins. The systematic review by Theola et al. showed that iron deficiency is associated with deficits in cognition, auditory and visual function, social-emotional development, and the neuroendocrine system. Such impairments are believed to be due to alterations in the myelination process associated with iron deficiency.[18] Additionally, McWilliam et al. carried out a scoping review of the associations between iron deficiency and neurodevelopmental disorders.[19] Iron deficiency during infancy is associated with poor motor and cognitive development, possibly through defects in myelination and metabolic alterations in monoamines, as well as decreased function of the hippocampus.[20] A history of iron deficiency is associated with lower motor development scores.[21] Akman et al found that iron-deficient infants were more likely to come from families with low socioeconomic status, have mothers with lower educational levels, shorter birth spacing intervals, fewer toys in the home, and a greater proportion of boys. A higher percentage of these infants started on cows' milk at an earlier age compared to breastmilk. This is because women with these risk factors may have limited breastfeeding, poor feeding practices, and lower levels of maternal education. The previous statements suggest that access to iron-rich nutrition is restricted, as are healthy iron statuses. But the changes seen after iron supplements suggest that at least some of those developmental effects can be reversed in part if iron deficiency is identified and treated early. Initial motor developmental score differences between the control and iron supplementation group were not significant after 3 months of giving oral iron supplementation. Hematological status was corrected after 3 months of iron therapy in the treatment group, while the control group showed no improvement with iron supplementation. Both iron deficiency anemia and iron deficiency alone may contribute to developmental delays, and these impairments appear to be reversible with iron therapy.[22]

In several studies included in this review, iron supplementation showed a beneficial effect on infant neurodevelopment. For instance, in one study, 6-month-old infants fed a monthly fortified rice-based cereal for 6 months had higher iron status at 12 months of age and lower rates of iron deficiency and IDA compared to control infants. This indicates that the iron supplementation provided by the study cereal was able to lower the risk of both iron deficiency and iron deficiency anemia by 58 % ($p = <0.0001$) and 77 %, respectively ($p = <0.0001$). They had statistically significantly higher BSID-III scores for motor development than the control group, who had a significantly higher prevalence of iron deficiency and iron deficiency anemia. This finding suggests that supplementing iron and maintaining iron status through fortified cereal intake may support optimal neurodevelopment. Infants consuming iron-fortified cereal showed improved iron status and more robust developmental outcomes compared to those without supplementation.[20] A near-significant improvement in motor development was observed among infants receiving standard-dose iron (2.2 mg/kg/day) compared to those given higher, variable doses (mean 10.4 mg/kg/day). This suggests iron supplementation may influence developmental domains differently, although the underlying mechanisms remain uncertain.[21] One randomized study that had done a 6-months and 24 months follow up-post supplementation in premature infants showed that premature infants are vulnerable to rapid depletion of iron stores, even when given standard oral iron supplementation. While ZnPP/H appears less reliable for short-term assessment, ferritin may be a more useful marker for evaluating iron status, underscoring the importance of closely monitoring and addressing iron deficiency in this population. At 6-months follow up, there was no difference between treatment and control groups' BSID-III motor developmental scoring (100±11 vs 98±16), motor (89±15 vs 88±16). At 24 months follow-up, there was no difference between treatment and control groups' BSID-III motor developmental scoring (100±11 vs 96±16), and there was also a trend toward greater motor delays in the control group, possibly linked to depleted iron stores during critical periods of brain development. Different doses of iron supplementation in premature infants resulted in similar ZnPP/H ratios by the end of the study, although the control group showed lower ferritin levels. Higher iron intake (~12 mg/kg/day) was well tolerated without significant side effects, and blood transfusions were associated with improved iron markers, reflected by lower ZnPP/H and higher ferritin levels. Oddly enough, higher iron dosing did not produce the expected changes in ZnPP/H, and predominantly breastfed infants showed higher ZnPP/H ratios for reasons that remain unclear.[21]

Evidence from randomized controlled trials has also explored whether iron supplementation improves neurodevelopmental outcomes in early infancy. Adequate iron intake during the complementary feeding period (6-12 months) is essential to prevent iron deficiency and iron deficiency anemia and to support optimal neurodevelopment.[20] One study evaluating low-dose iron supplementation in healthy breastfed infants administered 1 mg/kg/day of iron from 4 to 9 months of age showed insignificant improvements in developmental outcomes at 12, 24, or 36 months of age, nor did it significantly reduce the incidence of iron deficiency or iron deficiency anemia at 12 months.[23,24] These findings suggest that, in settings with high-income countries, routine supplementation may not provide measurable developmental benefits in otherwise healthy infants. Several explanations have been proposed for the absence of observed developmental effects. First, infants who are healthy and at low

risk for iron deficiency may not derive additional benefit from supplemental iron. Second, the intervention did not substantially alter iron status between groups, as reflected by similar iron stores after the intervention period. Previous studies have reported comparable findings, in which ferritin concentrations were temporarily higher in the low-dose supplemented group immediately after treatment, but the difference diminished during later follow-up assessments. This pattern may reflect physiological homeostatic regulation of intestinal iron absorption once supplementation ceases. Additionally, partial cessation of breastfeeding during infancy may reduce the overall risk of iron deficiency, further limiting the potential observable benefit of supplementation.[23,24] Although many literatures have suggested developmental benefits from supplementation, our pooled data did not demonstrate a large measurable improvement beyond normal developmental trajectories.

While our pooled analysis showed motor scores within normal ranges, the ferritin response was highly heterogeneous with wide confidence intervals. This discrepancy may indicate that ferritin is not a direct picture of iron storage in the brain. Ferritin level could be influenced by some factors, including infection. As noted by Simon et al., the pediatric population possesses a developing immune system, positioning them at a higher risk of infection due to immature innate and adaptive defense mechanisms.[25] This vulnerability was highlighted in a study by Brustad et al., which reported that children experience a high burden of infections during the first three years of life, with the common cold being the most frequent type.[26,27] Since ferritin acts as an acute-phase reactant, frequent viral episodes in this age group may cause serum levels to fluctuate, making it an unreliable marker for functional neurodevelopmental iron.

Moreover, motor development in children is multifactorial and not determined by iron level alone. It is heavily influenced by a combination of genetics, environmental stimulation, and overall nutritional status. Data from the Gemini Study demonstrated that motoric activity at 3 months old was equally influenced by genetic and family environment, with independent walking dominantly influenced by genetics.[28] The good effect of a good environment may stimulate better motoric development, as seen at study conducted by Saccani et al. The study found that infants with better access to stimulating materials and space had significantly higher motor development scores.[29] And for the last factor, overall nutrition remains a fundamental factor. A recent study by Yuningsih et al. on children aged 4 60 months confirmed a significant correlation between nutritional status and developmental progress, where children with good nutritional status demonstrated optimal development compared to those with malnutrition, independent of single nutrient factors.[30]

This study has several strengths. This is the first analysis to specifically pool Bayley Scale outcomes to evaluate motor development within this pediatric population, providing a more precise estimate of the effects of iron supplementation doses. This study was performed as per PRISMA guidelines by adhering to a transparent and robust protocol. A considerable strength of this review is that we limited ourselves to studies using standardized, objective neurodevelopmental testing as opposed to solely parental reporting, reducing the potential for information bias. In addition, the combination of both the biochemical markers and clinical motor outcomes provides an integrative perspective into the physiological and neurodevelopmental impact of iron intervention.

LIMITATIONS

This study has several important limitations. First, the relatively small number of eligible studies and the presence of substantial heterogeneity reduce confidence in the pooled estimates and limit their generalizability to the broader population. Second, several important potential confounders, such as nutritional status, birth weight, gestational age at delivery, and intercurrent illnesses were inconsistently reported across the included studies and were largely uncontrolled for. As a result, the observed associations may reflect the influence of these factors rather than a direct causal effect of iron supplementation.

Additionally, the available data were insufficient to allow comprehensive analyses of specific neurodevelopmental domains, including detailed motor development outcomes and other subcomponents. Consequently, the analysis relied primarily on pooled post-iron supplementation results, and conclusions regarding a direct effect of iron supplementation on motor development scores cannot be definitively established. High heterogeneity across studies emphasizes the need for future research employing standardized iron dosing regimens, consistent diagnostic thresholds, and uniform timing of neurodevelopmental assessments to improve comparability between studies.

CONCLUSION

In conclusion, this systematic review and meta-analysis found that post-supplementation motor development scores in pediatric populations receiving iron supplementation were generally within normal ranges. However, the available evidence was limited by substantial heterogeneity and inconsistent reporting of baseline and follow-up developmental data. Accordingly, the present findings should not be interpreted as evidence that iron supplementation directly improves motor development. Rather, they indicate that motor development outcomes after iron supplementation appear acceptable in the included studies, while the relationship between iron status and neurodevelopment remains uncertain. Further studies with standardized supplementation protocols and uniform developmental assessment methods are needed to clarify the true contribution of iron supplementation to neurodevelopmental outcomes in early life.

ETHICAL CLEARANCE

This study was conducted in accordance with established methodological guidelines for systematic reviews and meta-analyses, including the PRISMA statement. Ethical approval was not required as this study utilized data from previously published studies, and no individual participant data requiring consent were collected.

FUNDING

No external financial support or material resources were provided for the conduct of this article publication.

CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTION

After inserting search query results into Microsoft Excel® sheets, all studies in the initial search will be randomly and evenly allocated to each author in one group. One group consists of two authors (LAD and RKPT in group 1, VE and GVP in group 2) working as tandems, independent of the authors in the other group. Each group will independently screen and exclude duplicate studies. Any disagreements and uncertainties will be resolved through discussions with the third and fourth authors (RCS and WW). Following duplicate exclusion, non-duplicate studies will be randomly and evenly allocated to each author in one group. One group consists of two authors (LAD and RKPT in group 1, VE and GVP in group 2) working as tandems, independent of the authors in the other group. Each group will manually screen each study's titles and abstracts for eligibility. Any disagreements and uncertainties will be resolved through discussions with the third and fourth authors (RCS and WW). RCS will then attempt to retrieve full texts of studies eligible for full-text screening. Studies with irretrievable full text will be excluded. All studies with retrievable full text will be randomly and evenly allocated to each author in one group. One group consists of two authors (LAD and RKPT in group 1, VE and GVP in group 2) working as tandems, independent of the authors in the other group. Each group will manually screen each study's full text for eligibility. Any disagreement and uncertainty will be resolved through discussions with the third and fourth authors (RCS and WW).

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The authors declare that all contributions to the study were made solely by the listed authors above.

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