Chronic Iron Deficiency and Cognitive Function in Early Childhood

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abstract

BACKGROUND AND OBJECTIVES: A landmark longitudinal study, conducted in Costa Rica in the 1980s, found that children with chronic iron deficiency compared with good iron status in infancy had 8 to 9 points lower cognitive scores, up to 19 years of age. Our objective was to examine this association in a contemporary, high-resource setting.

METHODS: This was a prospective observational study of children aged 12 to 40 months screened with hemoglobin and serum ferritin. All parents received diet advice; children received oral iron according to iron status. After 4 months, children were grouped as: chronic iron deficiency (iron deficiency anemia at baseline or persistent nonanemic iron deficiency) or iron sufficiency (IS) (IS at baseline or resolved nonanemic iron deficiency). Outcomes measured at 4 and 12 months included the Early Learning Composite (from the Mullen Scales of Early Learning) and serum ferritin.

RESULTS: Of 1478 children screened, 116 were included (41 chronic, 75 sufficient). Using multivariable analyses, the mean between-group differences in the Early Learning Composite at 4 months was −6.4 points (95% confidence interval [CI]: −12.4 to −0.3, $P = .04$) and at 12 months was −7.4 points (95% CI: −14.0 to −0.8, $P = .03$). The mean between-group differences in serum ferritin at 4 months was 14.3 μg/L (95% CI: 1.3–27.4, $P = .03$) and was not significantly different at 12 months.

CONCLUSIONS: Children with chronic iron deficiency, compared with children with IS, demonstrated improved iron status, but cognitive scores 6 to 7 points lower 4 and 12 months after intervention. Future research may examine outcomes of a screening strategy on the basis of early detection of iron deficiency using serum ferritin.

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WHAT'S KNOWN ON THE SUBJECT: A landmark longitudinal study, conducted in Costa Rica in the 1980s, found that children with chronic iron deficiency in infancy had cognitive scores 8 to 9 points lower than those with iron sufficiency, up to 19 years of age.

WHAT THIS STUDY ADDS: In a contemporary, high-resource setting, we found that children with chronic iron deficiency, compared with children with iron sufficiency, demonstrated improved iron status, but cognitive scores 6 to 7 points lower at 4 and 12 months after intervention.

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A landmark longitudinal study by Lozoff and colleagues examined the association between chronic, severe iron deficiency in infancy and long-term cognitive function.[1–5] Between 1983 and 1985, Lozoff et al enrolled 191 Costa Rican infants aged 12 to 23 months, with varying iron status.[1] Children received iron or placebo for 3 months, and were subsequently categorized as: chronic iron deficiency (iron deficiency anemia [IDA] or nonanemic iron deficiency [NAID] not fully corrected after iron treatment) or good iron status (iron sufficiency [IS] before and/or after treatment). Cognitive performance was assessed up to 19 years of age, and was 8 to 9 points lower in those with chronic iron deficiency in infancy, with no catch-up throughout childhood.[4]

We designed a similar study in our primary care network in Toronto, Canada. We have previously described our screening strategy for iron deficiency using serum ferritin, and found a prevalence of 12% in a screened cohort of 1735 children aged 1 to 3 years.[6] For the current study, we included children from this screened cohort with varying iron status, spanning IDA, NAID, and IS and examined cognitive outcomes.[7] There is equipoise regarding the effectiveness of oral iron versus diet advice for children with NAID; therefore, we nested a randomized controlled trial of children with NAID within the cohort (children with IDA and IS were not included), which was recently published.[8] For those children with IDA, we deemed randomization to treatment to be unethical, given that usual practice is treatment with oral iron.[9]

The results of our nested trial of children with NAID showed no meaningful between-group differences on cognitive outcomes. Of note, all children receiving oral iron had resolution of iron deficiency, whereas one-third of children receiving diet advice alone had persistent iron deficiency at 4 months. One limitation of this nested trial was our inability to control for chronicity of iron deficiency at baseline because children with NAID were enrolled on the basis of a single measure of iron status.

We hypothesized that children with persistent NAID not corrected after intervention might have cognitive outcomes more similar to children with IDA; and that children with resolved NAID corrected after intervention might have cognitive outcomes more similar to children with IS. We also hypothesized that children with and without chronic iron deficiency would have different cognitive outcomes. Our prospective cohort of screened children with IDA, NAID, and IS provided an opportunity to examine this hypothesis. Follow-up data at 4 and 12 months from all 3 groups have not been previously reported.

We aimed to use a conceptual framework similar to that used by Lozoff and colleagues in a contemporary cohort in a high-resource setting. Our primary objective was to assess the association between chronic iron deficiency, compared with IS, and later cognitive function in young children. Our secondary objective was to assess the laboratory outcomes in these 2 groups.

METHODS

Study Design

This was a prospective observational study. The study protocol has been published.[7] The nested randomized trial of children with NAID has been published.[8]

Participants and Procedures

Healthy children were recruited while attending a scheduled health supervision visit at 1 of 8 primary care practices participating in a longitudinal cohort and practice-based research network called *TARGet Kids!* in Toronto, Canada (www.targetkids.ca).[10] The cohort focuses on outcomes of early life exposures for children aged birth to 5 years (ClinicalTrials.gov NCT01869530). Children attend multiple visits in the first 5 years of life in accordance with national guidelines, including at ~12, 15, 18, 24, and 36 months of age. Using *TARGet Kids!* eligibility criteria, children were excluded for the following reasons: genetic or chronic health conditions (except asthma), severe developmental delay, gestational age <32 weeks, acute illness, and parents unable to communicate in English.[10] During the visit, trained research personnel obtained child and family characteristics using a standardized questionnaire, the child's anthropometric measurements using a standardized method, and blood samples.[10] Blood samples were transported to the laboratory and analyzed within 4 to 6 hours, including hemoglobin, serum ferritin, and C-reactive protein (CRP). Hemoglobin was analyzed on the Sysmex XN-9000 Hematology Analyzer (Kobe, Japan); serum ferritin and CRP were analyzed on the Roche platform.

For this study, children from the screened cohort were eligible if they were aged 12 to 40 months and had complete baseline data, including questionnaires, anthropometric measures, and blood samples. Additional exclusion criteria were: currently receiving oral iron, gestational age <35 weeks, birth weight <2500 g, CRP ≥10 mg/L, or missing. An unanticipated exclusion was participation in another concurrently running study.[11]

Children were invited to participate if the results of their blood sample met criteria for 1 of 3 iron status categories:

1. IDA: hemoglobin <110 g/L, serum ferritin <14 μg/L;
2. NAID: hemoglobin ≥110 g/L, serum ferritin <14 μg/L; and
3. IS: hemoglobin ≥110 g/L, serum ferritin ≥14 μg/L.

Given the large number of children with IS, only a random sample was invited to participate. Children with anemia without iron deficiency (hemoglobin <110 g/L, serum ferritin ≥14 μg/L) were not invited to participate. Only those with parental consent were enrolled.

Parents of all enrolled children received diet advice with a written guide, developed by the investigators, for optimizing iron status.[8] Children with IDA received oral ferrous sulfate (6 mg elemental iron/kg/d) for 4 months in keeping with usual practice.[9] Children with NAID were randomized to ferrous sulfate (same dose and duration) or placebo as previously described in the nested randomized trial (because of a protocol deviation, 3 eligible children were not randomized and received ferrous sulfate).[8] Children with IS did not receive any oral product.

Data on iron status and cognitive function were collected at baseline, 4 months and 12 months after enrollment.

Exposure

Two iron status groups were defined according to the results of the laboratory tests at baseline and the 4 month follow-up. Chronic iron deficiency was defined as IDA at baseline or NAID at baseline, which was persistent at 4 months despite intervention. IS was defined as IS at baseline or NAID at baseline, which had resolved at 4 months after intervention.

Outcomes

The primary outcome was cognitive function, assessed at 4 and 12 months, using the Early Learning Composite (ELC) from the Mullen Scales of Early Learning.[12] The ELC is a summary of 4 cognitive skills (fine motor, visual reception, receptive language, expressive language). The standardized ELC has a mean of 100 and SD of 15.

Secondary outcomes included each individual cognitive skill measured in the ELC, and serum ferritin and hemoglobin at 4 and 12 months.

The same psychometrist (C.K.) and psychologist (E.M.) completed all cognitive assessments and were blind to laboratory results and iron status category. Parents, attending physicians, research assistants, and investigators were not blind to iron status category.

Sample Size

We planned to screen ~1500 children and anticipated ~10% to be enrolled. We aimed to enroll at least 60 children with NAID (30 receiving oral iron and 30 receiving diet advice alone), 25 with IDA, and 25 with IS. For children with NAID, the sample size was based on our published pilot study using the analysis of covariance method to detect a between-group difference of 6 points in the ELC.[8,13]

For children with IDA and IS, the sample size estimate is described in our published protocol.[7] We estimated that 1% to 2% of the 1500 children screened would have IDA. Given the large number of children expected to have IS, we randomly selected a similar number of children with IS; for each child with IDA enrolled, the next child identified with IS who agreed to participate was enrolled. We continued enrollment of children with IDA and IS until the sample size for children with NAID participating in the nested randomized trial was reached.

Analysis

Baseline characteristics of the 2 groups were described using means and SD for continuous variables and counts and percentages for categorical variables. We fit separate multivariable linear regression models to compare children with chronic iron deficiency versus IS on ELC scores at 4 and 12 months, adjusted for age, sex, and serum ferritin at baseline. Similar models were used for the secondary outcomes, including each individual cognitive skill measured in the ELC (fine motor, visual reception, receptive language, expressive language), and serum ferritin and hemoglobin at 4 and 12 months. Models for the individual cognitive skills and serum ferritin were adjusted for age, sex, and serum ferritin at baseline; models for hemoglobin were adjusted for age, sex, and hemoglobin at baseline. The estimated effects were reported as an adjusted mean difference with 95% confidence intervals (CIs) and *P* values.

Ethics

We obtained approval from the Hospital for Sick Children research ethics board (file number: 1000027782). Written informed consent was obtained from parents of all participants using different consent forms for the 3 iron status categories at baseline (IDA, NAID, IS). Each child's primary physician received laboratory results within 24 to 48 hours and cognitive reports within 4 weeks. We considered the provision of diet advice and assessment of outcomes at 4 months in all children to be consistent with

good clinical practice. If at 4 months, a child had IDA or NAID, they were treated and monitored by their primary physician, without involvement of the research team.[7]

RESULTS

Participants

The study was conducted between June 15, 2012, and November 9, 2018. Participant flow is shown in Fig 1. Of 1478 children meeting eligibility after screening, 130 were enrolled according to the 3 baseline iron status categories: IDA (n = 37), NAID (n = 63), and IS (n = 30). At 4 months, 116 children had exposure and outcome data available and were allocated to 1 of 2 groups, as defined in Methods: chronic iron deficiency (n = 41) or IS (n = 75). At 12 months, 91 children had ELC scores available: chronic iron deficiency (n = 31) or IS (n = 60). Participant characteristics at baseline in the 2 groups are shown in Table 1. Mean serum ferritin was 7.4 μg/L in children with chronic iron deficiency and 16.2 μg/L in children with IS.

At 4 and 12 months, no child had IDA. Of those with IDA at baseline and laboratory tests at 4 months, 1 of 32 (3%) had NAID at 4 months. Of those with NAID at baseline and laboratory tests at 4 months, 9 of 55 (16%) had persistent NAID at 4 months and met the definition for chronic iron deficiency. All 9 children with persistent NAID had received placebo (diet advice alone) and none had received oral iron.

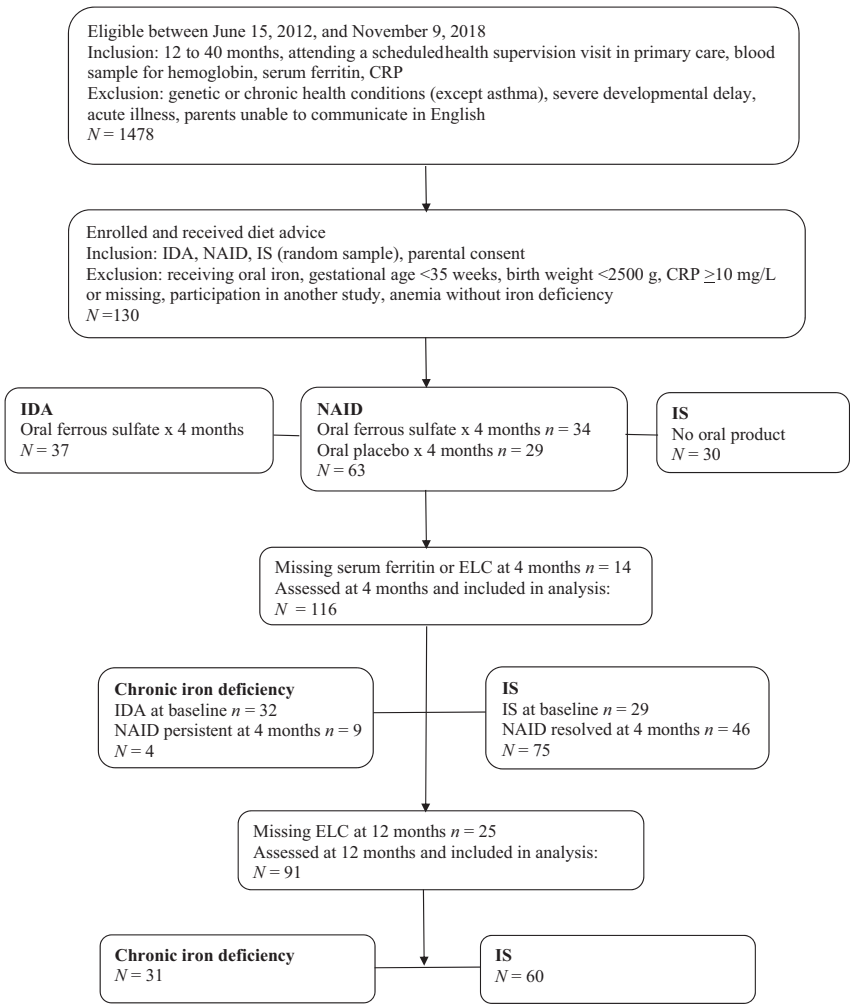

FIGURE 1
Participant flow diagram.

Primary Outcome: ELC at 4 and 12 Months

Using multivariable analyses, the mean between-group differences in ELC at 4 months was −6.4 points (95% CI: −12.4 to −0.3, P = .04) and at 12 months was −7.4 points (95% CI: −14.0 to −0.8, P = .03) (Table 2). Figure 2 shows the ELC in the 2 groups at baseline, 4 and 12 months.

Secondary Outcomes

Results for each of the 4 individual cognitive skills at 4 and 12 months are shown in Table 2. The mean between-group differences in visual reception at 4 months was −5.4 points (95% CI: −9.6 to −1.3, P = .01) and at 12 months was −8.9 points (95% CI: −13.4 to −4.5, P < .001).

Results for serum ferritin and hemoglobin are shown in Table 2. The mean between-group differences in serum ferritin at 4 months was 14.3 μg/L (95% CI: 1.3–27.4, P = .03) and at 12 months was 3.6 μg/L (95% CI: −2.0 to 9.1, P = .21) (Fig 3). There were no meaningful between-group differences in hemoglobin at 4 or 12 months.

DISCUSSION

In this prospective observational study, children with chronic iron deficiency in infancy (IDA at baseline or persistent NAID), compared with children with IS, had lower cognitive scores 4 and 12 months after intervention. The mean serum ferritin in the chronic iron deficiency group increased substantially at 4 months and was

TABLE 1 Participant Characteristics at Baseline According to Iron Status ($n = 116$)

Variables	Chronic Iron Deficiency, $n = 41$		IS, $n = 75$	
Child and family characteristics				
Age, mo, mean (SD)	21.7	(6.5)	24.9	(7.9)
Sex, male, No. (%)	20	(48.8)	41	(54.7)
Birth weight, kg, mean (SD)	3.2	(0.4)	3.4	(0.5)
Missing, No. (%)	4	(3.4)	0	(0)
Maternal education, postsecondary, No. (%)	37	(90.2)	71	(95.9)
Missing, No. (%)	1	(0.9)	0	(0)
Duration of breastfeeding, mo, mean (SD)	14.1	(4.4)	14.6	(6.9)
Volume of cow's milk, cups per d, mean (SD)	1.6	(1.3)	1.7	(1.3)
Laboratory measures				
Hemoglobin, g/L, mean (SD)	103.2	(16.9)	119.1	(6.2)
Serum ferritin, μg/L, mean (SD)	7.4	(3.1)	16.2	(9.5)
CRP, mg/L, mean (SD)	0.8	(1.4)	0.4	(1.1)
Missing, No. (%)	1	(0.9)	0	(0)
Cognitive scores, Mullen Scales of Early Learning, mean (SD)				
ELC	105.6	(13.7)	108.7	(12.8)
Fine motor	51.8	(8.7)	51.6	(7.7)
Visual reception	53.8	(9.7)	55.2	(8.6)
Receptive language	53.1	(11.9)	57.1	(9.7)
Expressive language	52.4	(9.2)	53.4	(9.2)

higher than the serum ferritin in the IS group. By 12 months, the mean serum ferritin values were similar in the 2 groups; hemoglobin values were similar in the 2 groups at both 4 and 12 months. Thus, despite laboratory correction, cognitive differences remained.

Lozoff and colleagues studied a cohort of Costa Rican infants and assessed outcomes in infancy, 5 years, 11 to 14 years, 15 to 18 years, and 19 years of age.[1–4] In our contemporary cohort in a high-resource setting, the magnitude of the difference in cognitive scores (6–7 points) was similar to that found in the Costa Rican cohort, persisting up to 19 years of age (8–9 points), and who subsequently reported poorer functional outcomes at 25 years of age.[4,5]

A Cochrane systematic review of randomized trials, first published in 2001 and updated in 2013, examined the effectiveness of iron therapy for improving cognitive function in children aged <3 years with IDA.[14,15] Only 2 studies were identified which examined outcomes >30 days after commencement of therapy (total $n = 160$, published in 1986 and 1993).[16,17] The authors of the systematic review concluded that the "effect of longer-term treatment remains unclear" and called for "further large randomized controlled trials with long-term follow-up."[15] However, in the >25 years since the last published trial, there have been no additional trials. We believe that such a trial would now be considered unethical.

Screening recommendations have focused on detection of anemia.

TABLE 2 Developmental and Laboratory Outcomes at 4- and 12-Month Follow-Up

	Chronic Iron Deficiency	*n*	IS	*n*	Adjusted Mean Difference (95% CI)	*P*
Developmental outcomes						
ELC, mean (SD)[a]						
4 mo follow-up	107.9 (13.4)	41	112.5 (14.5)	75	−6.35 (−12.40 to −0.29)	.04
12 mo follow-up	110.2 (15.0)	31	114.8 (13.7)	60	−7.35 (−13.95 to −0.75)	.03
Fine motor, mean (SD)[a]						
4 mo follow-up	51.5 (8.1)	41	51.9 (8.9)	75	−2.19 (−5.88 to 1.50)	.24
12 mo follow-up	53.4 (11.7)	31	53.6 (10.2)	60	−1.27 (−6.27 to 3.74)	.62
Visual reception, mean (SD)[a]						
4 mo follow-up	55.1 (10.0)	41	60.0 (9.7)	75	−5.43 (−9.56 to −1.29)	.01
12 mo follow-up	56.7 (9.5)	31	63.2 (9.7)	60	−8.94 (−13.37 to −4.52)	<.001
Receptive language, mean (SD)[a]						
4 mo follow-up	56.3 (9.7)	41	58.6 (9.4)	75	−4.49 (−8.53 to −0.45)	.03
12 mo follow-up	55.8 (8.0)	31	56.6 (8.9)	60	−4.49 (−8.53 to −0.45)	.29
Expressive language, mean (SD)[a]						
4 mo follow-up	52.8 (8.3)	41	55.6 (8.0)	75	−2.88 (−6.43 to 0.67)	.11
12 mo follow-up	54.5 (8.6)	31	56.4 (8.3)	60	−2.44 (−6.44 to 1.56)	.23
Laboratory outcomes						
Serum ferritin, μg/L, mean (SD)[a]						
4 mo follow-up	48.1 (41.0)	41	31.4 (21.6)	75	14.3 (1.3–27.4)	.03
12 mo follow-up	24.9 (9.9)	33	26.6 (13.2)	61	3.6 (−2.0 to 9.1)	.21
Hemoglobin, g/L, mean (SD)[b]						
4 mo follow-up	119.7 (9.2)	39	121.3 (7.2)	74	1.4 (−2.4 to 5.1)	.47
12 mo follow-up	117.4 (6.9)	33	119.8 (5.8)	61	−0.65 (−3.9 to 2.6)	.70

[a] Adjusted for baseline serum ferritin, age, sex.
[b] Adjusted for baseline hemoglobin, age, sex.

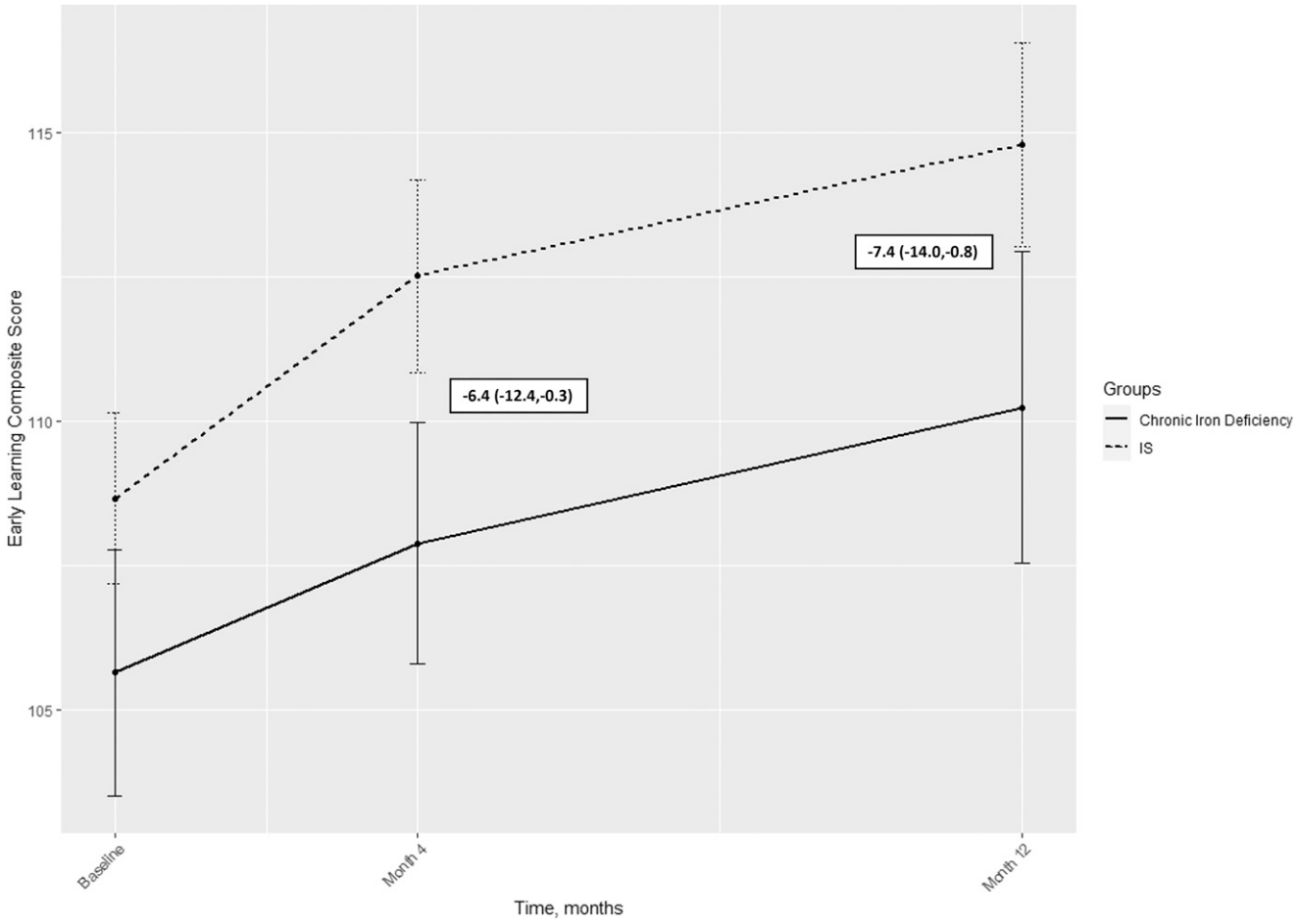

FIGURE 2

Mean (95% CI) ELC score, chronic iron deficiency versus IS at baseline, 4 months, 12 months. Mean between-group differences (95% CI) in ELC shown at 4 months and 12 months.

The American Academy of Pediatrics recommends universal screening for anemia using hemoglobin at 1 year of age.[18] However, hemoglobin lacks diagnostic accuracy for iron deficiency and may result in late detection, chronic iron deficiency, and poor outcomes. The 10 screening principles identified by Wilson and Jungner published by the World Health Organization in 1968 included "there should be a recognizable latent or early symptomatic stage."[19] This principle has been recently reaffirmed through a systematic review and consensus process because "there should be a detectable preclinical phase."[20] We recommend screening using serum ferritin (preclinical latent phase) rather than screening with hemoglobin (late symptomatic phase) for early detection of iron deficiency in young children, a strategy we assessed in >1700 children, aged 1 to 3 years.[6]

The American Academy of Pediatrics also recommends selective screening at any age and provides a list of risk factors.[18] In our screened cohort, we have identified similar risk factors, including longer duration of bottle use, longer breastfeeding duration, higher daily cow's milk intake, lower meat consumption, higher BMI (overweight and obesity), South Asian and West Asian/North African maternal ethnicities, and lower family income.[21–28] In a cost-utility analysis, we found that both universal and targeted screening strategies would be cost-effective over no screening, and both were well below a commonly used willingness-to-pay threshold.[29]

The 2015 recommendation statement from the US Preventive Services Task Force (USPSTF) also focuses on screening for anemia, noting that, "although the evidence is insufficient to recommend specific tests for screening, measurement of serum hemoglobin or hematocrit is often the first step,"[9] The USPSTF concluded that the "current evidence is insufficient to assess the balance of benefits and harms of screening for IDA in children aged 6 to

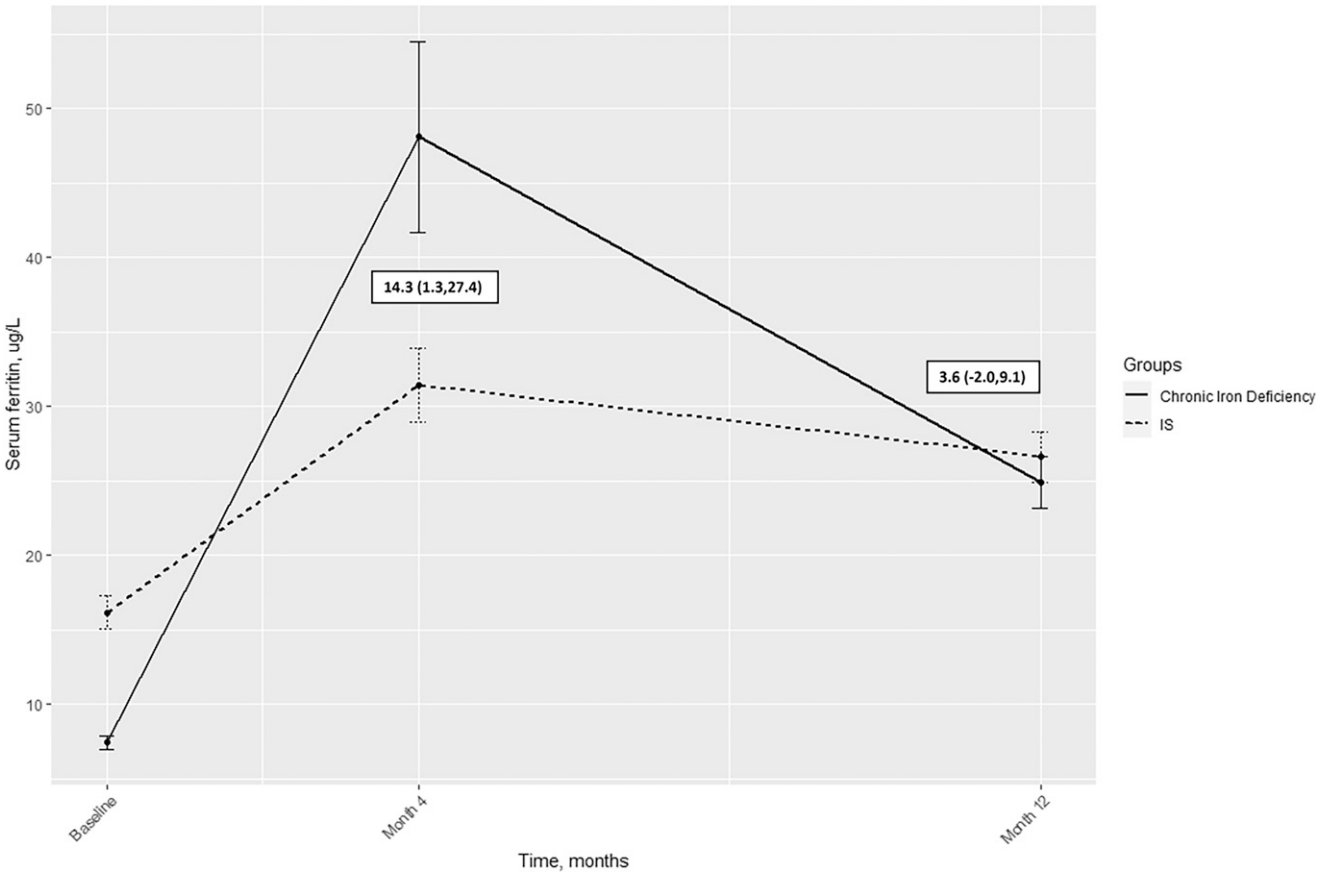

FIGURE 3

Mean (95% CI) serum ferritin μg/L, chronic iron deficiency versus IS at baseline, 4 months, 12 months. Mean between-group differences (95% CI) in serum ferritin shown at 4 months and 12 months.

24 months."[9] The USPSTF noted the absence of "recent studies that are generalizable to the current United States population" and highlighted the findings from the long-term study conducted in Costa Rica by Lozoff and colleagues, which suggest that "preventing IDA may be preferable to treating it once it develops."[9] The findings from our contemporary cohort in a high-resource setting may be more generalizable to the current United States population, and suggest that prevention of anemia through screening using serum ferritin for early detection of iron deficiency, followed by a good response to an intervention (resolution), may lead to more favorable outcomes than late detection using hemoglobin or a poor response to intervention (persistent iron deficiency).

A screening strategy using serum ferritin will identify children with NAID. Our nested randomized trial aimed to determine whether clinicians should recommend oral iron, plus diet advice, or diet advice alone in children identified with NAID ($n = 60$).[8] For serum ferritin outcomes, our results showed an important between-group difference favoring oral iron, plus diet advice. For cognitive outcomes, although the point estimates were most compatible with no meaningful between-group differences, the upper CI included a between-group difference of 6 to 10 points (at 4 and 12 months follow-up, respectively), favoring oral iron. We also noted that one-third of children ($n = 9$) with NAID receiving diet advice alone had persistent NAID 4 months later. If children with persistent NAID have cognitive outcomes similar to children with IDA, as assumed in the current analysis, careful consideration should be given to the addition of oral iron to diet advice, and to follow-up children identified with NAID on screening.

This study has limitations. First, our sample size was small, but adequate to identify meaningful between-group differences; our samples of children with persistent NAID ($n = 9$) or with low maternal education ($n = 7$) were too small to analyze separately. Second, our findings may be subject to selection bias because children with missing data at 4 months were excluded from the analyses; however, 89% were retained. Third, our study population with high maternal

education may limit generalizability, but also broadens current knowledge, which is largely based on studies conducted in low-resource settings. Fourth, this was an observational study, rather than a randomized trial of screening.

CONCLUSIONS

In a prospective cohort of young children screened for iron deficiency with hemoglobin, serum ferritin and CRP, followed by an intervention as indicated, children with chronic iron deficiency (IDA at baseline or persistent NAID), compared with children with IS (IS at baseline or resolved NAID), demonstrated improved iron status, but cognitive scores 6 to 7 points lower at 4 and 12 months after intervention. This study adds further evidence that more research is needed to examine short- and long-term outcomes of a screening strategy on the basis of early detection of iron deficiency using serum ferritin.

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ABBREVIATIONS

CI: confidence interval
CRP: C-reactive protein
ELC: Early Learning Composite
IDA: iron deficiency anemia
IS: iron sufficiency
NAID: nonanemic iron deficiency
USPSTF: US Preventive Services Task Force

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