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Oral iron supplementation and anaemia in children according to schedule, duration, dose and cosupplementation: a systematic review and meta-analysis of 129 randomised trials

Christopher T Andersen ,[1] Daniel M Marsden ,[2] Christopher P Duggan,[3,4,5] Enju Liu,[3,6] Dariush Mozaffarian,[7,8] Wafaie W Fawzi[4]

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For numbered affiliations see end of article.

Correspondence to
Dr Christopher T Andersen; chrisandersen@mail.harvard.edu

ABSTRACT

Introduction WHO guidelines on iron supplementation among children call for further research to identify the optimal schedule, duration, dose and cosupplementation regimen.

Methods A systematic review and meta-analysis of randomised controlled trials was undertaken. Randomised controlled trials providing ≥30 days of oral iron supplementation versus placebo or control to children and adolescents aged <20 years were eligible. Random-effects meta-analysis was used to summarise the potential benefits and harms of iron supplementation. Meta-regression was used to estimate iron effect heterogeneity.

Results 129 trials with 201 intervention arms randomised 34 564 children. Frequent (3–7/week) and intermittent (1–2/week) iron regimens were similarly effective at decreasing anaemia, iron deficiency and iron deficiency anaemia (p heterogeneity >0.05), although serum ferritin levels and (after adjustment for baseline anaemia) haemoglobin levels increased more with frequent supplementation. Shorter (1–3 months) versus longer (7+ months) durations of supplementation generally showed similar benefits after controlling for baseline anaemia status, except for ferritin which increased more with longer duration of supplementation (p=0.04). Moderate-dose and high-dose supplements were more effective than low-dose supplements at improving haemoglobin (p=0.004), ferritin (p=0.008) and iron deficiency anaemia (p=0.02), but had similar effects to low-dose supplements for overall anaemia. Iron supplementation provided similar benefits when administered alone or in combination with zinc or vitamin A, except for an attenuated effect on overall anaemia when iron was cosupplemented with zinc (p=0.048).

Conclusions Weekly and shorter duration iron supplementation at moderate or high doses might be optimal approaches for children and adolescents at risk of deficiency.

Trial registration number CRD42016039948.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior meta-analyses have established that paediatric oral iron supplementation is safe and effective for reducing anaemia.
⇒ Consequently, WHO recommends 3 months annually of daily oral iron supplementation for children aged 6 months to 12 years living in regions with a high burden of anaemia.
⇒ However, the 2016 WHO guidelines call for further research to identify the optimal schedule, duration, dose and cosupplementation regimen.

WHAT THIS STUDY ADDS

⇒ Our study adds to previous meta-analyses of paediatric iron supplementation by using meta-regression to compare the effect sizes of randomised controlled trials with different schedules, durations, doses and cosupplementation schemes.
⇒ As a result, we are able to marshal a much larger body of literature than prior studies which have been restricted to trials specifically designed to answer questions of effect heterogeneity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results generally support the WHO recommendations regarding the frequency, duration and dose of iron supplementation.
⇒ However, weekly iron supplementation might be considered as an alternative to the recommended daily regimen in some contexts, given evidence of similar efficacy.
⇒ Furthermore, vitamin A and zinc can be cosupplemented without reducing the benefits of iron.

BACKGROUND

Iron deficiency (ID) is the most common micronutrient deficiency globally, with children at particular risk.[1 2] Among children aged 6–59 months, approximately half of the 273 million cases of anaemia in 2011 were

estimated to be due to ID.[3 4] ID is furthermore a key risk factor for cognitive impairment, impaired immune function and decreased capacity for physical activity.[5–7]

WHO recommends daily oral iron supplementation for all children in regions with a prevalence of anaemia ≥40%. In malaria-endemic settings, iron supplementation is recommended in conjunction with measures to prevent, diagnose and treat malaria.[8] These recommendations are supported by prior meta-analyses establishing the benefits of iron supplementation in the treatment of anaemia along with safety in the presence of malaria control programmes.[9–12] However, prior meta-analyses have not investigated the optimal delivery of iron supplementation among children. The 2016 WHO guidelines therefore highlight the need for additional evidence regarding the optimal schedule, duration and dose of iron supplementation, as well as the efficacy of iron supplementation in the presence of cosupplemented micronutrients.[8]

We conducted a systematic review and meta-analysis of randomised controlled trials of oral iron supplementation among children and adolescents aged <20 years and compared the impact of interventions by schedule, duration, dose and cointerventions. Haematologic, anthropometric, infectious and developmental outcomes were included to assess both safety and efficacy.

METHODS

Search strategy and selection criteria

We adhered to the Cochrane Collaboration's guidelines for this review.[13] The protocol was pre-registered with the International Prospective Register of Systematic Reviews (CRD42016039948). Systematic literature searches were performed using PubMed, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials from inception through November 2020. References of eligible articles and previous systematic reviews were additionally reviewed. No language restrictions were placed on the search strategy, although studies were excluded if a translation could not be obtained for those published in a language not spoken by one of the authors. Search terms are presented in online supplemental appendix 1.

Studies were eligible for inclusion if they met the following criteria:

- Oral iron supplementation was randomly assigned.
- Oral iron supplementation was compared with control or placebo. (Studies comparing multiple doses of iron supplementation and which did not include a group randomised to no iron were excluded due to the lack of a common referent for meta-analysis.)
- Intervention groups differed by iron alone (eg, studies randomising children to iron folate vs placebo were not eligible unless the placebo also included folate, due to potential independent effects of these other components).
- Oral iron supplementation was administered for a minimum period of ≥1 month (≥30 days).
- Participants were aged <20 years.
- Participants did not have any chronic illness (eg, HIV) or belong to a special subpopulation (eg, athletes).

Data extraction and management

One reviewer screened the titles and abstracts of records identified by the search, and excluded those that indicated clear ineligibility. Two reviewers independently reviewed the full text of all positively screened studies to establish final eligibility, after which data were extracted from eligible studies in duplicate using standardised forms. Online supplemental appendix 2 provides a list of variables extracted from eligible studies. Discrepancies between reviewers were resolved through discussion or through arbitration with a third reviewer. Factorial trials were extracted as two separate experiments (iron vs control, iron+cointervention vs control+cointervention).

Assessment of risk of bias

Two authors independently assessed risk of bias using the Cochrane Risk of Bias Tool, and discrepancies were resolved by discussion.[13]

Outcomes

To assess the relative benefits and risks of oral iron supplementation among children and adolescents, we included the following outcomes: haemoglobin (g/L), anaemia (defined by study authors), serum ferritin (µg/L), ID (defined by study authors), iron deficiency anaemia (IDA, defined by study authors); physical growth (height-for-age, weight-for-height, weight-for-age, stunting, wasting and underweight; primarily using the National Center for Health Statistics reference and WHO growth standards and growth reference[14–16]); indicators of infection (diarrhoea, respiratory infection, malaria and intestinal helminths); and child development (standardised means of cognitive, motor and socioemotional domain scores). In order to account for repeated use of the same control group in trials comparing multiple iron treatments to a single control (n=18 trials), the variance of the outcome in the control group was adjusted by dividing the control group sample size by the number of comparisons.

Statistical analysis

Meta-analysis was conducted for outcomes reported by four or more trials. We used inverse-variance weighted random-effects meta-analysis to account for underlying differences in the trial populations.[17] Binary outcomes were summarised using risk ratios, prevalence ratios (PR) or rate ratios with 95% CIs. Continuous measures on the same scale were presented using mean differences, and measures reported on different scales using standardised mean differences (SMD). For ferritin, geometric means or medians were included when arithmetic means were not reported. Heterogeneity of effects was measured using the I^2 statistic. We assessed effect modification using univariate meta-regression for prespecified supplementation variables: schedule (1–2 times/week; 3–7 times/

week), duration (1–3 months; 4–6 months; ≥7 months), dose (age-adjusted tertiles; see online supplemental appendix 3) and cointerventions (zinc; vitamin A).[18 19] In secondary analyses, we explored effect modification by baseline anaemia (all anaemic; all non-anaemic; mixed population of anaemic and non-anaemic; missing baseline anaemia data), child age (0–5 months; 6–23 months; 2–4 years; 5–11 years; 12–19 years), child sex (all female; all male; mixed female and male; missing baseline sex data), WHO region (Africa; Americas; Eastern Mediterranean; Europe; South-East Asia; Western Pacific) and iron formulation (ferrous sulfate; ferrous fumarate; other or unspecified). We conducted multivariate meta-regression to investigate collinearity between potential effect modifiers.[20] Small study effects were assessed using funnel plots and Egger's test for all outcomes reported by ≥10 iron intervention groups. Sensitivity analyses correcting for small study effects were conducted using trim and fill.[21]

Role of the funder

The funder was not involved in the study design, data collection, analysis, interpretation or manuscript writing. The corresponding author had access to all data in the study and assumes full responsibility for the accuracy of the results.

Patient and public involvement

Our prior clinical and research experiences with iron-deficient paediatric patients led us to develop the idea for this study. No patients were involved in the meta-analysis design or conduct, though we aim to present findings of clinical relevance to patients. We anticipate that the results of this study would be of interest to clinicians and health policy makers globally, which could in turn contribute to improved patient care.

RESULTS

Literature search

A total of 12 350 unique publications were retrieved from PubMed, Scopus, Web of Science and Cochrane Central search. An additional 13 records identified from the reference lists of eligible articles or prior meta-analyses were also screened. Of these, 955 records were selected for full text review, of which 79 required discussion between independent reviewers to determine eligibility, and 13 required arbitration from a third coauthor. One hundred and forty-two studies met the final eligibility criteria for inclusion (figure 1). Online supplemental appendix 4 provides references to all included publications.

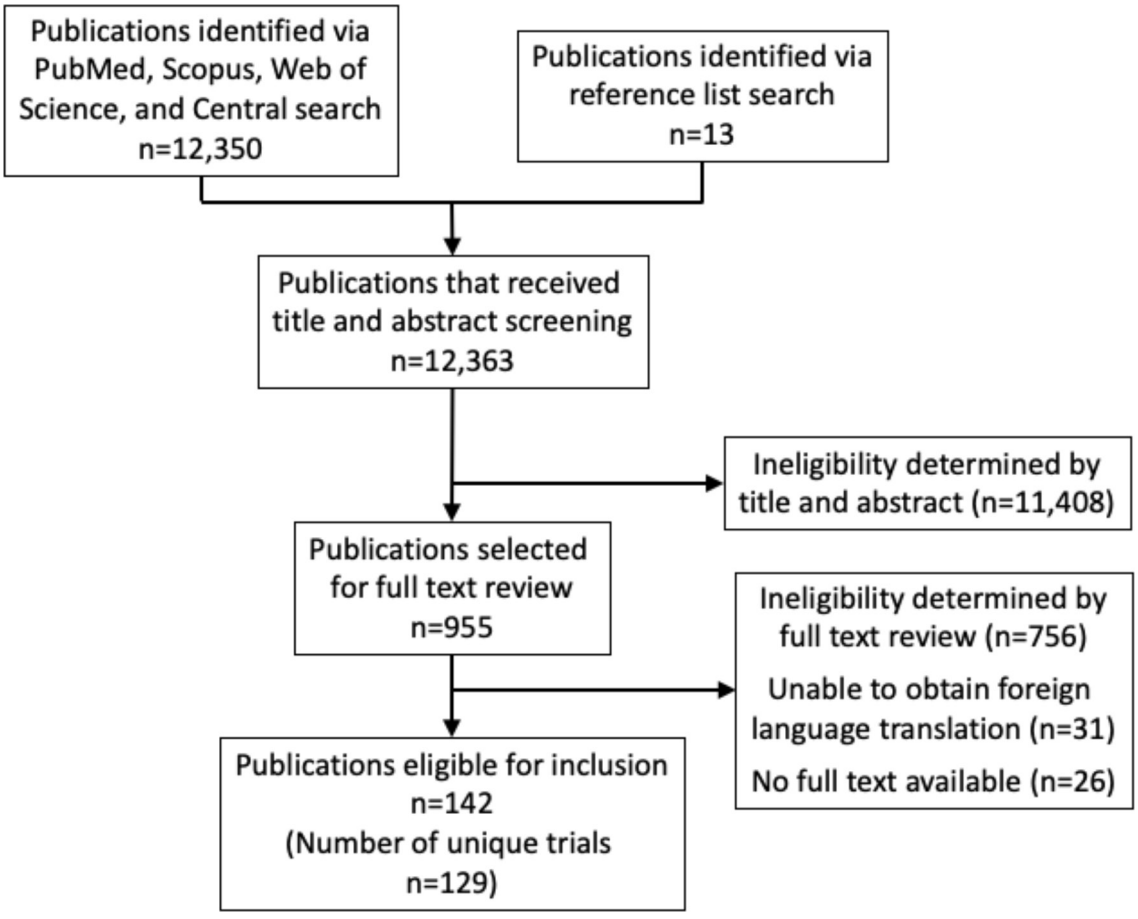

Figure 1 Flow diagram for selection process of eligible studies.

Trial characteristics

The 142 eligible publications represented 129 unique trials with 201 trial arms randomised to iron supplementation and 177 trial arms randomised to control or placebo, and 34 564 total participants analysed (table 1). Children under 5 years of age were most frequently studied, with children aged <6 months (n=45 trial arms, 22%), 6–23 months (n=44, 22%) and 2 to <5 years (n=37, 18%) representing roughly equal proportions of this population. School-age children of 5–11 years (n=50, 25%) and adolescents aged 12–19 years (n=25, 12%) were less frequently studied than children under 5. About half of studies were in anaemic only (n=36, 18%) or mixed anaemic and non-anaemic (n=70, 35%) children, and about 1 in 6 (n=32, 16%) in non-anaemic children; the remainder (n=63, 32%) did not report baseline anaemia status. Most studies (n=163, 81%) provided iron supplementation 3–7 days/week, although many (n=35, 17%) supplemented only 1–2 days/week. About half of studies (n=113, 56%) provided supplementation for 1–3 months; about one-third (n=62, 31%) for 4–6 months; and the remainder (n=26, 13%) for ≥7 months. About one-fifth (n=30, 23%) of eligible studies were factorial trials, among which the most frequent cointerventions were zinc (n=11) and vitamin A (n=6). The characteristics of individual studies are available in online supplemental appendix 5.

Main effects of iron supplementation on haematologic outcomes

In aggregate, oral iron supplementation versus placebo or control demonstrated clear benefits for haematologic indices (table 2). Haemoglobin levels rose by 6.3 g/L (95% CI 5.5, 7.1) along with serum ferritin increases of 18.5 ng/mL (16.1, 20.9). Iron supplementation reduced the prevalence of overall anaemia by 39% (33%, 45%), and even larger impacts were observed for ID (reduction of 70% (63%, 76%)) and IDA (reduction of 80% (69%, 87%)). Heterogeneity was observed between studies for these haematologic outcomes (I^2 ranging from 80% to 100%), which was further explored using meta-regression (see below).

Assessment of heterogeneity for haematologic outcomes

When comparing trials of frequent (3–7 times/week) versus intermittent (1–2 times/week) supplementation, no significant differences in treatment effects were observed for haemoglobin, anaemia, ID and IDA outcomes (table 3). However, trials of frequent supplementation achieved larger increases in serum ferritin than trials of intermittent supplementation (20.9 ng/mL (18.2, 23.7) vs 6.7 ng/mL (3.7, 9.6); p interaction <0.001). After control for baseline anaemia in the study population, frequent supplementation was associated with a larger increase in both ferritin and haemoglobin levels as compared with intermittent supplementation (online supplemental appendix 6).

Table 1 Characteristics of studies included in meta-analysis of randomised iron supplementation trials for child health

Study characteristics	
Eligible publications, n	142
Unique trials, n	129
Trial arms randomised to iron, n	201
Trial arms randomised to placebo or control, n	177
Individuals randomised to iron, n	18 142
Individuals randomised to placebo or control, n	16 422
WHO region, n (%)*	
Africa	40 (19.9)
Americas	36 (17.9)
Eastern Mediterranean	12 (6.0)
Europe	26 (12.9)
South-East Asia	67 (33.3)
Western Pacific	20 (10.0)
Decade of publication, n (%)†	
1970–1979	3 (2.1)
1980–1989	17 (12.0)
1990–1999	26 (18.3)
2000–2009	69 (48.6)
2010–2017	27 (19.0)
Population characteristics	
Age, n (%)*	
0–5 months	45 (22.4)
6–23 months	44 (21.9)
2 to <5 years	37 (18.4)
5 to <12 years	50 (24.9)
≥12 years	25 (12.4)
Per cent female, median (IQR)*	50.4 (47.0, 55.2)
All female, n (%)	28 (13.9)
All male, n (%)	6 (3.0)
Mixed male and female, n (%)	125 (61.2)
Missing baseline sex data, n (%)	42 (20.9)
Baseline per cent anaemic, median (IQR)*	55.2 (9.1, 100.0)
All anaemic, n (%)	36 (17.9)
All non-anaemic, n (%)	32 (15.9)
Mixed anaemic and non-anaemic, n (%)	70 (34.8)
Missing baseline anaemia data, n (%)	63 (31.3)
Intervention characteristics	
Frequency, n (%)*	
1–2 days/week	35 (17.4)
3–7 days/week	163 (81.1)

Continued

Table 1 Continued

Study characteristics	
Missing frequency data	3 (1.5)
Duration, n (%)*	
1–3 months	113 (56.2)
4–6 months	62 (30.9)
≥7 months	26 (12.9)
Weekly iron dose (mg) by child age category, median (IQR)*	
0–5 months	52.5 (49.0, 70.0)
6–23 months	70.0 (47.5, 162.8)
24–59 months	105.0 (60.0, 210.0)
5–11 years	265.1 (120.0, 403.1)
12–19 years	205.0 (85.0, 325.0)
Missing dose information, n	28
Formulation, n (%)*	
Ferrous sulfate	122 (60.7)
Ferrous fumarate	20 (10.0)
Other or unspecified	59 (27.7)
Factorial trials, n (%)‡	30 (23.3)
Zinc, n (%)§	11 (36.7)
Vitamin A, n (%)§	6 (20.0)
Other, n (%)§	13 (43.3)

*Denominator is the number of unique groups randomised to iron (n=201).
†Denominator is the number of publications (n=142).
‡Denominator is the number of unique trials (n=129).
§Denominator is the number of factorial trials (n=30).

Increasing duration of supplementation was generally associated with diminished impacts on haemoglobin, ID and IDA (table 3). However, trials of short duration were more likely to have a higher proportion of patients with anaemia, which could lead to larger effects. After controlling for baseline anaemia, no significant associations were observed between duration of supplementation and haemoglobin, anaemia, ID or IDA outcomes. Trials of longer duration were associated with greater increases in serum ferritin after adjustment for baseline anaemia (online supplemental appendix 6).

When we evaluated age-adjusted doses of supplementation (see online supplemental appendix 3 for the age-specific dose categories), trials in the lowest dose tertile across all ages used lower amounts than recommended by WHO (10–12.5 mg/day for ages 6–23 months, 30 mg/day for ages 24–59 months and 30–60 mg/day for ages 5–12 years).[8] Compared with lower age-adjusted doses of supplementation and adjusting for baseline anaemia, moderate doses were associated with greater improvements in haemoglobin, ferritin and IDA (table 3; online supplemental appendix 6). However, the lower dose still produced benefits; and no linear dose–response was seen: compared with lower dose, the highest doses were not associated with significantly greater effects.

When comparing the effect of iron stratified by the baseline prevalence of anaemia, trials conducted among entirely anaemic populations demonstrated approximately twofold increases in haemoglobin (global p interaction <0.001) and reductions in endline anaemia (global p interaction=0.004) relative to non-anaemic populations (online supplemental appendix 7). Heterogeneity was observed for some outcomes by child age and sex, although there was no consistent pattern. Effects of iron on haematologic outcomes were similar across WHO regions, except for the impact on IDA (global p interaction=0.007). Comparing types of supplements, ferrous sulfate was associated with the largest increases in haemoglobin (p=0.02) and serum ferritin (p=0.005) and the largest reduction in IDA (p<0.001) compared with other iron formulations.

Cosupplementation

In factorial trials of iron and zinc supplementation, a borderline interaction was seen for iron effects on the prevalence of anaemia, with stronger reductions in anaemia among children not receiving zinc (PR=0.41 (0.33, 0.50)) versus those receiving zinc (PR=0.64 (0.48, 0.84)) (p interaction=0.048) (table 4). No significant differences by zinc cosupplementation were seen for haemoglobin, ferritin, ID or IDA, although effects generally appeared qualitatively stronger without zinc cosupplementation for each of these outcomes. Zinc alone provided no statistically significant benefits for haematologic outcomes (online supplemental appendix 8). There was no statistically significant difference in the effect of iron supplementation when administered with or without vitamin A. Vitamin A alone improved haemoglobin and anaemia outcomes (online supplemental appendix 8).

Safety outcomes

No statistically significant changes due to oral iron supplementation were observed for anthropometric or infectious indices (table 2). In meta-regression analyses, no significant differential impacts of iron on these outcomes were seen by schedule, duration or dose, except for an observed increase in the cumulative incidence of respiratory illness associated with iron supplements that were 1–2 per week, low dose or lasting for ≥7 months (online supplemental appendix 9). However, these differential effects were due to a single factorial trial of iron and polyunsaturated fatty acids that differed from the other trials in terms of schedule, dose and duration[22]; excluding this trial, no significant difference remained. Iron increased height-for-age z score (HAZ) by 0.20 (95% CI 0.01, 0.40) in trial arms composed exclusively of anaemic children (but based on only n=2 trial arms); no effect on HAZ was seen among trial arms of non-anaemic children (−0.02 (−0.18, 0.14); n=3) or mixed anaemic and non-anaemic children (0.00 (−0.03, 0.02); n=25) (p interaction=0.013).

Table 2 Effect of oral iron supplementation versus placebo or control among children and adolescents aged <20 years

	n*	Estimate type	Estimate of effect (95% CI)	P value	I^2 (%)
Haematology					
Haemoglobin (g/L)	167	WMD	6.3 (5.5 to 7.1)	<0.001	94.1
Serum ferritin (ng/mL)	107	WMD	18.5 (16.1 to 20.9)	<0.001	99.5
Anaemia	69	RR	0.61 (0.55 to 0.67)	<0.001	85.8
Iron deficiency	48	RR	0.30 (0.24 to 0.37)	<0.001	90.1
Iron deficiency anaemia	27	RR	0.20 (0.13 to 0.31)	<0.001	79.7
Anthropometry					
Height-for-age Z score	43	WMD	0.00 (−0.03 to 0.03)	0.99	33.9
Weight-for-height Z score	26	WMD	0.01 (−0.05 to 0.08)	0.71	71.7
Weight-for-age Z score	43	WMD	0.01 (−0.04 to 0.05)	0.78	64.7
Stunting	13	RR	1.07 (0.96 to 1.18)	0.22	0
Wasting	6	RR	1.12 (0.85 to 1.48)	0.42	0
Infections					
Diarrhoea (cumulative incidence)	15	RR	0.97 (0.84 to 1.11)	0.63	0
Diarrhoea (incidence rate)	8	IRR	1.08 (0.98 to 1.19)	0.10	63.4
Respiratory illness (cumulative incidence)	8	RR	1.16 (0.93 to 1.45)	0.20	66.2
Respiratory illness (incidence rate)	9	IRR	0.98 (0.92 to 1.06)	0.66	0
Malaria (prevalence)	12	PR	1.12 (0.99 to 1.25)	0.07	0
Malaria (incidence rate)	7	IRR	0.91 (0.82 to 1.01)	0.08	0
Hookworm (prevalence)	4	PR	0.94 (0.85 to 1.03)	0.19	0
Ascaris lumbricoides (prevalence)	4	PR	1.04 (0.88 to 1.25)	0.68	0
Trichuris trichiura (prevalence)	4	PR	0.97 (0.90 to 1.06)	0.52	0
Development					
Bayley Mental Index	9	SMD	0.26 (0.00 to 0.51)	0.05	67.8
Bayley Psychomotor Index	9	SMD	0.21 (−0.06 to 0.48)	0.13	70.4

*Number of trial arms randomised to iron.
IRR, incidence rate ratio; PR, prevalence ratio; RR, risk ratio; SMD, standardised mean difference; WMD, weighted mean difference.

Improvements in cognitive development were seen in one trial arm among anaemic children (Bayley Cognitive SMD=1.39 (0.75, 2.04); Bayley Motor SMD=1.46 (0.81, 2.11)) compared with no effect seen in four trial arms among non-anaemic children (Bayley Cognitive SMD=0.29 (−0.12, 0.71); Bayley Motor SMD=0.03 (−0.31, 0.38)) or four trial arms among mixed anaemic and non-anaemic children (Bayley Cognitive SMD=0.07 (−0.10, 0.23); Bayley Motor SMD=0.11 (−0.16, 0.37)) (p interaction=0.020 for cognitive and 0.023 for motor scores).

Risk of bias

The risk of bias within each trial is reported in online supplemental appendix 10. Many trials (16%–75%) did not report sufficient information to calculate the risk of bias according to one or more of the five criteria (online supplemental appendix 11). Forty-eight of the 129 trials (37%) were judged to be at high risk of bias for at least one of the criteria, with incomplete outcome data being the most frequent reason for a study to be assessed at high risk of bias (n=24, 19%). In sensitivity analyses excluding these 48 studies, the effects of iron supplementation on haematologic outcomes were similar (online supplemental appendix 12).

Small study effects

For haematologic outcomes, studies with larger SEs tended to demonstrate more protective effect sizes (Egger's test p<0.001) (online supplemental appendix 13). Attenuated but still statistically significant benefits were obtained during trim-and-fill sensitivity analyses for haemoglobin (2.2 g/L (1.2, 3.1)) and ferritin (4.1 ng/mL (1.6, 6.5)).

Table 3 Comparison of iron supplementation effects across schedule, duration and dosing schemes

	Haemoglobin (g/L)*	Ferritin (ng/mL)*	Anaemia†	Iron deficiency†	Iron deficiency anaemia†
Weekly frequency					
Frequent (3–7 times/week)					
n	132	88	57	44	24
Estimate	6.6	20.9	0.62	0.31	0.20
95% CI	(5.6 to 7.6)	(18.2 to 23.7)	(0.56 to 0.69)	(0.24 to 0.38)	(0.13 to 0.32)
Intermittent (1–2 times/week)					
n	32	18	10	4	3
Estimate	4.8	6.7	0.61	0.24	0.22
95% CI	(3.4 to 6.2)	(3.7 to 9.6)	(0.41 to 0.92)	(0.09 to 0.66)	(0.06 to 0.77)
P value for interaction	0.14	<0.001	0.87	0.73	0.91
Duration‡					
1–3 months					
n	96	59	27	18	6
Estimate	7.3	13.9	0.53	0.38	0.23
95% CI	(6.0 to 8.6)	(11.7 to 16.1)	(0.45 to 0.62)	(0.25 to 0.57)	(0.07 to 0.81)
4–6 months					
n	53	41	34	26	19
Estimate	5.7	25.1	0.63	0.21	0.15
95% CI	(4.3 to 7.0)	(20.0 to 30.1)	(0.54 to 0.72)	(0.15 to 0.30)	(0.11 to 0.22)
≥7 months					
n	18	7	8	4	2
Estimate	2.6	11.8	0.84	0.84	0.86
95% CI	(1.4 to 3.8)	(5.9 to 17.7)	(0.69 to 1.03)	(0.67 to 1.06)	(0.63 to 1.18)
P value for interaction	0.01	0.01	0.07	0.05	<0.001
Dose					
Low (1st tertile for age)					
n	59	41	27	17	13
Estimate	4.4	13.7	0.68	0.33	0.26
95% CI	(3.2 to 5.6)	(9.5 to 17.9)	(0.57 to 0.81)	(0.22 to 0.50)	(0.17 to 0.41)
Moderate (2nd tertile for age)					
n	32	22	23	17	10
Estimate	8.6	26.0	0.55	0.27	0.08
95% CI	(5.9 to 11.4)	(19.0 to 32.9)	(0.47 to 0.66)	(0.18 to 0.40)	(0.05 to 0.14)
High (3rd tertile for age)					
n	37	25	9	9	2
Estimate	7.2	16.2	0.64	0.24	0.08
95% CI	(5.3 to 9.1)	(13.4 to 19.0)	(0.49 to 0.84)	(0.12 to 0.47)	(0.01 to 0.69)
P value for interaction	0.004	0.008	0.44	0.82	0.02

*Weighted mean difference.
†Pooled risk ratio.
‡Trials of short duration were more likely to have a higher proportion of patients with anaemia. No significant associations were observed between duration and haemoglobin, anaemia, iron deficiency and iron deficiency anaemia outcomes after controlling for baseline anaemia. After control for anaemia, an increase in serum ferritin was associated with trials of longer duration (see online supplemental appendix 5).

Table 4 Comparison of iron supplementation effects within factorial trials

	Haemoglobin (g/L)*	Ferritin (ng/mL)*	Anaemia†	Iron deficiency†	Iron deficiency anaemia†
Zinc					
Iron+zinc versus zinc					
n	10	9	6	6	5
Estimate	4.2	21.1	0.64	0.18	0.15
95% CI	(1.5 to 6.9)	(16.0 to 26.1)	(0.48 to 0.84)	(0.12 to 0.28)	(0.09, 0.24)
Iron versus control/placebo					
n	10	9	6	6	5
Estimate	6.6	28.8	0.41	0.15	0.08
95% CI	(3.6 to 9.6)	(22.2 to 35.4)	(0.33 to 0.50)	(0.09 to 0.24)	(0.05, 0.15)
P value for interaction	0.27	0.19	0.048	0.62	0.13
Vitamin A					
Iron+vitamin A versus vitamin A					
n	6	3	2	1	0
Estimate	4.7	5.6	0.54	0.51	–
95% CI	(1.5 to 7.8)	(–3.5 to 14.7)	(0.11 to 2.56)	(0.31 to 0.85)	–
Iron versus control/placebo					
n	6	3	2	1	0
Estimate	8.0	8.4	0.27	0.34	–
95% CI	(3.1 to 12.8)	(5.3 to 11.4)	(0.16 to 0.45)	(0.18 to 0.66)	–
P value for interaction	0.27	0.72	0.49	n/a	n/a

*Weighted mean difference.
†Pooled risk ratio.

DISCUSSION

This systematic review and meta-analysis of 129 randomised controlled trials, including 201 trial arms of oral iron supplementation in children, demonstrates significant benefits on haematologic outcomes including haemoglobin (+6.3 g/L; 95% CI 5.5, 7.1), ferritin (+18.5 ng/mL; 16.1, 20.9) and prevalence of anaemia (39% reduction; 33%, 45%), ID (70% reduction; 63%, 76%) and IDA (80% reduction; 69%, 87%). Children under age 5 years were most frequently studied (63% of trial arms), including trials throughout this age range, but with meaningful numbers of trials among children aged 5–11 years (25%) and adolescents aged 12–19 years (12%). In sum, these findings provide strong evidence for the benefits of iron supplementation among children.

Importantly, the number and diversity of identified trials allowed us to assess factors that might modify these benefits. Our results suggest that frequent (3–7 times/week) and intermittent (1–2 times/week) iron supplementation may be equally effective at increasing haemoglobin and decreasing anaemia, ID and IDA. While WHO recommends daily oral iron supplementation for all children in regions with an anaemia prevalence of 40% or more, the success of such programmes may be threatened by low adherence from adverse gastrointestinal reactions or high caregiver burden to provide daily supplements.[23] Weekly iron supplementation has been promoted as an alternative to reduce these barriers.[24 25] Furthermore, since mammalian gastrointestinal epithelial cells turn over every 2–6 days, weekly supplementation may not be at a great disadvantage relative to daily supplementation with respect to the total amount of absorbed iron.[26 27] Some evidence points to changes in gastrointestinal epithelial cells following a large bolus of iron that results in reduced transport of iron into portal blood.[28] A prior meta-analysis of 21 trials concluded that, compared with daily iron supplements, intermittent supplementation had similar effects on haemoglobin levels but was less effective in reducing anaemia.[29] Our findings, based on a much larger number of trials, suggest that frequent and intermittent supplementation are similarly effective in reducing anaemia.

Studies of longer duration were more likely to have a lower prevalence of baseline anaemia (online supplemental appendix 5). As a result, the apparently diminishing impacts of iron with increased duration were entirely explained on control for baseline anaemia (online supplemental appendix 6). Some prior studies have shown that impacts of iron on haemoglobin persist for several months after the cessation of supplementation,[30 31] though the period of durability likely depends on the availability of dietary iron, burden of infection and

degree of blood loss experienced by the population. The findings of this study support the current WHO recommendation of a 3-month course of iron supplementation, though a longer duration may be considered in order to maintain haemoglobin levels.

For all ages, the lowest dose tertile of iron received less than the WHO recommended daily supplement (10–12.5 mg/day for ages 6–23 months, 30 mg/day for ages 24–59 months, 30–60 mg/day for ages 5–12 years). Moderate age-adjusted doses appeared to be more effective than lower doses at increasing haemoglobin, but all doses effectively improved outcomes, even doses below current WHO recommendations. Interestingly, more frequent supplementation, longer durations of supplementation and higher doses each were associated with greater increases in serum ferritin. These novel findings can inform the design of future supplementation programmes, suggesting that flexibility is possible depending on specific aims.

Importantly, we found that benefits were generally similar across diverse ages from <5 months to >12 years, in males and in females and across world regions. This supports initiation of iron supplementation programmes in a diverse range of young populations. As might be expected, increases in haemoglobin and reductions in anaemia were approximately twice as large in populations in which all children were anaemic at baseline, compared with mixed or non-anaemic populations. Yet, even among children who were non-anaemic at baseline, iron supplementation effectively reduced the future risk of anaemia by 37%, and of ID and IDA by about 80%. These findings indicate that iron supplementation is effective for primary prevention among at-risk children.

Factorial trials of iron and zinc supplementation (n=11) found that cosupplementation of iron with zinc did not diminish impacts on haemoglobin, serum ferritin, ID or IDA. However, there was some evidence that iron supplementation alone decreases anaemia more than when given along with zinc supplementation. There was also a qualitative trend towards attenuated effects for all outcomes in children who received iron and zinc concurrently. Uptake of both iron and zinc is mediated by divalent metal transporter-1 and ferroportin, which may result in absorptive antagonism.[32 33] However, the evidence from this meta-analysis suggests that in contexts where prevalent zinc deficiency is suspected, cosupplementation of iron can still yield population benefits.

There was no statistically significant difference in the effect of iron comparing children in factorial trials randomised additionally to vitamin A versus those randomised to no vitamin A (n=6 trials). The mechanism of iron and vitamin A interaction remains incompletely understood. Prior research has indicated that vitamin A may increase nonheme iron absorption, which is perhaps achieved through mobilising iron stores or stimulating the synthesis of transferrin.[34–36] However, one bioavailability study in non-anaemic adults found that absorption of a single dose of iron (10 mg) was increased when cosupplemented with a dose of vitamin A of 1500 or 3000 IU, but inhibited when cosupplemented with dose of vitamin A of 6000 IU.[37] Two trial arms in this meta-analysis gave single vitamin A doses of 200 000 IU at enrolment, two trial arms gave daily doses of 5000 or 10 000 IU and two trial arms gave 15 000 IU weekly. On balance, the evidence from this meta-analysis suggests that vitamin A can be given in combination with iron in order to improve haematologic outcomes.

In our meta-analysis, iron supplementation had no significant effect on infections, although small effects on diarrhoea or malaria could not be excluded. Iron is an essential nutrient for pathogenic microbes, and several studies have investigated whether iron status or supplementation relates to infection risk.[38] One trial of iron-folic acid supplementation in a malaria-endemic region was halted early due to higher mortality among those randomised to iron[39]; and Cochrane review concluded that iron supplementation in malaria-endemic areas without malaria control programmes may increase the incidence of malaria, although iron may also reduce clinical malaria in regions where malaria control programmes are available.[10] Relatively few studies included in this meta-analysis reported data on infections, those which did reported varying outcomes (eg, incidence, prevalence, mean number of episodes, average duration) and several studies excluded children on the basis of an infection, creating a possibility of reporting and selection bias. Our findings add to the body of literature on iron and infection, and the interaction between iron supplementation and infection remains an important area for future study.

Forty-three trials reported data on height-for-age, and no significant effects were seen on child growth. This finding is consistent with results of prior meta-analyses based on fewer studies.[9 11 12] Furthermore, no effect modification was seen for growth-related outcomes for any of the eight potential modifiers that were investigated. Combined with the findings of prior research, this meta-analysis suggests that iron supplementation does not promote linear growth in children. With respect to cognitive function, a diverse set of measures and reporting scales was used; using the most frequently reported measure, the Bayley Index, we found some evidence of benefits of iron supplementation on mental performance (p=0.05).

Potential limitations of this research should be considered. Many studies had insufficient information that could be used to determine risk of bias, thereby impeding the exploration of iron effects according to study quality. Furthermore, when data were available on adherence to iron supplements, it was reported in numerous ways, similarly preventing a quantitative summary. As with all meta-analyses, publication bias cannot be ruled out; trim-and-fill methods suggested that effects were attenuated but still statistically significant when accounting for potentially missing studies. A large number of tests for effect heterogeneity were conducted (total of 25 tests

across tables 3 and 4, and 110 in online supplemental appendices 7 and 8) without adjustment for multiple comparisons, and the positive findings from these tests should be interpreted accordingly with caution. Lastly, results for effect heterogeneity can be confounded due to collinear effect modifiers. Although we conduct sensitivity analyses controlling for baseline anaemia, the lack of individual-level data reduces the degree to which this and other factors can be precisely controlled.

The 2016 WHO guidelines on iron supplementation in infants and children were informed by systematic reviews of randomised controlled iron supplementation trials that found clear benefits of iron supplementation on haematologic outcomes.[9–12] In this large systematic review of iron supplementation trials, our work extends these prior meta-analyses by exploring effect heterogeneity according to schedule, duration, dose and cosupplementation regimen. We find that the evidence supports the currently recommended dose and duration of iron supplementation, although weekly supplementation might be reasonable in certain contexts, especially at moderate or high doses. We also identified no evidence for harms of iron supplementation on anthropometrics or risk of infection, and possibly improved mental development. Furthermore, evidence from this meta-analysis suggests that cosupplementation of iron with zinc or vitamin A generally results in similar impacts on haematologic outcomes, although there is some evidence for these effects being attenuated for zinc. Our findings could be considered in clinical decision-making and the development of further guidelines on oral iron supplementation among children and adolescents.

Author affiliations
[1]Department of Epidemiology, Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[2]The George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[3]Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, Boston, Massachusetts, USA
[4]Department of Global Health and Population, Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[5]Department of Nutrition, Harvard T H Chan School of Public Health, Boston, Massachusetts, USA
[6]Institutional Centers of Clinical and Translational Research, Boston Children's Hospital, Boston, Massachusetts, USA
[7]Tufts University Friedman School of Nutrition Science and Policy, Boston, Massachusetts, USA
[8]Division of Cardiology, Tufts University School of Medicine, Boston, Massachusetts, USA

Contributors DM obtained funding. CTA, DM, CPD and WWF conceived the study idea and designed the search strategy. CTA, DMM and EL reviewed studies for eligibility, extracted data and assessed bias. CTA performed data analysis, wrote the first draft of the manuscript and is the guarantor. CTA, DMM, CPD, EL, DM and WWF interpreted the data analysis and critically revised the manuscript.

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ORCID iDs
Christopher T Andersen http://orcid.org/0000-0001-5599-6130
Daniel M Marsden http://orcid.org/0000-0002-6460-5733

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Appendices to "Oral iron supplementation and anemia in children according to schedule, duration, dose, and co-supplementation: a systematic review and meta-analysis of 129 randomized trials"

Table of Contents

Andersen CT, *et al. BMJ Global Health* 2023; 8:e010745. doi: 10.1136/bmjgh-2022-010745

Appendix 1: Search terms.

Title and abstract searches of the terms below were performed in PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials from inception through November 2020.

Infant OR Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR child OR child OR child* OR children* OR schoolchild* OR schoolchild OR "school child" OR adolescent OR adolescen* OR youth* OR teen* OR pubescen* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR school OR school* OR prematur* OR preterm* OR “Pregnant Women” OR Pregnancy OR pregnan* OR gravid OR obstetric OR antenatal OR antepartum OR gestation* OR lactation OR “breast feeding” OR lactation OR “breast feeding”[Title/Abstract] OR breast-fe* OR breastfe* OR breast-milk OR breastmilk OR “lactating mother*” OR “lactating woman” OR “lactating women”

AND

iron OR hematinics OR “ferrous” OR “ferric” OR “hematinic” OR “haematinic” OR “haematinics” OR “iron compounds”

AND

“randomized controlled trial” OR “controlled clinical trial” OR “clinical trial” OR randomized OR randomised OR placebo OR random* OR trial

Andersen CT, *et al. BMJ Global Health* 2023; 8:e010745. doi: 10.1136/bmjgh-2022-010745

Appendix 2: Variables extracted from eligible studies.

Study characteristics
Endnote Record Number
First author (last name)
Publication year
Corresponding author (full name)
Corresponding author (email address)
Study name
Country
Rural/Urban
Altitude for the study site (meters)
According to study report, is malaria endemic?
According to study report, are helminths endemic?
Is this a subgroup analysis of a priorly extracted study?
Which subgroup is being reported here?
Does this paper reference other publications using the same trial or data? If so, indicate the Endnote record numbers for those studies.
Notes on this paper
Intervention characteristics
Mode of supplementation
Dose of intervention (mg of elemental iron)
Dose of intervention (mg) per kg bodyweight
Mean body weight for the intervention group (kg).
Frequency of intervention
Unit of intervention frequency
Formulation of Iron
Total dose of supplement (used for conversion to elemental iron if elemental unavailable)
Unit for dose
Duration of the intervention (weeks) (there are 4.3 weeks per month)
Is outcome data post intervention endline available?
Year at baseline (if range pick median)
Were all children in the study dewormed as part of the study protocol?
What other compounds were given along with iron (to both intervention & control groups)?
Is this a factorial trial?
Daily dose consumed of other compound given.
Unit for daily dose of other compound given.
Did the control group receive a placebo?
Is the control group being compared to multiple intervention groups?
Population group targeted by intervention
List study inclusion and exclusion criteria
Is compliance reported in the paper?
Indicate the compliance data reported
Other notes on intervention
Population characteristics
Is population characteristic data given for the full sample or for the control group only? (Use the full sample data whenever possible.)

Proportion of female children at baseline (%)
Child age at supplementation start/baseline (mean/median months)
Child age at baseline (SD)
Child age at baseline (min)
Child age at baseline (max)
Child age at outcome assessment (mean/median months)
Child age at outcome assessment (SD)
Age reported if other than age at supplementation start
Mean HAZ at baseline
Mean WHZ at baseline
Mean WAZ at baseline
Mean BAZ at baseline
Proportion of iron deficient children if reported (%)
Cutoff used to define iron deficiency
Proportion of anemic children if reported (%)
Cutoff used to define anemia (g/dl)
Proportion of children with iron deficiency anemia (%)
Cutoff used to define iron deficiency anemia
Proportion of children stunted at baseline (%)
Proportion of children low birth weight at baseline (%)
Cutoff used to define low birth weight (g)
Proportion of children born premature (%)
Cutoff used to define prematurity (wks)
Maternal age at baseline (mean/median years)
Maternal age at baseline (SD)
If pregnant, gestational age at baseline (mean/median weeks)
If pregnant, gestational age (sd)
If any family socioeconomic status measures are reported, please describe
Proportion of mothers who are iron deficient, if reported (%)
Proportion of mothers anemic at baseline, if reported (%)
Outcome characteristics
Specify outcome
Outcome unit
Method of Assessment
Extra information pertaining to outcome
Comparator group
How many weeks after baseline was the outcome measured?
How many participants were initially recruited for treatment?
How many participants were initially recruited for control?
Intervention total group sample size (total analyzed)
Was the difference-in-differences measure calculated in an adjusted regression model?
Difference in the differences between baseline & follow-up between intervention & control group (mean)
Difference in the differences between baseline & follow-up between intervention & control group (SD)
Difference in the differences between baseline & follow-up between intervention & control group (SE)

Difference in the differences between baseline & follow-up between intervention & control group (LCI)
Difference in the differences between baseline & follow-up between intervention & control group (UCI)
Difference in the differences between baseline & follow-up between intervention & control group (p-value)
Intervention group baseline sample size
Intervention group baseline estimate (mean)
Intervention group baseline estimate (SD)
Intervention group baseline estimate (SE)
Intervention group baseline estimate (LCI)
Intervention group baseline estimate (UCI)
Intervention group baseline estimate (LIQR)
Intervention group baseline estimate (UIQR)
Intervention group follow-up sample size
Intervention group follow-up estimate (mean)
Intervention group follow-up estimate (SD)
Intervention group follow-up estimate (SE)
Intervention group follow-up estimate (LCI)
Intervention group follow-up estimate (UCI)
Intervention group follow-up estimate (LIQR)
Intervention group follow-up estimate (UIQR)
Was the intervention group difference measure calculated in an adjusted regression model?
Intervention group difference sample size
Intervention group difference in outcome between baseline & follow-up (mean)
Intervention group difference in outcome between baseline & follow-up (SD)
Intervention group difference in outcome between baseline & follow-up (SE)
Intervention group difference in outcome between baseline & follow-up (LCI)
Intervention group difference in outcome between baseline & follow-up (UCI)
Intervention group difference in outcome between baseline & follow-up (LIQR)
Intervention group difference in outcome between baseline & follow-up (UIQR)
Intervention group difference in outcome between baseline & follow-up (p-value)
Control group baseline sample size
Control group baseline estimate (mean)
Control group baseline estimate (SD)
Control group baseline estimate (SE)
Control group baseline estimate (LCI)
Control group baseline estimate (UCI)
Control group baseline estimate (LIQR)
Control group baseline estimate (UIQR)
Control group follow-up sample size
Control group follow-up estimate (mean)
Control group follow-up estimate (SD)
Control group follow-up estimate (SE)
Control group follow-up estimate (LCI)
Control group follow-up estimate (UCI)
Control group follow-up estimate (LIQR)

Control group follow-up estimate (UIQR)
Was the control group difference measure calculated in an adjusted regression model?
Control group difference sample size
Control group difference in outcome between baseline & follow-up (mean)
Control group difference in outcome between baseline & follow-up (SD)
Control group difference in outcome between baseline & follow-up (SE)
Control group difference in outcome between baseline & follow-up (LCI)
Control group difference in outcome between baseline & follow-up (UCI)
Control group difference in outcome between baseline & follow-up (LIQR)
Control group difference in outcome between baseline & follow-up (UIQR)
Control group difference in outcome between baseline & follow-up (p-value)
Flag indicating whether SD/SE was imputed during data entry
Note other outcomes reported in the study but not extracted
Subgroup data
Was sub-group data on outcome presented by gender?
Was sub-group data on outcome presented by age group?
Was sub-group data on outcome presented by SES group?
Was sub-group data on outcome presented by baseline anemia status?
Was sub-group data on outcome presented by baseline iron status?
Was sub-group data on outcome presented by baseline stunting/birthweight status?
Other subgroup reported? (specify)
Cochrane risk of bias assessment
Method for generating randomization sequence
How were individuals randomly assigned to treatment?
Number of clusters randomized (total)
Risk of bias due to randomization method?
Method for concealing treatment allocation
Risk of bias due to allocation concealment?
Were participants blinded?
Were supplementation providers blinded?
Bias due to lack of participant or supplement provider blinding?
Were outcome assessors blinded?
Bias due to lack of outcome assessor blinding?
Percent drop-out in intervention group
Percent drop-out in control group
Were reasons for withdrawals similar across treatment groups?
Were reasons for withdrawals associated with other important covariates?
If withdrawals were related to the outcome, describe the reason for withdrawal.
Were appropriate methods used to impute missing data?
Was an intention-to-treat analyses conducted (i.e. analyzed as randomized)?
Was a per protocol analysis conducted?
Risk of bias due to incomplete outcome data?
Were data reported for all pre-specified outcomes?
Were data reported for all pre-specified sub-group analyses
Risk of bias due to selective outcome reporting?

Appendix 3. Elemental iron supplementation dose tertile ranges.

	Tertile		
	Low	Middle	High
mg/week			
0 - 5 mo	18.2 – 50.0	51.5 – 70.0	79.8 - 99.4
6 - 23 mo	20.0 – 70.0	87.5 – 87.5	105.0 – 462.0
24 - 59 mo	20.0 – 100.0	114.0 – 207.9	210.0 – 420.0
5 - 11 y	18.2 – 120.0	143.6 – 380.8	403.1 – 650.0
12 - 19 y	50.0 – 100.0	120.0 – 250.0	300.0 – 1820.0
mg/day			
0 - 5 mo	2.6 – 7.1	7.4 – 10.0	11.4 – 14.2
6 - 23 mo	2.9 – 10.0	12.5 – 12.5	15.0 – 66.0
24 - 59 mo	2.9 – 14.3	16.3 – 29.7	30.0 – 60.0
5 - 11 y	2.6 – 17.1	20.5 – 54.4	57.6 – 92.9
12 - 19 y	7.1 – 14.3	17.1 – 35.7	42.9 – 260.0

Note 1: The recommended dose of iron increases as children age. To account for the strong correlation between age and dose, we grouped children into five age categories and then categorized them into low, moderate, or high tertiles based on the total amount of iron they received each week.
Note 2: Tertiles reported here are for studies which reported hematologic outcomes and had sufficient data to calculate dose (n=94 iron treatment groups).

Appendix 4. References to included studies.

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Appendix 5. Characteristics of included studies.

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Adish, 1997	Ethiopia	24 mo - 5 yr	30 mg elemental Fe as ferrous sulfate daily for 3 months	Placebo; or Placebo + Vitamin A (factorial trial)	n=399 total participants analyzed; n=196 treatment, n=203 control	Hemoglobin, Diarrhea, Respiratory infection
Aggarwal et al, 2005	India	50 days - 80 days	3 mg/kg elemental Fe as ferric ammonium citrate daily for 8 weeks	Placebo	n=26 total participants analyzed; n=13 treatment, n=13 control	Hemoglobin, Ferritin
Aguayo et al, 2000	Bolivia	6 yr - 12 yr	3 mg/kg elemental Fe as ferrous sulfate 1 time per week for 18 weeks	Placebo	n=64 total participants analyzed; n=33 treatment, n=31 control	Hemoglobin, Anemia, HAZ, WAZ
Akman et al, 2004	Turkey	6 mo - 30 mo	6 mg/kg elemental Fe as ferrous glisine-sulphate daily for 3 months	Control	n=40 total participants analyzed; n=21 treatment, n=19 control	Hemoglobin, Ferritin
Angeles et al, 1993	Indonesia	24 mo - 6 yr	30 mg elemental Fe as ferrous sulfate + Vitamin C daily for 2 months	Placebo + Vitamin C	n=76 total participants analyzed; n=39 treatment, n=37 control	Hemoglobin, Ferritin, HAZ, WHZ, WAZ, Diarrhea, Respiratory infection
Angulo-Barro et al, 2016	China	~1 mo (mean age)	1 mg/kg elemental Fe as iron protein succinylate daily for 7.5 months	Placebo; or Placebo + Maternal iron (factorial trial)	n=1196 total participants analyzed; n=610 treatment, n=586 control	Cognitive
Arcanjo et al, 2011	Brazil	~5 yr (mean age)	50 mg elemental Fe as ferrous sulfate 1 time per week for 14 weeks	Placebo	n=99 total participants analyzed; n=50 treatment, n=49 control	Hemoglobin, Anemia
Arcanjo et al, 2013	Brazil	12 mo - 24 mo	25 mg elemental iron (formulation not specified) 1 time per week for 4 months; 12.5 mg elemental iron (formulation not specified) daily for 4 months	Placebo	n=176 total participants analyzed; n=120 treatment, n=56 control	Hemoglobin, Anemia

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Aukett et al, 1986	United Kingdom	17 mo - 19 mo	24 mg elemental Fe as ferrous sulfate + Vitamin C daily for 2 months	Placebo + Vitamin C	n=97 total participants analyzed; n=48 treatment, n=49 control	Hemoglobin, Ferritin, Anemia, Iron deficiency
Ayoya et al, 2009	Mali	7 yr - 13 yr	60 mg elemental Fe as ferrous sulfate + Praziquantal 5 times per week for 12 weeks	Control + Praziquantal	n=202 total participants analyzed; n=105 treatment, n=97 control	Hemoglobin, Ferritin, Anemia, Iron deficiency anemia, Malaria
Ayoya et al, 2012	Mali	7 yr - 13 yr	60 mg elemental Fe as ferrous sulfate + Praziquantal 5 times per week for 12 weeks	Control + Praziquantal	n=202 total participants analyzed; n=105 treatment, n=97 control	Cognitive
Ballin et al, 1992	Israel	16 yr - 18 yr	105 mg elemental Fe as iron polystyrene sulfonate adsorbate daily for 2 months	Placebo	n=59 total participants analyzed; n=29 treatment, n=30 control	Iron deficiency
Baqui et al, 2003	Bangladesh	~6 mo (mean age)	20 mg elemental Fe as ferrous sulfate 1 time per week for 6 months	Placebo + Riboflavin; or Placebo + Zinc + Riboflavin (factorial trial)	n=249 total participants analyzed; n=125 treatment, n=124 control	Hemoglobin, Ferritin, Diarrhea, Respiratory infection
Barclay et al, 1991	United Kingdom	~1 mo (mean age)	13.8 mg elemental Fe as NaFeEDTA daily for 16 weeks; 7 mg elemental Fe as NaFeEDTA daily for 16 weeks	Control + Mutivitamin	n=55 total participants analyzed; n=36 treatment, n=19 control	Hemoglobin, Ferritin
Baumgartner et al, 2012	South Africa	6 yr - 12 yr	50 mg elemental Fe as ferrous sulfate 4 times per week for 8.5 months	Placebo + Vitamin C; or Placebo + n-3 fatty acids + Vitamin C (factorial trial)	n=294 total participants analyzed; n=145 treatment, n=149 control	Hemoglobin, Ferritin, HAZ, WHZ, WAZ

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Berger et al, 1997	Bolivia	3 yr - 8 yr	3-4 mg/kg elemental Fe as ferrous sulfate 1 time per week for 16 weeks; 3-4 mg/kg elemental Fe as ferrous sulfate 5 times per week for 16 weeks	Placebo	n=173 total participants analyzed; n=116 treatment, n=57 control	Hemoglobin, Anemia
Berger et al, 2000	Togo	6 mo - 3 yr	2-3 mg/kg elemental Fe as iron betainate daily for 3 months	Placebo	n=163 total participants analyzed; n=84 treatment, n=79 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Diarrhea, Respiratory infection, Malaria
Berger et al, 2006	Vietnam	4 mo - 7 mo	10 mg elemental Fe as ferrous sulfate 7 times per week for 6 months	Placebo + Vitamin A; or Placebo + Vitamin A + Zinc (factorial trial)	n=770 total participants analyzed; n=384 treatment, n=386 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia, HAZ, WHZ, WAZ, Stunting, Wasting, Diarrhea, Respiratory infection
Berglund et al, 2010	Sweden	~1 mo (mean age)	1 mg/kg elemental Fe as ferrous succinate daily for 4.5 months; 2 mg/kg elemental Fe as ferrous succinate daily for 4.5 months	Placebo	n=243 total participants analyzed; n=160 treatment, n=83 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Bhatia et al, 1993	India	~4 yr (mean age)	40 mg elemental iron (formulation not specified) daily for 6 months	Placebo	n=156 total participants analyzed; n=84 treatment, n=72 control	Hemoglobin
Black et al, 2004	Bangladesh	~7 mo (mean age)	20 mg elemental Fe as ferrous sulfate 1 time per week for 6 months	Placebo + Riboflavin + Vitamin A; or Placebo + Zinc + Riboflavin + Vitamin A (factorial trial)	n=186 total participants analyzed; n=92 treatment, n=94 control	Cognitive

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Bora et al, 2019	India	0 mo	2 mg/kg elemental Fe as ferrous ascorbate daily for 6 months	Placebo	n=180 total participants analyzed; n=90 treatment, n=90 control	Hemoglobin, Ferritin
Bruner et al, 1996	USA	13 yr - 19 yr	260 mg elemental Fe as ferrous sulfate daily for 8 weeks	Placebo	n=73 total participants analyzed; n=37 treatment, n=36 control	Hemoglobin, Ferritin
Burman et al, 1972	United Kingdom	~3 mo (mean age)	10 mg elemental Fe as colloidal ferric hydroxide daily for 21 months	Placebo	n=192 total participants analyzed; n=86 treatment, n=106 control	Hemoglobin
Buzina-Suboticanec et al, 1998	Croatia	8 yr - 10 yr	100 mg elemental Fe as ferri-glycine sulfate 6 times per week for 10 weeks	Placebo	n=60 total participants analyzed; n=31 treatment, n=29 control	Hemoglobin, Cognitive
Charoenlarp et al, 1980	Thailand	6 yr - 13 yr	40 mg elemental Fe as ferrous sulfate 5 times per week for 5 months	Placebo	n=72 total participants analyzed; n=33 treatment, n=39 control	Hemoglobin, Helminth Infection
Chen et al, 2011	China	3 yr - 7 yr	12 mg elemental Fe as NaFeEDTA + Vitamin A 5 times per week for 26 weeks	Placebo + Vitamin A	n=132 total participants analyzed; n=71 treatment, n=61 control	Hemoglobin, Ferritin
Chen et al, 2013	China	3 yr - 7 yr	1.5 mg/kg elemental Fe as ferrous sulfate 5 times per week for 6 months	Placebo; or Placebo + Vitamin A (factorial trial)	n=387 total participants analyzed; n=188 treatment, n=199 control	Diarrhea, Respiratory infection
Chen et al, 2014	China	3 yr - 6 yr	1-2 mg/kg elemental Fe as ferrous sulfate 5 times per week for 6 months	Control; or Control + Vitamin A (factorial trial)	n=387 total participants analyzed; n=188 treatment, n=199 control	Hemoglobin, Ferritin, Anemia, Iron deficiency
Cheng et al, 2001	China	7 yr - 12 yr	2.6 mg elemental Fe as daily for 1 month	Placebo	n=108 total participants analyzed; n=53 treatment, n=55 control	Hemoglobin

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Choe et al, 1999	Korea	10 yr - 18 yr	6 mg/kg elemental Fe as ferrous sulfate + H. pylori therapy (bismuth subcitrate, amoxicillin, metronidazole) daily for 10 weeks	Placebo + H. pylori therapy (bismuth subcitrate, amoxicillin, metronidazole)	n=11 total participants analyzed; n=6 treatment, n=5 control	Hemoglobin, Ferritin
Chwang et al, 1988	Indonesia	8 yr - 14 yr	2 mg/kg elemental Fe as ferrous sulfate 5 times per week for 12 weeks	Placebo	n=119 total participants analyzed; n=59 treatment, n=60 control	Hemoglobin, HAZ, WAZ
Das et al, 1984	India	6 mo - 7 yr	5 mg elemental Fe as neoferrum infants drop 5 times per week for 12 weeks; 10 mg elemental Fe as neoferrum infants drop 5 times per week for 12 weeks; 20 mg elemental Fe as neoferrum infants drop 2 times per week for 12 weeks; 40 mg elemental Fe as neoferrum infants drop 2 times per week for 12 weeks; 20 mg elemental Fe as neoferrum infants drop 1 time per week for 12 weeks; 40 mg elemental Fe as neoferrum infants drop 1 time per week for 12 weeks	Placebo	n=151 total participants analyzed; n=115 treatment, n=36 control	Hemoglobin
de Silva et al, 2003	Sri Lanka	5 yr - 11 yr	60 mg elemental Fe as ferrous sulfate daily for 8 weeks	Placebo	n=363 total participants analyzed; n=261 treatment, n=102 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Diarrhea, Respiratory infection

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Desai et al, 2003	Kenya	2 mo - 3 yr	3.83 mg/kg elemental Fe as ferrous sulfate daily for 12 weeks	Placebo; or Placebo + Antimalarial (sulfadoxine-pyrimethamine at 4 and 8 weeks) (factorial trial)	n=491 total participants analyzed; n=256 treatment, n=235 control	Hemoglobin, Anemia, Malaria
Devaki et al, 2008	India	15 yr - 19 yr	100 mg elemental Fe as iron(iii) hydroxide polymaltose complex 6 times per week for 8 months	Placebo	n=60 total participants analyzed; n=30 treatment, n=30 control	Hemoglobin, Ferritin
Dewey et al, 2002	Sweden	~6 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 5 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 5 months	Placebo	n=172 total participants analyzed; n=136 treatment, n=36 control	HAZ, WAZ, Diarrhea
Dijkhuizen et al, 2001	Indonesia	~4 mo (mean age)	10 mg elemental Fe as ferrous sulfate 5 times per week for 6 months	Placebo; or Placebo + Zinc (factorial trial)	n=360 total participants analyzed; n=172 treatment, n=188 control	Hemoglobin, Ferritin, Anemia, Iron deficiency anemia, HAZ, WHZ, WAZ, Stunting, Wasting
Dijkhuizen et al, 2008	Indonesia, Thailand, Vietnam	4 mo - 6 mo	10 mg elemental Fe as ferrous sulfate + Zinc to half the population 5-7 times per week for 6 months	Placebo	n=2451 total participants analyzed; n=1212 treatment, n=1239 control	HAZ, WHZ, WAZ, Stunting, Wasting, Underweight

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Domellöf et al, 2001	Sweden	~6 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 5 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 1 mg/kg elemental Fe as ferrous sulfate daily for 5 months	Placebo	n=171 total participants analyzed; n=136 treatment, n=35 control	Hemoglobin, Ferritin
Dossa et al, 2001	Benin	3 yr - 6 yr	60 mg elemental Fe as ferrous sulfate daily for 3 months	Placebo; or Placebo + Albendazole (factorial trial)	n=140 total participants analyzed; n=70 treatment, n=70 control	Hemoglobin, HAZ, WHZ
Dossa et al, 2001	Benin	18 mo - 30 mo	66 mg elemental Fe as ferrous fumarate daily for 6 weeks	Placebo	n=74 total participants analyzed; n=35 treatment, n=39 control	Hemoglobin
Eftekhari et al, 2006	Iran	14 yr - 19 yr	60 mg elemental Fe as ferrous sulfate 5 times per week for 12 weeks	Placebo; or Placebo + Iodine (factorial trial)	n=94 total participants analyzed; n=47 treatment, n=47 control	Hemoglobin, Ferritin
Elwood et al, 1970	United Kingdom	14 yr - 15 yr	10 mg elemental Fe as ferrous fumarate daily for 36 months; 30 mg elemental Fe as ferrous fumarate daily for 36 months	Placebo + Riboflavin	n=601 total participants analyzed; n=386 treatment, n=215 control	Hemoglobin
Engstrom et al, 2008	Brazil	5 mo - 7 mo	12.5 mg elemental Fe as ferrous sulfate daily for 24 weeks; 25 mg elemental Fe as ferrous sulfate 1 time per week for 24 weeks	Placebo	n=391 total participants analyzed; n=297 treatment, n=94 control	Hemoglobin, Anemia

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Ermis et al, 2002	Turkey	~5 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate every other day for 4 months; 2 mg/kg elemental Fe as ferrous sulfate every other day for 4 months; 2 mg/kg elemental Fe as ferrous sulfate every other day for 4 months	Placebo	n=107 total participants analyzed; n=84 treatment, n=23 control	Hemoglobin, Ferritin, Iron deficiency, Iron deficiency anemia
Fahmida et al, 2007	Indonesia	3 mo - 6 mo	10 mg elemental Fe as ferrous sulfate + Zinc + Vitamin A daily for 6 months	Placebo + Zinc + Vitamin A	n=377 total participants analyzed; n=186 treatment, n=191 control	Hemoglobin, Ferritin, Anemia, HAZ, WHZ, WAZ, Stunting, Wasting, Underweight
Fallahi et al, 2007	Iran	~11 yr (mean age)	20 mg elemental Fe as ferrous sulfate + Zinc 6 times per week for 4 months	Placebo + Zinc	n=54 total participants analyzed; n=26 treatment, n=28 control	Hemoglobin, Ferritin
Franz et al, 2000	Germany	~0 mo (mean age)	2-4 mg/kg elemental Fe as ferrous sulfate daily for 8 weeks	Control	n=133 total participants analyzed; n=68 treatment, n=65 control	Ferritin, Iron deficiency
Friel et al, 2003	Canada	~1 mo (mean age)	7.5 mg elemental Fe as ferrous sulfate daily for 5 months	Placebo	n=49 total participants analyzed; n=28 treatment, n=21 control	Hemoglobin, Ferritin, Iron deficiency, Iron deficiency anemia
Fujiu et al, 2004	Japan	~1 mo (mean age)	4 mg/kg elemental iron (formulation not specified) + Recombinant human erythropoietin daily for 8 weeks	Control + Recombinant human erythropoietin	n=24 total participants analyzed; n=12 treatment, n=12 control	Hemoglobin, Ferritin
Gebresellasie, 1996	Ethiopia	5 yr - 15 yr	60 mg elemental Fe as ferrous sulfate daily for 12 weeks	Placebo	n=480 total participants analyzed; n=239 treatment, n=241 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Malaria

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Geltman et al, 2001	USA	~6 mo (mean age)	10 mg elemental iron (formulation not specified) + Multivitamin (A, B, C, D, E) daily for 3 months	Placebo + Multivitamin (A, B, C, D, E)	n=240 total participants analyzed; n=117 treatment, n=123 control	Anemia, Iron deficiency
Geltman et al, 2004	USA	~6 mo (mean age)	10 mg elemental Fe as + Multivitamin daily for 3 months	Placebo + Multivitamin	n=284 total participants analyzed; n=138 treatment, n=146 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Gokcay et al, 2012	Turkey	~6 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate + Vitamin D daily for 6 months	Control + Vitamin D	n=105 total participants analyzed; n=51 treatment, n=54 control	Hemoglobin, Anemia
Gopaldas et al, 1985	India	8 yr - 16 yr	26.2 mg elemental Fe as ferrous sulfate daily for 2 months; 37.4 mg elemental Fe as ferrous sulfate daily for 2 months	Placebo	n=210 total participants analyzed; n=140 treatment, n=70 control	Hemoglobin, Anemia
Gopaldas et al, 1985	India	8 yr - 16 yr	30 mg elemental Fe as ferrous sulfate daily for 2 months; 40 mg elemental Fe as ferrous sulfate daily for 2 months	Placebo	n=48 total participants analyzed; n=32 treatment, n=16 control	Cognitive
Greisen et al, 1986	Zambia	5 yr - 16 yr	66 mg elemental Fe as ferrous fumarate 5 times per week for 6 weeks	Placebo	n=430 total participants analyzed; n=218 treatment, n=212 control	Hemoglobin
Hacıhamdioglu et al, 2013	Turkey	~4 mo (mean age)	10 mg elemental Fe as ferrous sulfate daily for 2 months	Control	n=53 total participants analyzed; n=27 treatment, n=26 control	Hemoglobin, Ferritin, Iron deficiency
Harvey et al, 1989	Papua New Guinea	8 yr - 13 yr	130 mg elemental Fe as ferrous sulfate 5 times per week for 16 weeks	Placebo	n=298 total participants analyzed; n=156 treatment, n=142 control	Hemoglobin, Malaria

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Hathirat et al, 1992	Thailand	9 yr - 12 yr	93.75 mg elemental Fe as ferrous sulfate 5 times per week for 16 weeks	Placebo	n=1772 total participants analyzed; n=885 treatment, n=887 control	Hemoglobin, Ferritin
Hess et al, 2002	Ivory Coast	5 yr - 15 yr	60 mg elemental Fe as ferrous sulfate 4 times per week for 16 weeks	Placebo	n=166 total participants analyzed; n=85 treatment, n=81 control	Hemoglobin, Ferritin, Anemia, Iron deficiency
Hettiarachchi et al, 2008	Sri Lanka	12 yr - 17 yr	50 mg elemental Fe as ferrous fumarate 5 times per week for 24 weeks	Placebo; or Placebo + Zinc (factorial trial)	n=774 total participants analyzed; n=392 treatment, n=382 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, HAZ, WAZ
Hieu et al, 2012	Vietnam	6 yr - 10 yr	1-2 mg/kg elemental Fe as ferrous fumarate 1 time per week for 21-23 weeks	Control	n=221 total participants analyzed; n=95 treatment, n=126 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Hop et al, 2005	Vietnam	6 mo - 12 mo	10 mg elemental Fe as ferrous fumarate 7 times per week for 6 months	Placebo	n=152 total participants analyzed; n=75 treatment, n=77 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, HAZ, WHZ, WAZ
Htet et al, 2019	Myanmar	~16 yr (mean age)	60 mg elemental iron (formulation not specified) 1 time per week for 12 weeks	Placebo + Folic acid; or Placebo + Vitamin A + Folic acid (factorial trial)	n=391 total participants analyzed; n=192 treatment, n=199 control	Hemoglobin, Ferritin
Idjradinata et al, 1993	Indonesia	12 mo - 18 mo	3 mg/kg elemental Fe as ferrous sulfate daily for 4 months	Placebo	n=119 total participants analyzed; n=60 treatment, n=59 control	Hemoglobin, Ferritin
Idjratinata et al, 1994	Indonesia	12 mo - 18 mo	3 mg/kg elemental Fe as ferrous sulfate daily for 16 weeks	Placebo	n=44 total participants analyzed; n=22 treatment, n=22 control	HAZ, WAZ

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Irigoyen et al, 1991	USA	~6 mo (mean age)	3 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 6 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Placebo	n=225 total participants analyzed; n=150 treatment, n=75 control	Hemoglobin, Ferritin, Diarrhea
Jalambo et al, 2018	Palestine	15 yr - 20 yr	200 mg elemental Fe as ferrous fumarate 1 time per week for 3 months	Control	n=87 total participants analyzed; n=45 treatment, n=42 control	Hemoglobin, Ferritin
Kapur et al, 2003	India	9 mo - 3 yr	20 mg elemental Fe as ferium, m/s emcure pharm india 1 time per week for 8 weeks	Placebo; or Placebo + Nutrition education (factorial trial)	n=232 total participants analyzed; n=116 treatment, n=116 control	Hemoglobin, Ferritin
Kashyap et al, 1987	India	8 yr - 15 yr	60 mg elemental Fe as ferrous sulfate daily for 4 months	Placebo	n=166 total participants analyzed; n=83 treatment, n=83 control	Hemoglobin, Anemia
Kashyap et al, 1987	India	8 yr - 15 yr	60 mg elemental Fe as ferrous sulfate daily for 4 months	Placebo	n=130 total participants analyzed; n=65 treatment, n=65 control	Cognitive
Kianfar et al, 2000	Iran	~16 yr (mean age)	50 mg elemental Fe as ferrous sulfate daily for 3 months; 50 mg elemental Fe as ferrous sulfate 2 times per week for 3 months; 50 mg elemental Fe as ferrous sulfate 1 time per week for 3 months	Control	n=268 total participants analyzed; n=194 treatment, n=74 control	Hemoglobin, Ferritin
Kordas et al, 2005	Mexico	~7 yr (mean age)	30 mg elemental Fe as ferrous fumarate daily for 6 months	Placebo	n=527 total participants analyzed; n=271 treatment, n=256 control	Cognitive

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Kusumastuti et al, 2018	Indonesia	25 mo - 5 yr	7.5 mg elemental iron (formulation not specified) daily for 3 months	Placebo; or Placebo + Zinc (factorial trial)	n=68 total participants analyzed; n=34 treatment, n=34 control	HAZ, WAZ
Lambert et al, 2002	New Zealand	12 yr - 18 yr	105 mg elemental Fe as ferrous sulfate daily for 8 weeks	Placebo	n=116 total participants analyzed; n=57 treatment, n=59 control	Hemoglobin, Ferritin
Latham et al, 1990	Kenya	~8 yr (mean age)	80 mg elemental Fe as ferrous sulfate daily for 15 weeks	Placebo	n=55 total participants analyzed; n=29 treatment, n=26 control	Hemoglobin, Malaria, Helminth Infection
Lawless et al, 1994	Kenya	6 yr - 12 yr	47 mg elemental Fe as ferrous sulfate daily for 14 weeks	Placebo	n=86 total participants analyzed; n=44 treatment, n=42 control	Hemoglobin, Ferritin, HAZ, WHZ, WAZ, Diarrhea, Malaria
Lee et al, 1997	Korea	12 yr - 16 yr	60 mg elemental Fe as ferrous sulfate daily for 9 weeks	Placebo	n=15 total participants analyzed; n=9 treatment, n=6 control	Hemoglobin, Ferritin
Leenstra et al, 2009	Kenya	12 yr - 19 yr	120 mg elemental Fe as ferrous sulfate + Vitamin A 1 time per week for 3 months	Placebo + Vitamin A	n=249 total participants analyzed; n=124 treatment, n=125 control	Hemoglobin, Ferritin, Anemia, Malaria
Lind et al, 2003	Indonesia	~6 mo (mean age)	10 mg elemental Fe as ferrous sulfate daily for 6 months	Placebo + Vitamin C; or Placebo + Vitamin C + Zinc (factorial trial)	n=549 total participants analyzed; n=272 treatment, n=277 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Lind et al, 2004	Indonesia	~6 mo (mean age)	10 mg elemental Fe as ferrous sulfate daily for 6 months	Placebo + Vitamin C; or Placebo + Zinc + Vitamin C (factorial trial)	n=656 total participants analyzed; n=324 treatment, n=332 control	HAZ, WHZ, WAZ, Stunting, Wasting, Underweight
Loría et al, 1979	Mexico	~2 mo (mean age)	1-2 mg/kg elemental Fe as ferrous sulfate daily for 16 months	Placebo; or Placebo + Prenatal iron (factorial trial)	n=92 total participants analyzed; n=48 treatment, n=44 control	Hemoglobin

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Lozoff et al, 2016	China	~2 mo (mean age)	1 mg/kg elemental Fe as iron proteinsuccinylate oral solution daily for 7.5 months	Placebo; or Placebo + Maternal iron (factorial trial)	n=1276 total participants analyzed; n=648 treatment, n=628 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia, HAZ, WHZ, WAZ
López de Romaña et al, 2005	Peru	6 mo - 12 mo	10 mg elemental Fe as ferrous fumarate 7 times per week for 6 months	Placebo	n=146 total participants analyzed; n=74 treatment, n=72 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, HAZ, WHZ, WAZ, Diarrhea, Respiratory infection
Majumdar et al, 2003	India	6 mo - 24 mo	2 mg/kg elemental iron (formulation not specified) daily for 4 months	Placebo	n=100 total participants analyzed; n=50 treatment, n=50 control	Hemoglobin, Ferritin
Malan et al, 2015	South Africa	6 yr - 12 yr	50 mg elemental Fe as ferrous sulfate 4 times per week for 8.5 months	Placebo + Vitamin C; or Placebo + n-3 fatty acids + Vitamin C (factorial trial)	n=296 total participants analyzed; n=146 treatment, n=150 control	Diarrhea, Respiratory infection
Massaga et al, 2003	Tanzania	3 mo - 4 mo	7.5 mg elemental Fe as ferric ammonium citrate daily for 6 months	Placebo; or Placebo + Amodaquine (antimalarial) (factorial trial)	n=291 total participants analyzed; n=146 treatment, n=145 control	Anemia, Malaria
Mebrahtu et al, 2004	Tanzania	4 mo - 6 yr	10 mg elemental Fe as ferrous sulfate + Placebo & Antihelminthic (Mebendazole) to half daily for 12 months	Placebo + Placebo & Antihelminthic (Mebendazole) to half	n=538 total participants analyzed; n=273 treatment, n=265 control	Malaria
Mejía et al, 1988	Guatemala	12 mo - 9 yr	3 mg/kg elemental Fe as ferrous sulfate daily for 2 months	Placebo; or Placebo + Vitamin A (factorial trial)	n=99 total participants analyzed; n=54 treatment, n=45 control	Hemoglobin

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Menendez et al, 1997	Tanzania	~2 mo (mean age)	12 mg elemental Fe as ferrous glycine sulphate daily for 16 weeks	Placebo; or Placebo + Malaria prophylaxis (Deltaprim) (factorial trial)	n=832 total participants analyzed; n=417 treatment, n=415 control	Malaria
Menendez et al, 2004	Tanzania	~2 mo (mean age)	12 mg elemental Fe as ferrous glycine sulphate daily for 4 months	Placebo; or Placebo + Malaria prophylaxis (Deltaprim) (factorial trial)	n=601 total participants analyzed; n=307 treatment, n=294 control	Ferritin, Iron deficiency
Metallinos-Katsaras et al, 2004	Greece	3 yr - 5 yr	15 mg elemental Fe as ferrous fumarate + Multivitamin (Vitamins A, B, C, D, E) 5 times per week for 2 months	Placebo + Multivitamin (Vitamins A, B, C, D, E)	n=48 total participants analyzed; n=31 treatment, n=17 control	Hemoglobin, Ferritin
Mitra et al, 1997	Bangladesh	2 mo - 4 yr	15 mg elemental Fe as ferrous gluconate + Multivitamin (A, C, D) daily for 15 months	Placebo + Multivitamin (A, C, D)	n=289 total participants analyzed; n=141 treatment, n=148 control	Diarrhea, Respiratory infection
Mozaffari-Koshravi et al, 2010	Iran	14 yr - 17 yr	150 mg elemental Fe as ferrous sulfate 1 time per week for 16 weeks	Control	n=193 total participants analyzed; n=96 treatment, n=97 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Mwanri et al, 2000	Tanzania	9 yr - 12 yr	40 mg elemental Fe as ferrous sulfate 3 times per week for 12 weeks	Placebo; or Placebo + Vitamin A (factorial trial)	n=136 total participants analyzed; n=68 treatment, n=68 control	Hemoglobin, Anemia
Nagpal et al, 2004	India	4 mo - 6 mo	2 mg/kg elemental Fe as ferric ammonium citrate daily for 8 weeks	Placebo	n=43 total participants analyzed; n=19 treatment, n=24 control	Hemoglobin, Ferritin
Nair et al, 2017	India	4 mo - 6 mo	2 mg/kg elemental Fe as colloidal iron daily for 7 months	Control	n=44 total participants analyzed; n=22 treatment, n=22 control	Hemoglobin, Anemia

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Nchito et al, 2009	Zambia	~10 yr (mean age)	60 mg elemental Fe as ferrous dextran 5 times per week for 10 months	Placebo; or Placebo + Multivitamin (factorial trial)	n=215 total participants analyzed; n=118 treatment, n=97 control	Helminth Infection
Northrop-Clewes et al, 1996	Pakistan	~14 mo (mean age)	15 mg elemental Fe as ferrous sulfate daily for 12 weeks	Placebo	n=191 total participants analyzed; n=95 treatment, n=96 control	Hemoglobin, Ferritin
Olsen et al, 2000	Kenya	4 yr - 16 yr	60 mg elemental Fe as ferrous dextran 2 times per week for 12 months	Placebo	n=200 total participants analyzed; n=108 treatment, n=92 control	Helminth Infection
Olsen et al, 2006	Kenya	~9 yr (mean age)	60 mg elemental Fe as ferrous dextran 2 times per week for 12 months	Placebo	n=200 total participants analyzed; n=108 treatment, n=92 control	Hemoglobin, Ferritin
Paganini et al, 2017	Kenya	6 mo - 9.5 mo	5 mg elemental Fe as NaFeEDTA and ferrous fumarate + Micronutrient powder daily for 4 months	Placebo + Micronutrient powder	n=97 total participants analyzed; n=49 treatment, n=48 control	Hemoglobin, Ferritin, Anemia, Iron deficiency anemia
Palupi et al, 1997	Indonesia	24 mo - 6 yr	30 mg elemental Fe as ferrous sulfate 1 time per week for 9 weeks	Placebo	n=194 total participants analyzed; n=96 treatment, n=98 control	Hemoglobin, Anemia, HAZ, WHZ, WAZ, Helminth Infection
Paracha et al, 1993	Pakistan	8 yr - 11 yr	76 mg elemental Fe as ferrous gluconate + Multivitamin daily for 11 weeks	Control + Multivitamin	n=119 total participants analyzed; n=61 treatment, n=58 control	Hemoglobin, Ferritin
Perrone et al, 1999	Italy	4 yr - 12 yr	12 mg elemental Fe as iron polymaltosate + Zinc daily for 12 months	Control + Zinc	n=20 total participants analyzed; n=10 treatment, n=10 control	Ferritin, HAZ, WAZ
Prasetyani et al, 2017	Indonesia	5 yr - 19 yr	100 mg elemental Fe as iron(iii)-hydroxide polymaltose complex 6 times per week for 8 weeks	Placebo	n=578 total participants analyzed; n=290 treatment, n=288 control	Hemoglobin, Ferritin, Malaria

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Reeves et al, 1985	USA	11 mo - 14 mo	3 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Placebo	n=179 total participants analyzed; n=77 treatment, n=102 control	Diarrhea
Rezaeian et al, 2014	Iran	14 yr - 19 yr	50 mg elemental Fe as ferrous sulfate 2 times per week for 16 weeks	Placebo	n=200 total participants analyzed; n=100 treatment, n=100 control	Hemoglobin
Richard et al, 2006	Peru	6 mo - 16 yr	15 mg elemental Fe as ferrous sulfate daily for 7 months	Placebo; or Placebo + Zinc (factorial trial)	n=758 total participants analyzed; n=378 treatment, n=380 control	Hemoglobin, HAZ, WAZ, Diarrhea, Respiratory infection, Malaria
Rosado et al, 1997	Mexico	18 mo - 3 yr	20 mg elemental Fe as ferrous sulfate 5 times per week for 12 months	Placebo; or Placebo + Zinc (factorial trial)	n=217 total participants analyzed; n=108 treatment, n=109 control	Hemoglobin, Ferritin, Iron deficiency, HAZ, WHZ, WAZ, Diarrhea, Respiratory infection
Rosado et al, 2006	Mexico	6 yr - 8 yr	30 mg elemental Fe as ferrous fumarate 5 times per week for 6 months	Placebo; or Placebo + Zinc (factorial trial)	n=517 total participants analyzed; n=265 treatment, n=252 control	Hemoglobin, Ferritin
Roschnik et al, 2004	Philippines	7 yr - 13 yr	108 mg elemental Fe as ferrous sulfate 1 time per week for 10 weeks	Control	n=1510 total participants analyzed; n=708 treatment, n=802 control	Hemoglobin, Anemia
Sarker et al, 2008	Bangladesh	24 mo - 6 yr	3 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Placebo; or Placebo + H-pylori treatment (factorial trial)	n=197 total participants analyzed; n=99 treatment, n=98 control	Hemoglobin, Ferritin
Seshadri et al, 1989	India	8 yr - 16 yr	30 mg elemental Fe as ferrous sulfate daily for 2 months; 40 mg elemental Fe as ferrous sulfate daily for 2 months	Placebo	n=113 total participants analyzed; n=97 treatment, n=16 control	Hemoglobin, Anemia
Smith et al, 1989	Gambia	6 mo - 6 yr	3-6 mg/kg elemental Fe as ferrous sulfate daily for 12 weeks	Placebo	n=186 total participants analyzed; n=97 treatment, n=89 control	Malaria

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Smuts et al, 2005	South Africa	6 mo - 12 mo	10 mg elemental iron (formulation not specified) daily for 6 months	Placebo	n=99 total participants analyzed; n=49 treatment, n=50 control	Hemoglobin, Ferritin, HAZ, WHZ, WAZ, Diarrhea, Respiratory infection
Smuts et al, 2014	South Africa	6 yr - 12 yr	50 mg elemental Fe as ferrous sulfate 4 times per week for 8.5 months	Placebo + Vitamin C; or Placebo + n-3 fatty acids + Vitamin C (factorial trial)	n=86 total participants analyzed; n=43 treatment, n=43 control	Cognitive
Soemantri et al, 1989	Indonesia	8 yr - 12 yr	2 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Placebo	n=130 total participants analyzed; n=71 treatment, n=59 control	Hemoglobin, Cognitive
Soewondo et al, 1989	Indonesia	~5 yr (mean age)	50 mg elemental Fe as ferrous sulfate daily for 8 weeks	Placebo	n=176 total participants analyzed; n=77 treatment, n=99 control	Hemoglobin, Ferritin
Stoltzfus et al, 2001	Tanzania (Zanzibar)	12 mo - 4 yr	10 mg elemental Fe as ferrous sulfate daily for 12 months	Placebo	n=538 total participants analyzed; n=277 treatment, n=261 control	Hemoglobin, Ferritin, Helminth Infection, Cognitive
Stoltzfus et al, 2004	Tanzania	6 mo - 29 mo	10 mg elemental Fe as ferrous sulfate daily for 12 months	Placebo; or Placebo + Mebendezole (factorial trial)	n=145 total participants analyzed; n=74 treatment, n=71 control	Anemia, Stunting
Sungthong et al, 2002	Thailand	6 yr - 14 yr	60 mg elemental Fe as ferrous sulfate daily for 16 weeks; 60 mg elemental Fe as ferrous sulfate 1 time per week for 16 weeks	Placebo	n=396 total participants analyzed; n=274 treatment, n=122 control	Hemoglobin, Ferritin, Iron deficiency anemia, HAZ, WAZ

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Sungthong et al, 2004	Thailand	6 yr - 14 yr	60 mg elemental Fe as ferrous sulfate 5 times per week for 16 weeks; 60 mg elemental Fe as ferrous sulfate 1 time per week for 16 weeks	Placebo	n=391 total participants analyzed; n=269 treatment, n=122 control	Cognitive
Teshome et al, 2017	Kenya	12 mo - 3 yr	3 mg elemental Fe as NaFeEDTA daily for 1 month; 12.5 mg elemental Fe as ferrous fumarate daily for 1 month	Placebo + Anti-malarial (dihydroartemisinin-piperaquine); anti-helminthic (albendazole, praziquantel); micronutrient powder (13 nutrients)	n=315 total participants analyzed; n=210 treatment, n=105 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Malaria
Thibault et al, 1993	France	6 mo - 4 yr	38.6 mg elemental Fe as hydroxyproline iron daily for 2 months	Placebo	n=70 total participants analyzed; n=32 treatment, n=38 control	Hemoglobin, Ferritin
Untoro et al, 2005	Indonesia	6 mo - 12 mo	10 mg elemental Fe as ferrous sulfate 7 times per week for 23 weeks	Placebo	n=134 total participants analyzed; n=69 treatment, n=65 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, HAZ, WHZ, WAZ, Diarrhea, Respiratory infection
van den Hombergh et al, 1996	Tanzania	0 mo - 30 mo	40 mg elemental Fe as ferrous sulfate + Malaria treatment + folic acid daily for 12 weeks	Placebo + Malaria treatment + folic acid	n=95 total participants analyzed; n=48 treatment, n=47 control	Hemoglobin, WAZ, Malaria
Verhoef et al, 2002	Kenya	2 mo - 3 yr	3 mg/kg elemental Fe as ferrous fumarate 2 times per week for 12 weeks	Placebo; or Placebo + Antimalarial (sulfadoxine-	n=328 total participants analyzed; n=164 treatment, n=164 control	Hemoglobin, Iron deficiency, Malaria

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
				pyrimethamine) (factorial trial)		
Wang et al, 2012	China	~4 mo (mean age)	1 mg/kg elemental Fe as for 2 months	Control	n=60 total participants analyzed; n=26 treatment, n=34 control	Hemoglobin, Ferritin
Wasantwisut et al, 2006	Thailand	4 mo - 6 mo	10 mg elemental Fe as ferrous sulfate daily for 6 months	Placebo + Vitamin C, A; or Placebo + Zinc + Vitamins C, A (factorial trial)	n=609 total participants analyzed; n=305 treatment, n=304 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia, HAZ, WHZ, WAZ
Wieringa et al, 2007	Indonesia, Thailand, Vietnam	4 mo - 6 mo	10 mg elemental Fe as ferrous sulfate 5-7 times per week for 6 months	Placebo; or Placebo + Zinc (factorial trial)	n=2049 total participants analyzed; n=1017 treatment, n=1032 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Yalçin et al, 2000	Turkey	~6 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Control	n=16 total participants analyzed; n=7 treatment, n=9 control	Hemoglobin, Ferritin, Anemia, Iron deficiency, Iron deficiency anemia
Yip et al, 1985	USA	11 mo - 13 mo	30 mg/kg elemental Fe as ferrous sulfate daily for 3 months	Placebo	n=291 total participants analyzed; n=146 treatment, n=145 control	Hemoglobin, Ferritin
Yurdakök et al, 2004	Turkey	~4 mo (mean age)	1 mg/kg elemental Fe as ferrous sulfate daily for 3 months; 7 mg/kg elemental Fe as ferrous sulfate 1 time per week for 3 months	Control	n=53 total participants analyzed; n=37 treatment, n=16 control	Hemoglobin, Ferritin
Zavaleta et al, 2000	Peru	12 yr - 19 yr	60 mg elemental Fe as ferrous sulfate 2 times per week for 17 weeks	Placebo	n=198 total participants analyzed; n=101 treatment, n=97 control	Anemia

Author & Year	Country	Age	Intervention	Comparison group	Sample size	Outcomes
Zhao et al, 2004	China	3 yr - 6 yr	4 mg elemental Fe as NaFeEDTA for 18 months	Placebo	n=213 total participants analyzed; n=120 treatment, n=93 control	Hemoglobin, Anemia
Ziegler et al, 2009	USA	4 mo - 4 mo	7.5 mg elemental Fe as ferrous sulfate daily for 5 months	Control	n=98 total participants analyzed; n=42 treatment, n=56 control	Hemoglobin, Ferritin
Ziegler et al, 2009	USA	~1 mo (mean age)	7 mg elemental Fe as ferrous sulfate + Multivitamins (A, C, D) daily for 4.5 months	Placebo + Multivitamins (A, C, D)	n=63 total participants analyzed; n=31 treatment, n=32 control	Hemoglobin, Ferritin, Iron deficiency, Iron deficiency anemia
Zlotkin et al, 2003	Ghana	8 mo - 20 mo	40 mg elemental Fe as ferrous fumarate daily for 6 months; 12.5 mg elemental Fe as ferrous sulfate daily for 6 months	Placebo	n=241 total participants analyzed; n=161 treatment, n=80 control	Hemoglobin, Ferritin, Anemia
Zlotkin et al, 2013	Ghana	6 mo - 4 yr	12.5 mg elemental Fe as microencapsulated ferrous fumerate + Ascorbic acid + vitamin a + zinc daily for 5 months	Placebo + Ascorbic acid + vitamin a + zinc	n=1815 total participants analyzed; n=900 treatment, n=915 control	Hemoglobin, Anemia, Iron deficiency, Malaria

Appendix 6. Modification of iron effects after control for baseline anemia.

	Hemoglobin (g/L) *	Ferritin (ng/mL) *	Anemia †	Iron deficiency †	Iron deficiency anemia †
Weekly frequency					
Frequent (3-7 times/week)	ref	ref	ref	ref	ref
n	95	60	48	29	15
Intermittent (1-2 times/week)					
n	23	16	9	4	3
Estimate	-3.1	-15.0	0.98	1.12	1.61
95% CI	(-5.9, -0.3)	(-24.7, -5.3)	(0.65, 1.48)	(0.24, 3.19)	(0.29, 8.84)
p-interaction	0.03	0.003	0.94	0.83	0.56
Duration					
1-3 months					
n	74	43	23	13	5
Estimate	ref	ref	ref	ref	ref
4-6 months					
n	39	30	30	20	13
Estimate	0.2	8.2	1.07	0.55	1.54
95% CI	(-2.4, 2.9)	(-1.0, 17.5)	(0.76, 1.52)	(0.25, 1.25)	(0.26, 9.28)
≥7 months					
n	8	4	6	0	0
Estimate	-1.3	40.7	1.38	n/e	n/e
95% CI	(-6.0, 3.5)	(1.7, 79.6)	(0.85, 2.24)		
Global p-interaction	0.83	0.04	0.40	0.15	0.61
Dose‡					
Low (1st tertile)					
n	36	26	21	9	8
Estimate	ref	ref	ref	ref	ref
Moderate (2nd tertile)					
n	27	21	22	15	9
Estimate	4.9	14.5	0.82	1.01	0.30
95% CI	(1.8, 8.0)	(5.9, 23.1)	(0.59, 1.13)	(0.40, 2.57)	(0.14, 0.69)
High (3rd tertile)					
n	31	20	8	6	1
Estimate	2.1	6.4	1.07	0.96	0.24
95% CI	(-1.0, 5.1)	(-2.4, 15.1)	(0.68, 1.70)	(0.24, 3.93)	(0.01, 6.80)
Global p-interaction	0.008	0.006	0.33	1.00	0.008

* Difference in the weighted mean effect of iron in the index category compared to the weighted mean effect of iron in the reference category, adjusting for baseline anemia.

† Ratio of the prevalence ratio for iron in the index category relative to the prevalence ratio for iron in the reference category, adjusting for baseline anemia.

‡ Age-adjusted dose tertiles; see Appendix 3.

Abbreviations: CI, confidence interval; ref, reference category; n/e, not estimable

Appendix 7. Effect modification of iron by baseline anemia, child age, child sex, WHO region, and iron formulation.

	Hemoglobin (g/L) *	Ferritin (ng/mL) *	Anemia †	Iron deficiency †	Iron deficiency anemia †
Baseline anemia					
All anemic					
n	33	17	9	5	1
Estimate	10.6	13.1	0.35	0.19	0.15
95% CI	(7.3, 13.9)	(8.0, 18.2)	(0.26, 0.47)	(0.06, 0.61)	(0.02, 1.26)
Mixed anemic and non-anemic					
n	54	30	40	23	13
Estimate	6.5	22.7	0.63	0.26	0.13
95% CI	(5.4, 7.5)	(17.4, 27.9)	(0.55, 0.71)	(0.19, 0.36)	(0.08, 0.22)
All non-anemic					
n	28	20	10	5	4
Estimate	5.1	18.7	0.62	0.20	0.21
95% CI	(3.5, 6.7)	(13.5, 23.9)	(0.41, 0.93)	(0.11, 0.36)	(0.06, 0.70)
Missing baseline anemia data					
n	52	40	10	15	9
Estimate	3.3	16.6	0.82	0.61	0.48
95% CI	(2.4, 4.2)	(13.4, 19.8)	(0.70, 0.95)	(0.48, 0.78)	(0.29, 0.78)
Global p-interaction	<0.001	0.28	0.002	0.13	0.06
Child age					
0 to 5 months					
n	39	33	18	19	17
Estimate	5.2	25.1	0.57	0.23	0.17
95% CI	(3.7, 6.7)	(19.7, 30.5)	(0.48, 0.70)	(0.15, 0.35)	(0.10, 0.31)
6 to 23 months					
n	31	23	23	15	5
Estimate	5.1	14.4	0.77	0.38	0.32
95% CI	(3.3, 6.9)	(8.7, 20.0)	(0.67, 0.90)	(0.27, 0.53)	(0.14, 0.69)
2 to <5 years					
n	25	10	6	4	0
Estimate	5.7	19.5	0.76	0.31	n/e
95% CI	(3.8, 7.7)	(11.3, 27.7)	(0.53, 1.09)	(0.14, 0.67)	
5 to <12 years					
n	29	13	13	6	4
Estimate	8.5	17.9	0.48	0.27	0.19
95% CI	(5.7, 11.4)	(10.9, 24.9)	(0.38, 0.60)	(0.11, 0.69)	(0.06, 0.56)
≥12 years					
n	21	20	5	3	1
Estimate	6.6	10.9	0.49	0.30	0.09
95% CI	(4.4, 8.7)	(9.1, 12.7)	(0.31, 0.79)	(0.11, 0.80)	(0.01, 1.64)
Global p-interaction	0.18	0.01	0.047	0.73	0.57
Child sex					

All female					
n	22	17	5	2	1
Estimate	6.6	9.3	0.39	0.74	0.09
95% CI	(4.2, 9.1)	(7.7, 10.9)	(0.28, 0.55)	(0.46, 1.19)	(0.01, 1.64)
All male					
n	6	0	2	0	0
Estimate	12.1	n/e	0.54	n/e	n/e
95% CI	(10.1, 14.2)		(0.46, 0.64)		
Mixed female and male					
n	100	70	58	38	25
Estimate	5.5	20.1	0.63	0.33	0.21
95% CI	(4.6, 6.4)	(16.8, 23.5)	(0.57, 0.70)	(0.26, 0.41)	(0.13, 0.32)
Missing baseline sex data					
n	39	20	4	8	1
Estimate	7.6	21.5	0.61	0.17	0.11
95% CI	(4.9, 10.3)	(12.3, 30.6)	(0.43, 0.86)	(0.09, 0.31)	(0.01, 1.99)
Global p-interaction	0.07	0.04	0.41	0.14	0.85
WHO region					
Africa					
n	26	11	20	10	2
Estimate	6.1	17.6	0.70	0.28	0.35
95% CI	(3.9, 8.3)	(13.1, 22.1)	(0.60, 0.82)	(0.16, 0.49)	(0.21, 0.56)
Americas					
n	29	13	13	7	3
Estimate	4.6	19.3	0.63	0.75	0.66
95% CI	(2.6, 6.7)	(13.1, 25.5)	(0.43, 0.91)	(0.51, 1.09)	(0.20, 2.14)
Eastern Mediterranean					
n	12	11	1	1	1
Estimate	8.6	8.9	0.14	0.79	0.09
95% CI	(6.1, 11.2)	(5.8, 12.0)	(0.03, 0.62)	(0.48, 1.29)	(0.01, 1.64)
Europe					
n	21	19	5	10	6
Estimate	4.4	17.4	0.32	0.28	0.16
95% CI	(2.8, 6.0)	(11.8, 23.1)	(0.14, 0.70)	(0.20, 0.41)	(0.06, 0.45)
South-East Asia					
n	56	34	20	12	10
Estimate	8.2	25.4	0.57	0.23	0.13
95% CI	(6.5, 9.7)	(19.4, 31.5)	(0.48, 0.67)	(0.16, 0.33)	(0.09, 0.18)
Western Pacific					
n	18	14	10	8	5
Estimate	5.4	14.1	0.58	0.38	0.53
95% CI	(3.6, 7.3)	(8.3, 19.9)	(0.44, 0.76)	(0.25, 0.57)	(0.29, 0.96)
Global p-interaction	0.06	0.06	0.20	0.44	0.007
Iron formulation					
Ferrous sulfate					
n	110	66	46	27	20
Estimate	7.2	21.8	0.56	0.21	0.12

95% CI	(6.1, 8.3)	(18.5, 25.1)	(0.49, 0.64)	(0.15, 0.30)	(0.09, 0.17)
Ferrous fumarate					
n	15	11	8	9	1
Estimate	4.8	16.7	0.69	0.29	0.40
95% CI	(2.2, 7.4)	(12.7, 20.8)	(0.53, 0.91)	(0.18, 0.47)	(0.08, 2.01)
Other or unspecified					
n	41	29	14	12	5
Estimate	4.2	10.3	0.78	0.56	0.81
95% CI	(2.8, 5.6)	(5.3, 15.3)	(0.62, 0.97)	(0.44, 0.73)	(0.58, 1.14)
Global p-interaction	0.02	0.005	0.13	0.03	<0.001

* Weighted mean difference

† Pooled risk ratio

Abbreviations: CI, confidence interval; n/e, not estimable

Appendix 8. Comparison of iron supplementation effects within factorial trials, using double placebo as a common referent group.

	Hemoglobin (g/L) *	Ferritin (ng/mL) *	Anemia †	Iron deficiency †	Iron deficiency anemia †
Zinc					
n	10	9	6	6	5
Double placebo	ref	ref	ref	ref	ref
Iron + Placebo	6.6 (3.6, 9.6)	28.8 (22.2, 35.4)	0.41 (0.33, 0.50)	0.15 (0.09, 0.24)	0.08 (0.05, 0.15)
Zinc + Placebo	0.1 (-1.5, 1.6)	-0.4 (-2.0, 1.2)	0.93 (0.78, 1.10)	1.06 (0.95, 1.17)	1.04 (0.81, 1.34)
Iron + Zinc	4.2 (1.9, 6.5)	21.0 (16.7, 25.3)	0.59 (0.46, 0.75)	0.19 (0.12, 0.31)	0.16 (0.09, 0.27)
Vitamin A					
n	6	3	2	1	0
Double placebo	ref	ref	ref	ref	n/a
Iron + Placebo	7.6 (3.0, 12.2)	8.4 (5.3, 11.4)	0.27 (0.16, 0.45)	0.34 (0.18, 0.66)	n/a
Vitamin A + Placebo	6.0 (3.2, 8.8)	-4.0 (-17.6, 9.5)	0.49 (0.36, 0.67)	1.24 (0.83, 1.84)	n/a
Iron + Vitamin A	10.5 (6.0, 14.9)	0.6 (-4.1, 5.3)	0.25 (0.07, 0.94)	0.63 (0.38, 1.07)	n/a

* Weighted mean difference

† Pooled risk ratio

Abbreviations: CI, confidence interval

Appendix 9. Effect heterogeneity p-values for anthropometric, infectious, and development outcomes.*†

	Modifiers							
	Frequency	Duration	Dose for age tertile	Baseline percent anemic	Age category	Baseline percent female	Factorial trial	Formulation
Anthropometry								
Height-for-age Z score	0.255	0.598	0.835	0.013	0.256	n/e	0.048	0.272
Weight-for-height Z score	0.970	0.665	0.291	n/e	0.311	n/e	0.559	0.843
Weight-for-age Z score	0.524	0.508	0.861	0.709	0.250	n/e	0.363	0.847
Stunting	n/e	0.452	0.393	n/e	0.378	0.378	0.700	n/e
Wasting	n/e	n/e	0.522	n/e	n/e	n/e	0.336	n/e
Infections								
Diarrhea (cumulative incidence)	0.136	0.282	0.274	0.358	0.884	n/e	0.642	0.904
Diarrhea (incidence rate)	0.962	0.471	0.435	n/e	0.446	n/e	0.760	0.760
Respiratory illness (cumulative incidence)	0.006	0.018	0.032	0.125	n/e	n/e	0.129	0.683
Respiratory illness (incidence rate)	0.902	0.866	0.750	n/e	0.887	n/e	0.421	0.421
Malaria (prevalence)	n/e	n/e	0.996	0.910	n/e	n/e	0.225	0.622
Malaria (incidence rate)	n/e	0.469	0.965	0.871	n/e	n/e	0.463	0.467
Hookworm (prevalence)	0.968	0.812	0.880	n/e	n/e	n/e	n/e	0.823
Ascaris lumbricoides (prevalence)	0.390	0.456	0.647	n/e	n/e	n/e	n/e	0.932
Trichuris trichiura (prevalence)	0.501	0.501	0.431	n/e	n/e	n/e	n/e	0.584
Development								
Bayley Mental Index	0.651	0.892	0.888	0.020	n/e	n/e	0.280	0.454
Bayley Psychomotor Index	0.807	0.432	0.738	0.023	n/e	n/e	0.672	0.634

* Categories used for modifiers: Frequency (1-2 times per week vs. 3-7 times per week); Dose for age tertile (1st vs. 2nd vs. 3rd); Baseline percent anemic (<20% anemic vs. 20-39% anemic vs. ≥40% anemic); Age category (0-5 mo vs. 6-23 mo vs. 24-59 mo vs. 5-11 y vs. 12-19 y); Baseline percent female (All participants female vs. no participants female vs. some participants female); Factorial trial (Yes vs. no); Formulation (Ferrous sulfate vs. ferrous fumarate vs. other)

† P-values calculated from meta-regression Wald tests.

Abbreviations: n/e, not estimable.

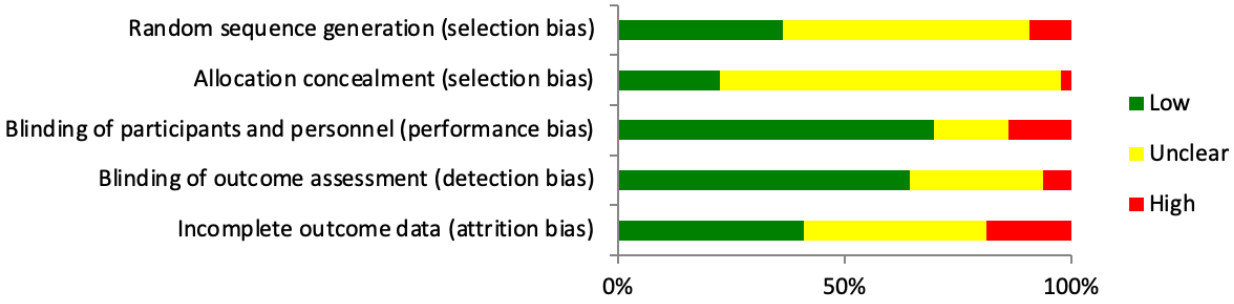
Appendix 10. Risk of bias within included studies.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of partici-pants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)
Adish 1997	Unclear	Unclear	Low	Low	Low
Aggarwal 2005	Low	Unclear	Low	Low	High
Aguayo 2000	Low	Unclear	Low	Low	Low
Akman 2004	Low	Unclear	High	Low	Low
Angeles 1993	Unclear	Unclear	Unclear	Unclear	Low
Angulo-Barro 2016	Low	Low	Low	Low	Unclear
Arcanjo 2011	High	Unclear	Low	Low	Unclear
Arcanjo 2013	High	Unclear	Low	Low	Unclear
Aukett 1986	Unclear	Low	Low	Low	Low
Ayoya 2009	Unclear	Unclear	High	Low	High
Ayoya 2012	Unclear	Unclear	High	Low	High
Ballin 1992	High	High	Low	Low	Unclear
Baqui 2003	Unclear	Unclear	Unclear	Unclear	Low
Barclay 1991	Unclear	Unclear	High	High	Unclear
Baumgartner 2012	Low	Unclear	Low	Low	High
Berger 1997	Unclear	Unclear	Low	Unclear	Low
Berger 2000	Unclear	Unclear	Low	Low	Unclear
Berger 2006	Low	Low	Low	Low	High
Berglund 2010	Low	Unclear	Low	Low	High
Bhatia 1993	High	Unclear	Unclear	Unclear	Unclear
Black 2004	Unclear	Unclear	Low	Low	Low
Bora 2019	Low	Low	Unclear	Unclear	Low
Bruner 1996	Low	Unclear	Low	Low	High
Burman 1972	High	Unclear	High	High	High
Buzina-Suboticanec 1998	High	Unclear	Low	Low	Unclear
Charoenlarp 1980	Unclear	Unclear	Unclear	Unclear	Unclear
Chen 2011	Unclear	High	Unclear	Low	Unclear
Chen 2013	Low	Unclear	Low	Low	Low
Chen 2014	Low	Unclear	High	High	Low
Cheng 2001	Unclear	Unclear	Unclear	Unclear	Unclear
Choe 1999	Low	Unclear	Low	Low	Unclear
Chwang 1988	Unclear	Unclear	Low	Low	Low
Das 1984	High	Unclear	Unclear	Unclear	Low
de Silva 2003	Unclear	Unclear	Low	Low	Unclear
Desai 2003	Low	Low	Low	Low	High
Devaki 2008	Unclear	Unclear	Unclear	Unclear	Low
Dewey 2002	Unclear	Unclear	Low	Low	Low
Dijkhuizen 2001	Low	Low	Low	Low	Low
Dijkhuizen 2008	Low	Low	Low	Low	Unclear
Domellöf 2001	Unclear	Unclear	Low	Low	Unclear
Dossa 2001	Low	Unclear	Low	Low	Low
Dossa 2001	Unclear	Unclear	Low	Low	Unclear
Eftekhari 2006	Unclear	Unclear	Low	Low	High
Elwood 1970	Unclear	Unclear	Unclear	Unclear	Unclear
Engstrom 2008	Unclear	Unclear	High	High	Unclear
Ermis 2002	Unclear	Unclear	Unclear	Unclear	Unclear
Fahmida 2007	Unclear	Unclear	Low	Low	Low

Fallahi 2007	Unclear	Unclear	Low	Unclear	Low
Franz 2000	Unclear	Unclear	Unclear	Unclear	High
Friel 2003	Unclear	Unclear	Low	Low	High
Fujiu 2004	Unclear	Unclear	Unclear	Unclear	Low
Gebresellasie 1996	Low	Low	Low	Low	Low
Geltman 2001	Unclear	Low	Low	Low	Unclear
Geltman 2004	Low	Unclear	Low	Low	Unclear
Gokcay 2012	Unclear	Unclear	High	Unclear	High
Gopaldas 1985	Unclear	Unclear	Low	Low	Low
Gopaldas 1985	Unclear	Unclear	Low	Low	Low
Greisen 1986	Unclear	Unclear	Unclear	Unclear	Unclear
Hacıhamdioglu 2013	Unclear	Unclear	High	Unclear	Unclear
Harvey 1989	Unclear	Unclear	Low	Low	Low
Hathirat 1992	Unclear	Unclear	Low	Unclear	Unclear
Hess 2002	Unclear	Unclear	Low	Low	Low
Hettiarachchi 2008	Unclear	Unclear	Low	Low	Low
Hieu 2012	Low	Low	Low	Low	Unclear
Hop 2005	Low	Low	Low	Low	Unclear
Htet 2019	Low	Low	Low	Low	Low
Idjradinata 1993	Low	Unclear	Low	Low	Low
Idjratinata 1994	Low	Unclear	Unclear	Unclear	Unclear
Irigoyen 1991	Unclear	Unclear	Low	Low	High
Jalambo 2018	Unclear	Unclear	High	Low	Low
Kapur 2003	Low	Unclear	Low	Unclear	Unclear
Kashyap 1987	Unclear	Unclear	Low	Unclear	Unclear
Kashyap 1987	Unclear	Unclear	Low	Unclear	Unclear
Kianfar 2000	Unclear	Unclear	High	Unclear	Unclear
Kordas 2005	Low	Low	Low	Low	High
Kusumastuti 2018	Low	Low	Low	Low	Unclear
Lambert 2002	Unclear	Unclear	Low	Low	Unclear
Latham 1990	Unclear	Unclear	Low	Unclear	Low
Lawless 1994	Low	Unclear	Low	Low	Low
Lee 1997	Unclear	Unclear	Low	Unclear	Unclear
Leenstra 2009	Low	Unclear	Low	Low	Low
Lind 2003	Unclear	Low	Low	Low	Low
Lind 2004	Low	Low	Low	Low	Low
López de Romaña 2005	Low	Low	Low	Low	Low
Loría 1979	Unclear	Unclear	Unclear	Unclear	Unclear
Lozoff 2016	Low	Unclear	Low	Low	Low
Majumdar 2003	Unclear	Unclear	Low	Unclear	High
Malan 2015	Low	Unclear	Low	Low	High
Massaga 2003	Low	Low	Low	Low	Low
Mebrahtu 2004	Unclear	Low	Low	Low	Unclear
Mejía 1988	Low	Low	High	Unclear	Unclear
Menendez 1997	Low	Low	Low	Low	High
Menendez 2004	Low	Low	Low	Low	High
Metallinos-Katsaras 2004	Unclear	Unclear	Low	Low	Unclear
Mitra 1997	Unclear	Unclear	Low	Low	Low
Mozaffari-Koshravi 2010	High	Unclear	High	Unclear	Low
Mwanri 2000	Low	Unclear	Low	Low	Low
Nagpal 2004	Low	Unclear	Low	Low	High
Nair 2017	High	High	Unclear	Unclear	Low
Nchito 2009	Unclear	Unclear	Low	Low	High

Northrop-Clewes 1996	Unclear	Unclear	Low	Low	Unclear
Olsen 2000	Unclear	Unclear	Low	Low	Low
Olsen 2006	Low	Low	Unclear	Unclear	Unclear
Paganini 2017	Low	Low	Low	Low	Low
Palupi 1997	Unclear	Unclear	Low	Low	Unclear
Paracha 1993	Unclear	Unclear	Low	Unclear	Unclear
Perrone 1999	Unclear	Unclear	High	Unclear	Unclear
Prasetyani 2017	Low	Unclear	Low	Low	Low
Reeves 1985	High	Unclear	Unclear	Unclear	High
Rezaeian 2014	High	Unclear	Low	Low	Low
Richard 2006	Unclear	Unclear	Low	Low	Low
Rosado 1997	Unclear	Unclear	Low	Low	Low
Rosado 2006	Low	Unclear	Low	Low	Unclear
Roschnik 2004	Low	Unclear	High	Unclear	Unclear
Sarker 2008	Low	Low	Low	Low	Unclear
Seshadri 1989	Unclear	Unclear	Low	Low	Low
Smith 1989	Unclear	Unclear	Low	Low	Unclear
Smuts 2005	Unclear	Low	Low	Low	High
Smuts 2014	Low	Unclear	Low	Low	Unclear
Soemantri 1989	Unclear	Unclear	Low	Unclear	Unclear
Soewondo 1989	Unclear	Unclear	Low	Low	Unclear
Stoltzfus 2001	Low	Low	Low	Low	Unclear
Stoltzfus 2004	Unclear	Unclear	Low	Low	High
Sungthong 2002	Low	Low	Low	Low	Low
Sungthong 2004	Low	Low	Low	Low	Low
Teshome 2017	Low	Low	Low	Low	Unclear
Thibault 1993	Unclear	Unclear	Low	Low	Unclear
Untoro 2005	Unclear	Unclear	Low	Low	Low
van den Hombergh 1996	Unclear	Unclear	Unclear	High	Low
Verhoef 2002	Low	Low	Low	Low	Low
Wang 2012	Unclear	Low	Low	Unclear	High
Wasantwisut 2006	Low	Low	Low	Low	Low
Wieringa 2007	Low	Low	Low	Low	High
Yalçin 2000	Unclear	Unclear	High	High	High
Yip 1985	High	Unclear	Unclear	Unclear	Unclear
Yurdakök 2004	Unclear	Unclear	High	High	Low
Zavaleta 2000	Unclear	Unclear	Low	Low	Low
Zhao 2004	Unclear	Unclear	Low	Low	High
Ziegler 2009	Unclear	Unclear	High	High	Unclear
Ziegler 2009	Unclear	Unclear	Low	Low	Unclear
Zlotkin 2003	Low	Low	High	Low	Low
Zlotkin 2013	Low	Unclear	Low	Low	Low

Appendix 11. Cochrane risk of bias assessment of included studies (n=129).



Appendix 12. Effect of oral iron supplementation versus placebo among children and adolescents aged <20 years among trials judged to not be at "high" risk of bias.

	n*	Estimate type	Estimate of effect (95% CI)	p-value	I^2 (%)
Hemoglobin (g/L)	105	WMD	6.5 (5.4, 7.6)	<0.001	95.5
Serum ferritin (ng/mL)	68	WMD	20.9 (17.4, 24.3)	<0.001	99.5
Anemia	42	RR	0.58 (0.51, 0.65)	<0.001	87.1
Iron deficiency	31	RR	0.31 (0.24, 0.41)	<0.001	91.1
Iron deficiency anemia	17	RR	0.27 (0.17, 0.44)	<0.001	79.9

* Number of trial arms randomized to iron

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PR, prevalence ratio; RR, risk ratio; SMD, standardized mean difference; WMD, weighted mean difference

Appendix 13. Assessment of small study bias for outcomes reported by ≥10 groups randomized to iron.