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Neurodevelopmental Impairments as Long-term Effects of Iron Deficiency in Early Childhood: A Systematic Review

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Background: Numerous studies have reported neurodevelopmental disorders in children with a history of early-life iron deficiency (ID), though findings vary.

Aims: To evaluate the long-term impact of early childhood ID on neurodevelopmental outcomes.

Study Design: Systematic review.

Methods: A literature search was conducted across five electronic databases (PubMed, Cochrane, Scopus, Sage, and Embase) using the keywords "iron deficiency anemia" and "infant." The JBI critical appraisal tool for cohort studies was used to evaluate study quality.

Results: Seventeen relevant cohort studies were identified through the systematic search. Of these, 14 were rated as high quality, while 3 were classified as moderate quality. The neurodevelopmental domains assessed included cognitive deficits (seven studies), motor deficits (four studies), verbal deficits (seven studies), behavioral deficits (nine studies), auditory function (one study), and neuroendocrine function (two studies).

Conclusion: Early-life ID disrupts neurodevelopment, leading to persistent cognitive, motor, behavioral, and neuroendocrine impairments. Children with a history of early childhood ID demonstrate poorer cognitive, motor, and behavioral outcomes compared with their non-ID counterparts. Preventing ID within the first 1,000 days of life is essential to mitigate irreversible deficits in motor, cognitive, and behavioral functions.

INTRODUCTION

Sufficient nutrition intake during the first 1,000 days of life, from conception to the second year, is essential for optimal neurodevelopment.[1] During this period, children have the highest iron demands.[2] Early childhood is marked by rapid growth and development, making iron requirements between 6 and 24 months greater than at any other stage of life.[3] Inadequate iron intake during this critical phase increases the risk of iron deficiency (ID) in infants and young children. ID accounts for approximately 30-50% of anemia cases in children.[4] Iron plays a vital role in brain development by supporting myelination, neurotransmitter synthesis, and oxygen transport in hemoglobin.[5] ID within the first 1,000 days of life can lead to long-term, irreversible impairments in motor function, cognition, and behavior.[2] A systematic review evaluating iron status in pregnant women found that low maternal iron levels, particularly during the third trimester, are linked to neurodevelopmental disorders in offspring, including deficits in behavior, cognition, and academic performance.[6] Therefore, ID during pregnancy can adversely affect fetal brain development.[7]

ID results from a reduction in iron stores and can progress to iron deficiency anemia (IDA) if left uncorrected. It is identified by low ferritin levels while hemoglobin and normal mean corpuscular volume (MCV) remain within normal ranges. The subsequent stage, ID without anemia, is marked by low ferritin and MCV levels but normal hemoglobin levels. The final stage, IDA, is characterized by low levels of hemoglobin, MCV, and ferritin.[8] Although anemia is a severe outcome of ID, ID without anemia can also affect a child's brain development even before anemia occurs.[9,10]

In humans, the brain, particularly the hippocampus, undergoes rapid development from late pregnancy to approximately 2-3 years

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of age. During this period, iron utilization increases alongside the formation of new neurons, dendrites, myelin, synapses, and neurotransmitters. Hippocampus-dependent memory begins to develop and strengthen between 3 and 18 months. The generation of new neurons in the hippocampus occurs at a much faster rate before birth and in the early postnatal years. These neurons integrate into neural networks and are thought to play a crucial role in learning and memory. Consequently, during these critical developmental stages, environmental factors such as ID, which can impair neuronal growth or maturation, may influence both immediate and long-term behavior.[11]

Early childhood ID is thought to impair attention, memory, and motor skills, even when iron supplementation is provided. These deficits primarily affect the prefrontal cortex, hippocampus, and sensorimotor regions.[12-16] Research has also shown that early childhood ID disrupts not only cognitive and motor functions but also verbal, behavioral, emotional, and psychosocial development.[17-28] Additionally, several studies have reported differences in neuroendocrine activity between children with a history of early childhood ID and those without.[19,24]

Several studies have documented neurodevelopmental disorders in children with a history of early childhood ID, though their findings have varied considerably. This systematic review aims to evaluate the long-term impact of early childhood ID on neurodevelopmental outcomes in children.

MATERIALS AND METHODS

Ethics statement

This systematic review was registered in an international database (International Prospective Register of Systematic Reviews, CRD42024559247). As this study is a systematic review, informed consent and ethics committee approval were not required.

Eligibility criteria

The clinical question was structured using the PICO framework: Population, children under 18 years of age; issue (I), diagnosed with ID within the first 2 years of life; comparators, children with no history of childhood ID; and outcomes, neurodevelopmental impairments identified after a minimum follow-up of 1 year. Studies were included if they met the following criteria: (a) pediatric patients (under 18 years) diagnosed with ID within the first 2 years of life, (b) cohort study design, (c) long-term follow-up of more than 1 year, (d) reporting neurodevelopmental outcomes, (e) published in English, and (f) full text available. Exclusion criteria were as follows: (a) presence of comorbidities other than ID, (b) insufficient data, (c) not published in English, or (d) full text unavailable.

Search strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[29] The literature search was carried out from June 13th to 20th, 2023, using keywords aligned with the PICO framework. A Boolean search using OR and AND operators was conducted across five databases: PubMed, Cochrane, Scopus, Sage, and Embase, with the keywords "ID anemia" and "infant." The Medical Subject Headings (MeSH) terms and search strategy are shown in Table 1. Filters were applied to limit the results to clinical trials, randomized clinical trials (RCTs), and research articles only. An example of the PubMed search query is as follows: (("ID anemia"[All Fields] OR "anemia, iron deficiency"[MeSH Terms] OR ("anemia"[All Fields] AND "iron deficiency"[All Fields]) OR "iron-deficiency anemia"[All Fields] OR ("iron"[All Fields] AND "deficiency"[All Fields] AND "anemia"[All Fields]) OR "ID anemia"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]).

Study selection process

The initial database search and screening were conducted independently by two authors (J.T. and M.A.). Title and abstract screening were also done independently by both authors to identify studies with eligible designs that addressed the clinical question (specifically cohort studies). Duplicate articles were removed through multiple rounds of screening. Full-text selection was based

TABLE 1. Search Strategy and Keywords.

Database	Keyword	Filter	Hits
PubMed	(("ID anemia"[All Fields] OR "anemia, iron deficiency"[MeSH Terms] OR ("anemia"[All Fields] AND "iron deficiency"[All Fields]) OR "iron-deficiency anemia"[All Fields] OR ("iron"[All Fields] AND "deficiency"[All Fields] AND "anemia"[All Fields]) OR "iron deficiency anemia"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	CT and RCT	502
Cochrane	iron deficiency anemia AND infant	Trials	761
Scopus	TITLE-ABS-KEY (iron AND deficiency AND anemia) AND TITLE-ABS-KEY (infant) AND TITLE-ABS-KEY (development) AND (LIMIT-TO (DOCTYPE, "ar"))	Article	771
Sage	iron deficiency anemia AND infant AND long-term	Research article	863
Embase	('iron deficiency anemia'/exp OR "iron deficiency anemia" OR (('iron'/exp OR iron) AND ('deficiency'/exp OR deficiency) AND ('anemia'/exp OR anemia))) AND ('infant'/exp OR infant) AND ('long-term" OR (long AND term))	No filter applied	245

on the availability of complete articles. Studies were included if all authors agreed they met the eligibility criteria. Disagreements were resolved through consensus, and if consensus could not be reached, the first author made the final decision.

Data extraction and outcome domains

Two authors independently extracted data from the included studies. For each study, we recorded the first author's name, study design, study location, population at the start (both exposed and control groups), age at ID diagnosis, iron therapy (if applicable), follow-up duration, outcomes, measurement tools, and statistical significance of the results. The data were entered into Microsoft Excel. To minimize the extraction bias, data extraction was carried out independently by both authors. If disagreements could not be resolved through discussion, the first author made the final decision. We extracted data on all neurodevelopmental domains affected by ID: cognitive, motor (both gross and fine), verbal, auditory, behavior, and neuroendocrine.

Statistical analysis

Statistical analysis was not performed, as this study is a systematic review with heterogeneous data outcomes, making meta-analysis unsuitable. Funnel plot analysis was also not applicable due to the inability to conduct meta-analysis. To minimize publication bias, we followed the PRISMA guidelines for systematic analysis across multiple databases. The cohorts and longitudinal RCT studies were assessed using the JBI critical appraisal tool for cohort studies.[30] A study was classified as high quality (low risk of bias) if the score was > 80%, moderate quality (moderate risk of bias) if the score was between 50% and 80%, and low quality (high risk of bias) if the score was < 50%. In case of differing opinions among the authors, further discussion was held to reach a consensus. If disagreements persisted, the first author made the final decision.

RESULTS

The search and selection process is outlined in Figure 1. Out of 3,142 retrieved articles, 17 relevant studies were included in this systematic review. Based on the quality assessment using the JBI critical appraisal tool, 3 studies were of moderate quality with a moderate risk of bias,[24,25,31] while the remaining 14 studies were of high quality with a low risk of bias[15,17-23,26-28,32-34] (Table 2). The studies included in this review showed high heterogeneity, as they were conducted in various locations and examined different neurodevelopment domains using diverse measurement tools. As a result, a qualitative analysis was performed by summarizing the extracted data in a summary table (Table 3).

ID was diagnosed as early as birth and as late as age 24. Several studies reported iron supplementation durations ranging from at least 3 months[27] to 6 months or up to 1 year, depending on the child's age.[19,20,26,32,33] Follow-up and assessment were conducted as early as age 4 years[25,32,33] and as late as age 17 years.[28] All studies met the inclusion and exclusion criteria. The tools used to assess neurodevelopmental outcomes varied across the studies. The outcomes assessed included not only cognitive functions but also behavior, verbal skills, motor skills, and neuroendocrine function. This systematic review found that ID in early life leads to long-term neurodevelopmental impairments.

Cognitive function in children with a history of early childhood ID was assessed at ages 4 years,[32] 8-9 years,[20] and 10 years.[24,26] Seven studies evaluated cognitive function as one of the neurodevelopmental aspects.[15,20,22-24,26,32] Of these, three studies found significantly lower cognitive function in children with early childhood ID,[24,26,32] one study did not report significance,[20] and three studies found no significant differences.[15,22,23]

Several studies also reported motor function impairments in children with early childhood ID, assessed at ages 4 years,[33] 5 years,[15] 6 years,[31] and 5-12 years.[34] Four studies evaluated motor function using different methods and found that children with a history of early childhood ID had lower motor function compared to those without ID.[15,31,33,34] Among these studies, one assessed fine motor performance only,[31] one assessed both gross and fine motor functions,[15] one assessed overall motor scores without specifying gross or fine motor,[34] and one assessed motor activity during daytime sleep.[33]

In this systematic review, verbal function in children with a history of early childhood ID was assessed at ages 5 years,[27] 8-9 years,[20] and 10 years.[24,26] Seven out of the seventeen studies included in this review evaluated verbal function.[15,20,22-24,26,27] Among these, two studies found that verbal function was significantly lower in children with early childhood ID compared to those without ID,[24,27] two studies showed similar results without stating significance,[20,26] and the remaining studies found no significant differences.[15,22,23] Regarding auditory function, one study found that children with early childhood ID had normal hearing function at age 10.[24]

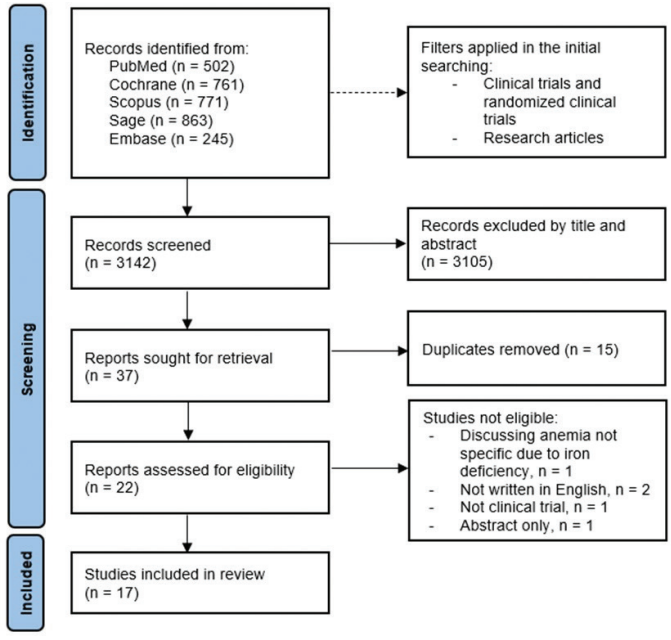

FIG. 1. PRISMA flow diagram.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

TABLE 2. Critical Apraisal.

Included articles	Were the groups comparable and selected from the same population?	Were the exposures measured consistently for both the exposed and unexposed groups?	Was the exposure measured using a valid and reliable method?	Were confounding factors identified?	Were strategies to manage confounding factors described?	Were the groups/ participants free of the outcome at the start of the study (or at the time of exposure)?	Were the outcomes measured using a valid and reliable method?	Was the follow-up period sufficient?	Was the follow-up complete, and if not, were the reasons for loss to follow-up explained and investigated?	Were strategies to handle incomplete follow-up employed?	Was an appropriate statistical analysis conducted?	Score (% of "yes" answers)	Quality
Algarín et al.,[32] 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Angulo-Barroso et al.,[33] 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Chang et al.,[25] 2011	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	75%	Moderate
Congdon et al.,[26] 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Corapci et al.,[27] 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Doom et al.,[28] 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
East et al.,[17] 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	83.3%	High
East et al.,[18] 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	83.3%	High
Felt et al.,[19] 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Gunnarsson et al.,[31] 2007	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	75%	Moderate
Hossain et al.,[20] 2023	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	83.3%	High
Hua et al.,[21] 2023	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Lozoff et al.,[15] 1991	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
McCarthy et al.,[22] 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Shafir et al.,[34] 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Thorisdottir et al.,[23] 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	91.7%	High
Yehuda and Yehuda,[24] 2006	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	66.7%	Moderate

High-quality studies (low-risk of bias), score > 80%; moderate-quality studies (moderate-risk of bias), score 50-80%; low-quality studies (high-risk of bias), score < 50%.

TABLE 3. Summary of Studies.

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
Algarín et al.,[32] 2003 (cohort, Chile)	6, 12, and 18 months	Age 6 months: 15 mg/day ferrous sulfate for 1 year Age 12 and 18 months: 30 mg/day for at least 6 months	Age 4 years	Auditory brainstem responses	Nicolet compact four machine	29 early childhood IDA vs. 35 control	The early childhood IDA group had longer absolute latencies (ms) in wave I (1.64 ± 0.02 vs. 1.51 ± 0.02, $p < 0.001$), wave III (3.78 ± 0.03 vs. 3.63 ± 0.02, $p < 0.001$), and wave IV (5.7 ± 0.03 vs. 5.4 ± 0.03, $p < 0.001$)
				Visually evoked potentials	Nicolet compact four machine	40 early childhood IDA vs. 40 control	The early childhood IDA group had a longer P100 latency (ms) (104.7 ± 0.7 vs. 97.3 ± 0.7, $p < 0.001$)
Angulo-Barroso et al.,[33] 2013 (cohort, Chile)	6, 12, and 18 months	Age 6 months: 15 mg/day ferrous sulfate for 1 year Age 12 and 18 months: 30 mg/day for at least 6 months	Age 4 years	Motor activity during daytime sleep	Actigraph	23 early childhood IDA vs. 24 control	The early childhood IDA group had more leg movements in active sleep (3.5 movement units/15 min ± 3.9 vs. 2.0 movement units/15 min ± 1.6, $p = 0.04$)
				Intra-individual variability in motor activity during daytime	Actigraph	23 early childhood IDA vs. 24 control	The early childhood IDA group had a larger IIV in active sleep compared to the controls (114.3 ± 69.3 vs. 83.4 ± 46.2, $p = 0.04$)
Chang et al.,[25] 2011 (cohort, China)	< 24 months	Food supplement (6 mg iron, 4.1 mg zinc, 385 calcium, 0.2 mg vitamin B12, 7 ug vitamin D, 3.8 g protein), vitamin A every 6 months	Age 4 years	Positive effect during delay of gratification	Designed the laboratory assessment	27 early childhood IDA vs. 64 control	Lower in the early childhood IDA group (4.7 ± 5.2 vs.11 ± 3.4, $p < 0.05$)
						70 corrected IDA vs. 64 control	Not significantly different ($p > 0.05$) between corrected IDA vs. control (9.7 ± 3.2 vs. 11 ± 3.4)
				Frustration tolerance	Designed the laboratory assessment	27 early childhood IDA vs. 64 control	Lower in the early childhood IDA group (7.8 ± 11.4 vs. 24.8 ± 7.9, $p < 0.05$)
						70 corrected IDA vs. 64 control	Not significantly different ($p > 0.05$) between corrected IDA vs. control (21.1 ± 3.5 vs. 24.8 ± 7.9)
				Passive behavior	Designed the laboratory assessment	27 early childhood IDA vs. 64 control	Higher in the early childhood IDA group (23 ± 6.6 vs. 14.8 ± 4.3, $p < 0.05$)
						70 corrected IDA vs. 64 control	Not significantly different ($p > 0.05$) between corrected IDA vs. control (18.1 ± 4.2 vs. 14.8 ± 4.3)
Congdon et al.,[26] 2012 (cohort, Chile)	6, 12, and 18 months	Age 6 months: 15 mg/day ferrous sulfate for 1 year Age 12 and 18 months: 30 mg/day for at least 6 months	Age 10 years	Behavior	Reaction time first phase (ms)	50 early childhood IDA vs. 41 control	Early childhood IDA group was slower than the control (1,085 ms ± 176 vs. 1,003 ms ± 205, $p = 0.044$)
					Reaction time second phase (ms)	49 early childhood IDA vs. 42 control	The article only stated that there is no significant difference and did not present exact numbers
				Memory searching process	FN400 latency (ms)	49 early childhood IDA vs. 40 control	Early childhood IDA group was slower than the control (1,085 ms ± 176 vs. 1,003 ms ± 205, $p = 0.044$)
				Neuronal process of wording	P300 amplitude	50 early childhood IDA vs. 42 control	Early childhood IDA is lower than control (presented by a figure in the article); there was a main effect of childhood IDA with electrode interaction, F(2.87) = 4,878, $p = 0.030$
Corapci et al.,[27] 2006 (cohort, Costa Rica)	12-23 months	IM iron or 3 mg/kg/day ferrous sulfate orally divided into two doses for 3 months	5 years	Positive effect	PARCHISY and EC-HOME	40 early childhood ID vs. 102 control	Control group is higher (OR: 0.43, 95% CI: 0.22-0.86, $p = 0.02$)
				Physical activity	PARCHISY and EC-HOME	40 early childhood ID vs. 102 control	Control group is higher (OR: 0.31, 95% CI: 0.15-0.66, $p = 0.01$)
				Verbalization	PARCHISY and EC-HOME	40 early childhood ID vs. 102 control	Control group is higher (OR: 0.39, 95% CI: 0.18-0.81, $p = 0.01$)

TABLE 3. Continued

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
Doom et al.,[28] 2018 (cohort, Chile)	12 and 18 months	No iron formula, high iron formula (12 mg/l), low iron formula (2.3 mg/l)	Age 11-17 years	Social problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater social problems in adolescents (T-score contrast estimate = 2.71, 95% CI: 0.58-4.85, $p = 0.01$)
				ADHD problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater ADHD problems in adolescents (T-score contrast estimate = 2.63, 95% CI: 0.6-4.67, $p = 0.01$)
				Oppositional defiant problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater oppositional defiant problems in adolescents (T-score contrast estimate = 3.33, 95% CI: 1.35-5.31, $p = 0.01$)
				Conduct problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	Early childhood ID has greater conduct problems in adolescents (T-score contrast estimate = 0.05, 95% CI: 0.02-0.08, $p = 0.004$)
				Aggressive problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater aggressive problems in adolescents (T-score contrast estimate = 3.86, 95% CI: 1.56-6.16, $p = 0.001$)
				Rule-breaking problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater rule-breaking problems in adolescents (T-score contrast estimate = 0.04, 95% CI: 0.01-0.07, $p = 0.02$)
				PTSD problems	Youth self-report and child behavior checklist	Early childhood ID (310) and IDA (135) vs. control (545)	The early childhood ID group had greater PTSD problems in adolescents (T-score contrast estimate = 2.52, 95% CI: 0.22-4.83, $p = 0.03$)
East et al.,[17] 2017 (cohort, Chile)	6, 12, and 18 months	Iron supplementation is considered as a covariate	Age 5 years	Dull effect	CABI	Early childhood ID (248) vs. control (483)	Early childhood ID was not significantly related to dull effect at 5 years (beta = 0.06, B = 0.21, SE = 0.23)
						Early childhood IDA (142) vs. control (483)	Early childhood IDA was significantly related to dull effect at 5 years (beta = 0.09, B = 0.5, SE = 0.26, $p < 0.05$)
East et al.,[18] 2019 (cohort, Chile)	6, 12, and 18 months	Iron supplementation is considered as a covariate	Age 5 years	Dull effect at 5 years	CABI	Early childhood ID (254) and IDA (140) vs. control (481)	Early childhood ID was significantly related to dull effect at 5 years (beta = 0.1, B = 0.26, SE = 0.12, $p < 0.05$)
Felt et al.,[19] 2012 (cohort, Chile)	6, 12, and 18 months	Oral iron 15 mg/day for 1 year for infants identified at 6 months; oral iron 30 mg/day for at least 6 months for children identified at 12 and 18 months	Age 10 years	Cortisol 30 min and 45 min after venipuncture	Electrochemiluminescence assays	Early childhood IDA at age 6 (13) vs. control (23)	The article only stated that there is no significant difference and did not present exact numbers
						Early childhood IDA at age 12 (24) vs. control (23)	The early childhood IDA group at age 12 months had lower cortisol level significantly (30 min, 43.4 ± 13.5 mcg/dl vs. 97.8 ± 13.3 mcg/dl; 45 min, 36.4 ± 12.7 mcg/dl vs. 90.1 ± 12.5 mcg/dl) The curvature of the response pattern was significantly blunted for IDA-12 compared with the control (41.1 vs. -88.3, $p < 0.001$)
Gunnarsson et al.,[31] 2007 (cohort, Iceland)	1 year	Not stated	Age 6 years	Fine motor score	Icelandic developmental inventory	Early childhood ID (10) vs. control (56)	Lower score in the early childhood ID group (46.7 ± 4.1 vs. 49.3 ± 2, $p = 0.011$)
						Early childhood iron depletion (26) vs. control (40)	Lower score in the iron-depleted group (48 ± 3.3 vs. 49.5 ± 1.8, $p = 0.045$)

TABLE 3. Continued

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
Hossain et al.,[20] 2023 (cohort, Bangladesh)	6-24 months	IDA, 30 mg iron syrup daily for 6 months; stimulation, weekly play sessions at home for 9 months using a curriculum designed in Jamaica	After 6 years (age 8-9 years)	FSIQ, combined from the PRI and the VCI	WASI-II	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower FSIQ in the early childhood IDA group (63.1 ± 7.2 vs. 65.7 ± 7), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower FSIQ int he early childhood IDA group (62.2 ± 6.1 vs. 62.8 ± 6.5), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
				PRI	WASI-II	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower PRI int he early childhood IDA group (71.8 ± 7.6 vs. 74.4 ± 8.2), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower PRI in the early childhood IDA group (70.2 ± 7.4 vs. 71 ± 7.6), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
				VCI	WASI-II	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower VCI in the early childhood IDA group (57.4 ± 10.3 vs. 61.3 ± 10.5), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower VCI in the early childhood IDA group (58.2 ± 8.3 vs. 58.5 ± 8.2), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
				Word reading	Wide Range Achievement test	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower word reading in the early childhood IDA group (88.1 ± 24.5 vs. 96.5 ± 22.6), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower word reading in the early childhood IDA group (91.5 ± 23 vs. 92.5 ± 21.9), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
				Word spelling	Wide Range Achievement test	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower word spelling in the early childhood IDA group (80.8 ± 22.9 vs. 89.8 ± 21.4), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower word spelling in the early childhood IDA group (83 ± 21.3 vs. 88.2 ± 20.8), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
				Math computation	Wide Range Achievement test	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower math computation in the early childhood IDA group (74 ± 14.8 vs. 80.6 ± 14.6), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
						Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Lower math computation in the early childhood IDA group (77 ± 17.2 vs. 78 ± 16.5), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)

TABLE 3. Continued

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
				Motor development	MABC-2	Early childhood IDA with stimulation (102) vs. non-anemic with stimulation (92)	Lower motor development in the early childhood IDA group (24 ± 6.8 vs. 25.2 ± 6.9), analysis of variance not performed between the IDA and non-anemic groups (significancy not reported)
					MABC-2	Early childhood IDA no stimulation (94) vs. non-anemic with no stimulation (84)	Higher motor development in the early childhood IDA group (22.6 ± 7.6 vs. 22 ± 7.1), analysis of variance not performed between the IDA and non-anemic groups (significances not reported)
Hua et al.,[21] 2023 (cohort, China)	9 months	Iron therapy was given but not clearly described	Age 8-9 years	Behavioral performance (overall accuracy)	Computer-based behavioral task	Early childhood ID at 9 months (24) vs. control (27)	Lower in the early childhood ID group (beta-coefficient = -0.08; 95% CI: -0.12–-0.04)
Lozoff et al.,[15] 1991 (cohort, Costa Rica)	12-23 months	Iron therapy was given but not clearly described	Age 5 years	Gross motor	Bruininks-Oseretsky test of motor proficiency	Early childhood IDA (30) vs. control (64)	Lower in the early childhood IDA group (52.1 ± 14.3 vs. 57.7 ± 13.3, $p < 0.05$)
						ID corrected (50) vs. control (64)	Higher in the early childhood ID-corrected group (62.1 ± 12.7 vs. 57.7 ± 13.3, not significant $p > 0.05$)
				Fine motor	Bruininks-Oseretsky test of motor proficiency	Early childhood IDA (30) vs. control (64)	Lower in the early childhood IDA group (37 ± 11.6 vs. 41.9 ± 11, $p < 0.05$)
						ID corrected (50) vs. control (64)	Higher in the early childhood ID-corrected group (43.9 ± 10.3 vs. 41.9 ± 11, not significant $p > 0.05$)
				Verbal IQ	WPPSI	Early childhood IDA (30) vs. control (64)	Lower in the early childhood IDA group (101.1 ± 13.3 vs. 101.8 ± 12.3, not significant $p > 0.05$)
						ID corrected (50) vs. control (64)	Higher in the early childhood ID-corrected group (105.6 ± 11.9 vs. 101.8 ± 12.3, not significant $p > 0.05$)
				Performance IQ	WPPSI	Early childhood IDA (30) vs. control (64)	Lower in the early childhood IDA group (98.9 ± 12.1 vs. 105.2 ± 11.2, $p < 0.05$)
						ID corrected (50) vs. control (64)	Lower in the early childhood ID corrected group (105.1 ± 10.7 vs. 105.2 ± 11.2, not significant)
				FSIQ	WPPSI	Early childhood IDA (30) vs. control (64)	Lower in the early childhood IDA group (100 ± 12.1 vs. 103.8 ± 11.3, $p > 0.05$)
						ID corrected (50) vs. control (64)	Lower in the early childhood ID-corrected group (105.9 ± 10.9 vs. 103.8 ± 11.3, not significant $p > 0.05$)
McCarthy et al.,[22] 2021 (cohort, Ireland)	At birth	Not stated	Age 5 years	Internal problems	CBCL	Early childhood ID at birth (45) vs. control (534)	Higher in the early childhood ID group [7 (2.5-12) vs. 5 (3-9.3), not significant $p = 0.089$]
				External problems	CBCL	Early childhood ID at birth (45) vs. control (534)	Higher in the early childhood ID group [7 (4-12.5) vs. 5 (2-10), $p = 0.018$]
				Total problems	CBCL	Early childhood ID at birth (45) vs. control (534)	Higher in the early childhood ID group [21 (14-35) vs. 17 (9-29), not significant $p = 0.054$]

TABLE 3. Continued

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
				Verbal knowledge	KBIT-2	Early childhood ID at birth (37) vs. control (499)	Lower in the early childhood ID group [101 (99-105) vs. 109 (101-114), not significant $p = 0.254$]
				Non-verbal knowledge	KBIT-2	Early childhood ID at birth (37) vs. control (500)	Lower in the early childhood ID group [97 (94-100) vs. 100 (94-104), not significant $p = 0.320$]
				IQ composite	KBIT-2	Early childhood ID at birth (37) vs. control (497)	Lower in the early childhood ID group [101 (99-105) vs. 104 (99-110), not significant $p = 0.070$]
Shafir et al.,[34] 2006 (cohort, Costa Rica)	12-23 months	Iron therapy was given but not clearly described	Age 5-12 years	Motor scores	Bruininks-Oseretsky	Early childhood ID (53) vs. control (132)	Early childhood ID group has lower motor score across all age (5-12 years), $p < 0.001$
Thorisdottir et al.[23] 2013 (cohort, Iceland)	12 months	Not stated	Age 6 years	Gross motor	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -2.9, 95% CI: -6.9, 1.1), not significant $p = 0.152$
				Fine motor	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -0.2, 95% CI: -2.6, 2.3), not significant $p = 0.896$
				Self-help	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -4, 95% CI: -7.4, -0.7, $p = 0.019$)
				Comprehension	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -0.7, 95% CI: -3.6, 2.1), not significant $p = 0.612$
				Expression	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Higher in the early childhood iron-depleted group (adjusted mean diff 1.1, 95% CI: -2, 4.1), not significant $p = 0.493$
				Learning	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Higher in the early childhood iron-depleted group (adjusted mean diff 0.7, 95% CI: -5.4, 6.7), not significant $p = 0.831$
				Motor, combined	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -5.5, 95% CI: -11.1, 0.03), not significant $p = 0.051$
				Verbal, combined	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -0.3, 95% CI: -8.3, 7.7), not significant $p = 0.939$
				Total developmental index	Icelandic-Developmental Inventory	Early childhood iron depletion (6) vs. control (102)	Lower in the early childhood iron-depleted group (adjusted mean diff -2.6, 95% CI: -8.1, 2.8), not significant $p = 0.336$

TABLE 3. Continued

Study	Age diagnosed	Iron therapy	Follow-up	Outcome	Measurement	Test subject	Result
Yehuda and Yehuda,[24] 2006 (cohort, Israel)	12 months	Not stated	Age 10 years	Auditory function	Auditory test	Early childhood ID (17) vs. control (17)	Both groups showed normal function (hearing threshold < 20 dB)
				FSIQ	WISC revised	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (96.7 ± 2.1 vs. 105.1 ± 1.3, significant $p = 0.001$)
				Verbal IQ	WISC	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (99.1 ± 2.4 vs. 104.5 ± 1.8, significant $p = 0.05$)
				Performance IQ	WISC	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (95.9 ± 2.2 vs. 104.9 ± 2.4, significant $p = 0.001$)
				Behavioral: appetite	5-point rating scale	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (3.5 ± 0.6 vs. 4.9 ± 0.7, not significant $p > 0.05$)
				Behavioral: good mood	5-point rating scale	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (3.8 ± 0.8 vs. 4.8 ± 0.8, not significant $p > 0.05$)
				Behavioral: ability to concentrate	5-point rating scale	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (3.5 ± 0.6 vs. 4.7 ± 0.5, not significant $p > 0.05$)
				Behavioral: fatigue during the day	5-point rating scale	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (3 ± 0.5 vs. 4.5 ± 0.8, significant $p = 0.05$)
				Behavioral: organizing academic materials	5-point rating scale	Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (4 ± 0.6 vs. 4.8 ± 0.6, not significant $p > 0.05$)
				Behavioral: quality of sleep		Early childhood ID (17) vs. control (17)	Lower in the early childhood ID group (3.1 ± 1.3 vs. 4.8 ± 1, significant $p = 0.05$),
				Morning saliva cortisol levels	Radioimmunoassay	Early childhood ID (17) vs. control (17)	Higher in the early childhood ID group (2.8 ± 0.4 nmol/l vs. 2.5 ± 0.7 nmol/l, significant $p = 0.001$)

ID, iron deficiency; IDA, iron deficiency anemia; PARCHISY, Parent-Child Interaction System; EC-HOME, Early Childhood version of the Home Observation for Measurement of the Environment; OR, odds ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; PTSD, posttraumatic stress disorder; CABI, Children Adaptive Behavior Inventory; FSIQ, Full-Scale Intelligence Quotient, PRI, Performance Reasoning Index; VCI, Verbal Comprehension Index; WASI, Wechsler Abbreviated Scale of Intelligence; MABC, Movement Assessment Battery for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; CBCL, Child Behavior Checklist; KBIT, Kaufman Brief Intelligence Test; WISC, Wechsler Intelligence Scale for Children.

Behavioral problems were assessed in the included studies at ages 4 years,[25] 5 years,[17,18,22] 6 years,[23] 8-9 years,[21] 10 years,[26] and 11-17 years.[28] The behavioral parameters varied across studies. Of the nine studies evaluating behavioral problems, seven reported significantly higher behavioral issues in children with a history of early childhood ID.[17,18,22,23,25,26,28] One study reported lower behavioral performance in children with ID but did not state significance,[21] while only one study found no significant differences in behavior between children with and without early childhood ID.[24]

Regarding neuroendocrine function, one study found that 10-year-old children with early childhood ID had significantly lower serum cortisol levels compared to normal children.[19] In contrast, another study reported higher morning salivary cortisol levels in children with a history of early childhood ID at the same age, compared to those without ID.[24]

DISCUSSION

Cognitive outcomes encompass various aspects, including memory, overall intelligence quotient, non-verbal knowledge, comprehension, learning, and mathematical abilities. The studies included in this review found that children with a history of early childhood ID exhibited lower cognitive function when assessed at ages 4 years,[32] 8-9 years,[20] and 10 years.[24,26] These children showed a slower rate of cognitive improvement compared to those without a history of ID.[26] This delay may be linked to myelin dysfunction caused by ID, as myelin formation is a prolonged process that can take months or years in different brain regions.[35,36] Disturbances in early brain development can have long-lasting effects, and disruptions in iron homeostasis during neurodevelopment may alter myelin composition, leading to irreversible changes despite treatment. Even children with a history of early childhood ID who did not experience anemia still demonstrated significantly lower cognitive function than those without a history of ID.[24] However, several studies noted lower cognitive function in children with a history of ID, though the differences were not statistically significant.[15,20,22,23] Verbal function was also significantly impacted by childhood ID[24] with most studies indicating lower verbal abilities in children with a history of ID, even if the differences were not statistically significant.[20,22,23,26,27]

The auditory brainstem and visual evoked potential responses were slower in children with a history of early childhood ID, even after receiving therapy.[32] As mentioned earlier, disruptions in myelination lead to developmental disorders that manifest later. Oligodendrocytes, which are crucial for myelination, rely on iron availability for proper functioning. Impaired iron availability during development affects myelination.[37] The latency of auditory brainstem response and visual evoked potential is influenced by the conduction velocity during axonal myelination.[32] Regarding auditory function, one study found that children with a history of early childhood ID had normal hearing,[24] suggesting that the delayed brainstem auditory response was likely due to central nervous system dysfunction caused by early childhood ID.[32]

Several studies included in this review reported motor impairments in children with a history of childhood ID when assessed at ages 4 years,[33] 5 years,[15] 6 years,[31] and 5-12 years.[34] The previously discussed myelination disorders also impact the corticospinal tract, which affects motor skills.[38] The corticospinal tract forms pyramidal tract fibers that connect the sensory and motor areas of the cerebral cortex to the spinal cord, serving as the main pathway for motor signals from the brain to the limbs.[39] Myelination of the pyramidal tract begins in early life and is completed within a few years.[40] One study specifically examined the relationship between early childhood ID and motor activity during daytime sleep, finding that children with early childhood ID exhibited more leg movements and higher intra-individual variability (IIV) compared to normal children, indicating a neurodevelopmental delay.[33] Elevated IIV suggests a delay, as IIV typically decreases with age.[41] Full myelination of the central nervous system reduces IIV in the sensorimotor system, while the elimination of transient central nervous system connections also decreases IIV.[42] Since iron is essential for myelination, the IIV observed in children with early childhood ID is linked to impaired central nervous system maturation due to myelination disorders.[33]

ID in infancy is believed to impact social-emotional development during adolescence through both psychosocial and neurobiological pathways.[28] The effect of early childhood ID on brain development depends on the timing of the deficiency and the specific brain regions requiring iron at that time.[43] Neurotransmitters such as dopamine, serotonin, and norepinephrine regulate neuronal signaling, influencing behavior as well as cognitive and emotional processes in infants.[22] Damage to dopamine terminals during the neonatal phase leads to lifelong hyperreactivity to new objects and environments[44] and is thought to have long-term effects on attention and emotional responses.[45] However, another hypothesis worth considering, which may warrant further research, suggests that children with a history of early childhood ID engage less with caregivers, resulting in fewer developmentally supportive interactions. Over time, this leads to reduced social and environmental stimulation, which may present challenges later in life.[17] This is significant as behavior and psychosocial development are broad concepts that go beyond neurobiological factors and also encompass psychosocial elements.

ID in early childhood is believed to affect the neuroendocrine hypothalamic-pituitary-adrenal axis later in life. One study found that 10-year-old children with early childhood ID had significantly lower serum cortisol levels compared to normal children. This study also reported lower plasma cortisol concentrations and a blunted stress response in children with a history of early childhood ID.[19] However, another study found the opposite result, with children who had early childhood ID showing higher morning salivary cortisol levels compared to their peers without ID.[24] The discrepancy between these findings may be due to differences in sample type, assessment timing, and sampling methods. Nevertheless, both studies suggest a potential link between early ID and neuroendocrine function, warranting further investigation.

Our study addresses whether early-life ID has long-term effects despite treatment. However, it has several limitations. This systematic review includes studies using various tools and methods to assess the same outcomes. The populations, study designs, methods, and

follow-up durations also varied, which limits the generalizability of the findings and prevents the application of a meta-analysis. Therefore, we suggest that future studies use standardized outcome measures to enable comparisons and meta-analyses. While cognitive and motor impairments are well-documented in several studies, verbal, behavioral, auditory, and neuroendocrine outcomes are less consistently evaluated, and the imbalance in reported findings may introduce reporting bias. Additionally, the assessment times across studies range from as early as age 4 to as late as adolescence (11-17 years), which may introduce bias into our study.

ID in early childhood disrupts neurodevelopmental processes, leading to long-term effects on cognition, motor skills, behavior, and neuroendocrine function. Children with a history of childhood ID were reported to have lower cognitive, motor, behavior, and neuroendocrine functions compared to those without a history of ID. Our study emphasizes the importance of the neurodevelopmental process, as disturbances during this phase, particularly ID, can result in long-term neurological impairments. Therefore, we stress the importance of preventing ID, especially during the first 1,000 days of life, as it can lead to irreversible deficits in motor function, cognitive ability, and behavior.

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Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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