Effects of Daily Iron Supplementation in 2- to 5-Year-Old Children: Systematic Review and Meta-analysis

abstract

BACKGROUND AND OBJECTIVES: Iron deficiency (ID) is the most common cause of anemia worldwide. The prevalence is highest among preschool-aged children. Iron is widely administered to children with or at risk for ID, but evidence of benefit among 2- to 5-year-old children has not been evaluated by systematic review. We summarize the evidence for the benefit and safety of daily iron supplementation with regard to hematologic, growth, and cognitive parameters in 2 to 5 year olds.

METHODS: Electronic databases, regional databases, thesis repositories, gray literature, and references of studies and previous reviews were searched. We included randomized controlled trials that compared daily oral iron supplementation with control in 2 to 5 year olds. A random-effects meta-analysis was used to synthesize predefined outcomes reported by at least 2 studies.

RESULTS: Of 9169 references, 15 studies met the inclusion criteria, none of which were at low risk of bias. Children receiving iron supplementation had a mean end point hemoglobin of 6.97 g/L ($P = .00001; I^2 = 82\%$) greater than controls, whereas mean end point ferritin was 11.64 mg/L ($P = .0001; I^2 = 48\%$) greater. No trials reported the effects of iron supplementation on ID or iron deficiency anemia, and only one reported on anemia. Limited evidence suggested that iron supplementation produced a small improvement in cognitive development but had no effect on physical growth.

CONCLUSIONS: In 2 to 5 year olds, daily iron supplementation increases hemoglobin and ferritin. There is a concerning lack of data on the effect of iron supplementation on clinically important outcomes including anemia, ID anemia, ID, and cognitive development. Additional interventional studies in this age group are needed. Pediatrics 2013;131:739–753

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KEY WORDS iron, anemia, child, preschool, meta-analysis, systematic review

ABBREVIATIONS CI—confidence interval
Hb—hemoglobin
ICC—intraclass correlation coefficients
ID—iron deficiency
IDA—iron deficiency anemia
MD—mean difference
SMD—standard mean difference
WHO—World Health Organization

Ms Thompson screened papers for eligibility, extracted data, analyzed the results, wrote the manuscript, and approved the final manuscript as submitted; Dr Biggs wrote the manuscript and approved the final manuscript as submitted; and Dr Pasricha conceived the systematic review design, developed the search strategy, undertook the search, screened papers for eligibility, extracted data, analyzed the results, wrote the manuscript, and approved the final manuscript as submitted.

This review has been registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42011001208).

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Worldwide, 47.4% of children 0 to 5 years of age are anemic,\(^1\) with the burden being greatest in low- and middle-income countries. Iron deficiency (ID) is considered the most common cause of anemia, accounting for \(\sim 50\%\) of all cases.\(^2\) The prevalence of ID varies between locations but is estimated by the World Health Organization (WHO) to be 2.5 times higher than that of ID anemia (IDA) in most settings.\(^2\)

Children are at particular risk of ID because of rapid growth with expanding erythroid mass and high tissue iron requirements.\(^3\) In infants, antenatal and perinatal factors can influence iron status. Low birth weight and preterm infants are born with lower iron stores and are at increased risk of IDA.\(^4\) Prolonged milk feeding is associated with IDA, ID, and other micronutrient deficiencies.\(^1,5\)

Causes and epidemiology of anemia in 2 to 5 year olds appear to differ from those in infants. As children reach their third year and growth velocity decreases, daily iron requirements reduce, and children may self-correct ID. Recent national surveys show the prevalence of anemia at 12 to 23 and 48 to 59 months is, respectively, 69.1% and 38.2% in Ethiopia, 83.0% and 53.0% in India, 72.7% and 42.0% in Malawi, 70.6% and 20.7% in Nepal, and 71.5% and 45.6% in Zimbabwe.\(^6\) ID may be a less common cause of anemia after 2 years of age; for example, a Brazilian study found that anemia prevalence was 64% in 12- to 16-month-old infants, \(>90\%\) of which was because of ID, whereas 3 to 4 year olds had an anemia prevalence of 38%, of which \(<20\%\) was caused by ID, with other causes in this age group including malnutrition, vitamin \(B_{12}\) and folate deficiency, and hemoglobinopathies.\(^7\) Similarly, in Southeast Asia (Cambodia), younger preschool-aged children were at increased risk of anemia, with hemoglobinopathies, vitamin A deficiency, and ID combining as important causes of anemia.\(^8\) Children 2 to 5 years of age are more likely to be ambulant, and where sanitation is poor, can acquire hookworm infection, which can result in ID.\(^9\) The burden of anemia from malaria may also decline after infancy.\(^10\) Finally, younger children are transitioning from breastfeeding, but 2- to 5-year-old children are able to receive an essentially adult diet.\(^11\) The 2- to 5-year age group should therefore be considered distinct because of these significant differences in nutrition and anemia epidemiology.

ID in children may have functional consequences beyond anemia, including impaired motor and cognitive development and physical growth.\(^2\) Iron supplementation has been thought to improve these outcomes,\(^12-15\) but some impairment may be irreversible.\(^14\) Conversely, there are concerns that iron may produce adverse effects, including increased susceptibility to infection.\(^15\) Evidence for the benefits and risks of daily oral iron supplementation in 2 to 5 year olds has not been specifically evaluated in a systematic review.

Daily iron supplementation is considered a standard approach for treatment and prevention of ID.\(^16\) WHO previously recommended that, as a public health measure, all preschool-aged children receive a course of daily iron supplementation where the baseline prevalence of anemia is \(>40\%\).\(^2\) Intermittent iron supplementation in preschool-aged and school-aged children has recently been evaluated by a systematic review, which found that intermittent iron was effective in reducing anemia, although less so than daily iron.\(^17\) The study did not include a comparison of daily iron with control. On the basis of this analysis, WHO revised the guidelines recommending intermittent iron for prevention of anemia in children.\(^18,19\)

This systematic review aims to summarize the evidence for effects of daily iron supplementation administered to children 2 to 5 years of age. These data should assist policy makers and clinicians to understand the benefits and safety of daily iron supplementation in this age group.

**METHODS**

**Protocol and Registration**

A detailed protocol for this review has been published on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42011001208).

**Study Eligibility**

We included randomized and quasi-randomized controlled trials that gave oral iron supplementation \(\geq 5\) days per week to children 2 to 5 years of age. Oral "iron supplement" comprised iron salts and other compounds including carbonyl iron and colloidal iron. We excluded parenteral iron, home fortification, and delivery through fortified condiments or foods. Studies that included a cointervention were included, provided that the cointervention was also applied identically in the control arm. If a study did not specifically recruit subjects from the 2- to 5-year age range, we included the study if the mean or median age fell within 2 to 5 years or if \(>75\%\) of subjects fell within the designated age range. If this information was not available, we included the study if the majority of its designated age range overlapped 2 to 5 years.

Studies recruiting subjects from all demographic and geographic settings were eligible. We included subjects with any baseline hemoglobin (Hb) or iron status, with the exception of studies exclusively recruiting subjects with severe anemia (Hb \(< 70 \text{ g/L}\)), because this condition may represent a different
pathophysiology. We excluded studies specifically targeting children of low birth weight, preterm infants, or those suffering from a medical condition that substantially alters iron metabolism.

Primary outcomes were as follows: (1) Hb concentration; (2) anemia (defined by authors); (3) iron status (defined by median ferritin or iron indices); (4) cognitive or school performance (eg, Bayley Mental Development Index); (5) psychomotor performance (eg, Bayley Psychomotor Development Index); (6) physical growth (height and weight: absolute, z-scores); (7) safety.

A meta-analysis was undertaken for outcomes reported by more than one eligible trial.

**Information Sources, Search, and Study Selection**

We searched the following computerized biomedical bibliographic databases: SciVerse Scopus (Scopus) (encompassing Embase and Medline), Medline (separately), Cochrane Controlled Clinical Trials Register, Proquest Digital Theses, Australian Digital Theses Database, and OpenSigle. We also searched WHO regional databases (African Index Medicus [AIM], WHO Regional Office for Africa [AFRO] Health Sciences Library, Latin American and Caribbean Health Science Literature Database [LILACS], Index Medicus for South-East Asia Region [IMEMR]), The Western Pacific Region Index Medicus [WPRIM], and The Index Medicus for the Eastern Mediterranean Region (JMEMR). We reviewed references of identified articles and previous systematic reviews. We applied no language restrictions. The search strategy used for Scopus is presented in the Appendix. Searches were undertaken during March to April 2012.

**Data Collection**

Studies identified by our search strategy were stored in Endnote software. Studies were excluded where title and abstract indicated clear ineligibility. Authors JT and S-RP screened full text studies for eligibility and extracted data from eligible studies except where studies were only available in hard copy accessible by only 1 author (S-RP, 2 studies). Eligibility screens and extracted data were recorded in pretested electronic forms using Microsoft Excel. One author (JT) entered the data into Review Manager software (RevMan 5.1, 2011). The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and data were checked by S-RP. Discrepancies in eligibility screening, data extraction, entry to RevMan, and analysis were resolved through discussion.

**Assessment of Risk of Bias**

Risk of bias was assessed using the Cochrane risk-of-bias tool, which addresses selection, performance, attrition, detection, and reporting bias through evaluation of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other possible bias sources. Studies were considered at low risk of bias if they were at low risk of both selection and allocation bias and one of detection, performance, or reporting bias. Studies were otherwise classified as high risk. Risk of bias is summarized in Fig 2.

**Analysis**

Random effects meta-analysis was used to synthesize predefined outcomes reported by at least 2 studies. The mean difference (MD) was calculated for continuous data measured on the same scale, whereas the standardized MD (SMD) was calculated for data using different scales. Dichotomous data results were presented as risk ratios. Many studies reported end point data only, and SDs for change from baseline were often unavailable. Accordingly, end point rather than change-from-baseline data were meta-analyzed.

We combined results from cluster and individually randomized trials because study designs were otherwise comparable, and choice of randomization unit was unlikely to affect outcome (Table 1). For studies with $2 \times 2$ factorial designs (eg, randomized to iron versus control and then a second randomization to another intervention versus control), data were extracted separately for iron alone versus control alone comparisons and iron plus cointervention versus cointervention alone comparisons, with all participants included only once in the meta-analysis. Examination of funnel plots to assess publication bias was planned for outcomes with $>10$ studies, but no outcome contained this many studies.

The methodology and risk of bias of all studies were assessed to determine methodological heterogeneity. Clinical heterogeneity was assessed by determining similarity between subjects and outcomes of included studies. Statistical heterogeneity was determined using $I^2$ tests. All data were analyzed by using a random-effects model. Pre-specified subgroup analysis was performed on outcomes containing $>3$ studies. Reported subgroups included gender; baseline Hb, baseline iron status, baseline IDA state, breastfeeding status, daily dose of iron supplementation, duration of supplementation, and malaria endemicity of the setting. A subgroup of total overall iron dose taken (calculated by multiplying dose by duration with subgroups of $<2500$ and $>2500$ mg) was added post hoc to evaluate heterogeneity in Hb and ferritin.

**RESULTS**

Our search identified 9169 references. Nineteen studies reported in 25 references were selected for full text review. Four of these 19 studies were excluded, 2 because the age range was outside 2 to 5 years and 2 because the full text could not be obtained. Fifteen studies reported in 21 references met the criteria for inclusion (Fig 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participant Age at Recruitment</th>
<th>Baseline Anemia, ID Status</th>
<th>Intervention</th>
<th>Control</th>
<th>Sample Size: Participants Randomized, Attrition Where Reported</th>
<th>Duration of Supplementation</th>
<th>Outcomes</th>
<th>Risk of Bias</th>
<th>Overall Risk of Bias</th>
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</thead>
<tbody>
<tr>
<td>Angeles et al 1993&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Indonesia</td>
<td>2–5 y</td>
<td>Anemic (hemoglobin 80–110g/L), Iron deficient</td>
<td>Iron 30mg (as ferrous sulfate) + vitamin C 10mg daily</td>
<td>Vitamin C 20 mg</td>
<td>Iron + Vit C: 40 Vit C alone: 40 Total: 80 Attrition: Overall: 4/80</td>
<td>2 mo</td>
<td>Hemoglobin, MCV, ferritin, weight, height, weight for age, height for age, morbidity from fever, respiratory infection and diarrhea</td>
<td>U, U, L, L, L</td>
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<td>Bhatia and Seshadri 1993&lt;sup&gt;23&lt;/sup&gt; (C)</td>
<td>India</td>
<td>3–5 y</td>
<td>Anemic and not anemic, Iron status unknown</td>
<td>Elemental Iron 40mg daily (preparation unknown)</td>
<td>Placebo</td>
<td>Iron: 84 Control: 72 Total: 156</td>
<td>6 mo</td>
<td>Hemoglobin, height, weight, weight for age, other growth parameters</td>
<td>U, U, U, L, U</td>
<td>H</td>
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<td>Deinard et al 1986&lt;sup&gt;27&lt;/sup&gt;</td>
<td>United States</td>
<td>18–60 mo</td>
<td>Mixed/unknown</td>
<td>Elemental Iron 6mg/kg, daily (preparation unknown)</td>
<td>Placebo</td>
<td>Iron: 22 Control: 23 Total: 45</td>
<td>6 mo</td>
<td>Cognitive development (Bayley’s and Stanford Binet combined)</td>
<td>L, U, U, U, U</td>
<td>H</td>
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<tr>
<td>Dossa et al 2001&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Benin</td>
<td>3–5 y</td>
<td>Mixed/unknown</td>
<td>60mg ferrous sulfate OR 60mg ferrous sulfate + albendazole</td>
<td>Placebo OR albendazole alone</td>
<td>Iron: 36 Iron + albendazole: 34 Placebo: 32 Albendazole alone: 38 Total: 140 Attrition:</td>
<td>3 mo</td>
<td>Hemoglobin, height, weight, other growth parameters</td>
<td>U, U, U, L, L</td>
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<td>Study</td>
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<td>Intervention</td>
<td>Control</td>
<td>Sample Size: Participants Randomized, Attrition Where Reported</td>
<td>Duration of Supplementation</td>
<td>Outcomes</td>
<td>Risk of Bias: Random Allocation; Allocation Concealment; Incomplete Outcome; Blinding of Participants, Personnel, and Outcome Detection; Selective Reporting</td>
<td>Overall Risk of Bias</td>
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<tr>
<td>Gara et al 2001&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Nigeria</td>
<td>6–60 mo</td>
<td>Anemic, iron status unknown</td>
<td>2mg/kg ferric ammonium citrate + 5mg folate daily</td>
<td>5 mg folate daily</td>
<td>170 recruited, 168 completed study, 140 included in final analysis</td>
<td>1 mo</td>
<td>Hematocrit</td>
<td>U, U, L, H, U</td>
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<td>Metallinos-Katsaras et al 2004&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Greece</td>
<td>3–4 y</td>
<td>Anemic, not anemic; iron deficient, iron replete</td>
<td>Iron 15mg (as ferrous sulfate) + multivitamins</td>
<td>Multivitamins</td>
<td>Iron + multivit: 31 Multivit alone: 17 Total: 48</td>
<td>2 mo</td>
<td>Hemoglobin, serum iron, ferritin&lt;sup&gt;a&lt;/sup&gt;, transferrin saturation, cognitive outcomes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>U, U, U, L, H</td>
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<td>Nwanyanwu et al 1996&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Malawi</td>
<td>&lt;5 y</td>
<td>Mixed/unknown</td>
<td>Children 4-5 y: 65mg iron as ferrous sulfate + 25mg sulphadoxine and sulphadoxine and pyrimethamine Children under 4 y: 65mg iron as ferrous</td>
<td>Children 4-5 y: 25 mg sulphadoxine and pyrimethamine; children &lt;4 y: 12.5 mg sulphadoxine</td>
<td>Iron + sulphadoxine and pyrimethamine: 77 sulphadoxine and pyrimethamine alone: 75</td>
<td>28 d</td>
<td>Malarial outcomes and hematologic outcomes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>U, U, U, H, L</td>
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<td>Study</td>
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<td>Risk of Bias: Allocation; Blinding of Participants, Personnel, and Outcome Detection; Selective Reporting</td>
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<td>Pereia et al 1978†</td>
<td>India</td>
<td>2–5 y</td>
<td>Mixed/unknown</td>
<td>sulfate + 12.5 mg sulphadoxine and pyrimethamine and pyrimethamine</td>
<td>20 mg ferrous sulfate + 5 mcg cyanocobalamin + 200 mcg folic acid</td>
<td>5 mcg cyanocobalamin + 200 mcg folic acid</td>
<td>First study: 7 mo</td>
<td>Hemoglobin, ferritin, packed cell volume, transferrin saturation, serum iron, height, weight</td>
<td>U, U, H, L, U H</td>
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<td>1st Study: 20 mg ferrous sulfate + 5 mcg cyanocobalamin + 200 mcg folic acid</td>
<td>First study: 12 mo</td>
<td>Placebo OR 20 mg zinc daily</td>
<td>Second study: 12 mo</td>
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<td>AND second study: 30 mg ferrous sulfate + 5 mcg cyanocobalamin + 200 mcg folic acid</td>
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<td>20 mg iron + cyanocobalamin + folic acid: 12</td>
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<td>30 mg iron + cyanocobalamin + folic acid: 10</td>
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<td>Cyancobalamin + folic acid: 22</td>
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<td>Total: 44</td>
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<td>Attrition: First study: some children left the school after 3.5 mo and did not complete study. No further details.</td>
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<td>Rosado et al 1997†</td>
<td>Mexico</td>
<td>12 mo</td>
<td>Mixed/unknown</td>
<td>20 mg ferrous sulfate daily OR 20 mg ferrous sulfate + 20 mg zinc daily</td>
<td>Placebo</td>
<td>Iron: 53</td>
<td>12 mo</td>
<td>Hemoglobin, ferritin, height, weight, morbidity from diarrheal and respiratory illness</td>
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<td>Placebo: 55</td>
<td>Zinc alone: 54</td>
<td>Total: 419</td>
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<td>Overall: 25/419</td>
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<td>Smith et al 1989† (C)</td>
<td>Gambia</td>
<td>6 mo–5 y</td>
<td>Anemic, iron deficient</td>
<td>3-6 mg/kg iron as ferrous sulfate</td>
<td>Placebo</td>
<td>Iron: 700</td>
<td>3 mo</td>
<td>Malarial outcomes, and hematologic outcomes</td>
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<td>Placebo</td>
<td>882</td>
<td>Total: 1382</td>
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<td>Study</td>
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<td>Outcomes</td>
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<tr>
<td>Soewondo et al 1989&lt;sup&gt;38&lt;/sup&gt; (Soewondo et al 1995)&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Indonesia</td>
<td>Mean age iron-replete subjects: 57.5 mo, mean age ID subjects: 54.2 mo</td>
<td>Anemic, not anemic, iron deficient, iron replete</td>
<td>50mg iron daily (preparation unknown)</td>
<td>Placebo</td>
<td>Iron: 77</td>
<td>2 mo</td>
<td>Hemoglobin, hematocrit, ferritin, transferrin saturation, cognitive outcomes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>U, U, U, U, H, H</td>
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<td>van Hensbrock et al 1995&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Gambia</td>
<td>Average age = 51.7 mo</td>
<td>Mixed/unknown</td>
<td>Children under 20kg: 82.5mg iron as sodium iron edetate OR Children over 20kg: 123.75mg iron as sodium iron edetate</td>
<td>Placebo</td>
<td>Iron: 167</td>
<td>28 days</td>
<td>Malarial outcomes</td>
<td>U, U, L, H, L, H</td>
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</table>

<sup>a</sup> Units presented for ferritin values appeared incorrect. For this meta-analysis, adjustments were made to the presumed incorrect units.

<sup>b</sup> Data for cognitive outcomes were not extractable because no measure of error was included.

<sup>c</sup> Unit of randomization unclear. Mitra et al indicate that subjects were divided into clusters and were then individually randomized. Rahman et al state that subjects were randomized by household. For this meta-analysis, it was assumed that individual randomization was performed.

<sup>d</sup> Data for hematological outcomes were not extractable because no measure of error was included.

<sup>e</sup> Two separate studies. Data were combined in the report.

<sup>f</sup> Variance data given appeared to represent SEs yet was documented as SDs. The data were extracted as documented.

<sup>g</sup> Data for hematological outcomes were not extractable because figures were unable to be interpreted and results were not reported in the paper.

<sup>h</sup> Cognitive development data were combined for iron and deworming agents and were not presented separately for iron alone, iron + deworming agent, placebo, or deworming agent alone.
been found to be ferritin in cluster trials have generally extracted (Bhatia and Seshadri29 and which data for these outcomes were considered necessary in the 2 studies from Stoltzfus et al 28). Stoltzfus et al 28 reported that regression coefficients (ICCs) for Hb and 0.001 to 0.051,31 which are sufﬁciently low that correction for clustering was considered necessary. Adherence was documented in only 2 studies. Rosado et al27 reported that the supplement was consumed on an average of 97% of days by each child over 12 months, whereas Mitra et al35 documented average dose consumption of 80% over the 15-month study duration. Risk of Bias No eligible study reported on the speciﬁc sequence generation and/or allocation concealment, and all studies were therefore considered at high risk of bias (Fig 2). Baseline characteristics of treatment and control groups were similar in all studies except for Metallinos-Katsaras et al,36 where baseline iron indices differed signiﬁcantly between intervention and control arms.

Hb Concentration
Iron supplementation resulted in a mean Hb difference between intervention and control groups of 6.97 g/L (9 studies, 2154 subjects, 95% conﬁdence interval [CI] 4.21–9.72, P < .00001, \( \hat{f} = 82\% \)). Subgroup analysis showed that iron supplementation resulted in a greater improvement in Hb in anemic subjects (4 studies, MD = 11.77 g/L, P < .00001, \( \hat{f} = 82\% \)) compared with nonanemic subjects (3 studies, MD = 3.91 g/L, P = .03, \( \hat{f} = 62\% \)). Children with unspecified or mixed anemia status also showed improved Hb (5 studies, MD = 6.60 g/L, P = .002, \( \hat{f} = 79\% \)). A substantial improvement in Hb was seen in baseline iron-deﬁcient subjects (3 studies, MD = 9.06 g/L, P = .0006, \( \hat{f} = 0\% \)). Iron did not improve Hb among subjects who were iron replete at baseline (2 studies, MD = 2.28 g/L, P = .07, \( \hat{f} = 0\% \)).

Subgroup analysis identiﬁed signiﬁcant differences in effects of various doses and durations of supplementation. Iron supplementation at 12.6 to 30 mg daily resulted in a mean Hb difference between intervention and control groups of 9.2 g/L (5 studies, P < .0001, \( \hat{f} = 28\% \)). Lower doses (<12.6 mg daily) were less effective (1 study, mean Hb difference = 1.0 g/L, P = .52), whereas higher doses (31–59 mg daily and >60 mg) resulted in Hb differences similar to those for the 12.6- to 30-mg dose (2 studies and 1 study, 8.2 and 5.4 g/L, P = .1 and .03, respectively). Treatment duration of 1 to 3 months resulted in a mean Hb difference of 1.77 g/L (5 studies, P < .0001, \( \hat{f} = 79\% \)), with no data being available for shorter courses, whereas durations >3 months had no clear beneﬁt (4 studies, MD = 5.6 g/L, P = .15, \( \hat{f} = 90\% \)). Total iron intake of ≥2500 mg elemental iron resulted in a mean Hb difference of 7.7 g/L (5 studies, P < .0001, \( \hat{f} = 79\% \)), with total doses >2500 mg showing no additional advantage (7 studies, MD = 6.4 g/L, P = .002, \( \hat{f} = 87\% \)).

Study Characteristics

Characteristics of the included studies are presented in Table 1. Iron was given as ferrous sulfate in 7 studies, 3 studies speciﬁed a different formulation (ferrous gluconate, ferrous fumarate, ferric ammonium citrate), and 4 studies did not specify the formulation. Four studies were 2 × 2 factorial studies that were extracted as iron versus control and iron with another intervention versus that intervention alone with arms combined during meta-analysis.25–29 Three studies28–30 were cluster randomized trials, none of which reported that results as presented had been corrected for clustering (although Stoltzfus et al28 reported that regression coefﬁcients had been corrected). Intraclass correlation coefficients (ICCs) for Hb and ferritin in cluster trials have generally been found to be <0.001 to 0.051,51 which are sufﬁciently low that correction for sample size was not considered necessary in the 2 studies from which data for these outcomes were extracted (Bhatia and Seshadri29 and Stoltzfus et al28). Stoltzfus et al28 reported on cognitive outcomes and randomized by household but did not provide ICC values.32 Birth spacing in Tanzania is ∼33 months,53 and the eligible age range of this study was 6 to 59 months, implying that 1 to 2 children per household would have been included. The ICC for cognitive development has previously been suggested to be ∼0.2.34 Assuming that 1 to 2 children per household were included in the study of Stoltzfus et al, no correction for clustering was considered necessary.

Adherence was documented in only 2 studies. Rosado et al27 reported that the supplement was consumed on an average of 97% of days by each child over 12 months, whereas Mitra et al35 documented average dose consumption of 80% over the 15-month study duration.

FIGURE 1
Results of search.
Anemia, ID, and IDA

Only 1 trial, Stoltzfus et al, reported on the effects of iron on anemia and found no significant effect (144/183 (79%) anemic in iron group, 142/176 (81%) anemic in control group). No trials reported specifically on correction of either ID or IDA by iron.

Ferritin

A significant improvement in ferritin levels was shown in iron-supplemented subjects (5 studies, 1407 subjects, MD = 11.64 μg/L, 95% CI 6.02–17.25, P < .0001). Subjects with ID had a greater improvement compared to those with IDA (P = .03). Similarly, iron increased ferritin in subjects with iron deficiency (3 studies, MD = 13.01 μg/L, P = .02), and those with mixed baseline iron status (2 studies, MD = 15.11 μg/L, P = .0003), but not in nonanemic subjects (2 studies, MD = 13.6 μg/L, P = .13). Similarly, iron increased ferritin in subjects with iron deficiency (3 studies, MD = 13.01 μg/L, P = .02), and those with mixed baseline iron status (2 studies, MD = 15.11 μg/L, P = .0003), but not in subjects who were iron replete at baseline (2 studies, MD = 14.34 μg/L, P = .16).

Subgroup analysis showed differences between trials using different total iron doses. Ferritin levels appeared to improve more with higher total doses. A total dose ≤2500 mg resulted in a mean ferritin difference of 7.0 μg/L (2 studies, P = .01), whereas a dose >2500 mg resulted in a mean difference of 16.53 μg/L (3 studies, P < .00001).

Studies did not specifically discuss or account for the effect of inflammation or infection on ferritin.

Other Hematologic Parameters

Iron supplementation did not affect transferrin saturation (3 studies, 268 subjects, MD = 6.70% [95% CI 1.68–11.72], P = .04), hematocrit (3 studies, MD = 0.00 [95% CI –0.01 to 0.01], P = .66), or mean cell volume (2 studies, MD = 2.49 fl [95% CI –1.10 to 6.08], P = .17).

Cognitive Development

Four studies presented cognitive development data, but only 2 (Deinard et al and Stoltzfus et al) presented extractable data. Deinard et al reported combined Stanford-Binet and Bayley scores and showed no significant improvement with iron supplementation. Stoltzfus et al reported a benefit from iron on language development scores in a rural African cohort (0.8-point improvement on a 20-point scale, P = .01). When these studies were combined for meta-analysis, a significant benefit was found with iron supplementation (294 subjects, SMD = 0.25 [95% CI 0.06–0.45].

PEDIATRICS Volume 131, Number 4, April 2013

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Two additional studies reporting on cognitive development contained data that were not extractable because no estimation of error was provided. Metallinos-Katsaras et al. reported that iron produced a significant improvement in discrimination and selective attention in anemic subjects (14% improvement in errors of commission, \( P < .05 \); 8% improvement in accuracy, \( P < .05 \); 1.09 z-score points in efficiency, \( P < .05 \)) but produced no effect in nonanemic subjects. Soewondo et al. reported baseline deficits in visual attention and concept acquisition in anemic subjects and suggested that receipt of iron (compared with placebo) was a covariate in improvement seen in these parameters after treatment.

### Physical Growth

The meta-analysis found no significant effect of daily iron supplementation on physical growth. Three studies reported end point height (MD = 0.19 cm [95% CI -1.33 to 0.94], \( P = .74 \); \( I^2 = 0\% \)) and weight (MD = 0.15 kg [95% CI -0.22 to 0.51], \( P = .44 \); \( I^2 = 38\% \)). Four studies reported change from baseline in height (MD = 0.26 cm [95% CI -0.49 to 1.01], \( P = .5 \); \( I^2 = 5\% \)) and weight (MD = -0.06 kg [95% CI -0.14 to 0.02], \( P = 15 \); \( I^2 = 0\% \)). Subgroup analysis did not identify any differences in effect with different dose or duration of iron. Three studies reported change in height z-score from baseline (MD = -0.01 [95% CI -0.14 to 0.12], \( P = .86 \); \( I^2 = 83\% \)), and 2 studies reported change in weight z-score from baseline (MD = -0.04, [95% CI -0.12 to 0.05], \( P = .43 \); \( I^2 = 0\% \)). Stoltzfus et al. was the only trial to report stunting and showed no significant difference between iron supplemented and control groups.

### Infection

Three trials reported on fever. Angeles et al. found that fever episodes occurred 1.7 times more frequently in controls than in the treatment group (13.5 vs 7.7, no statistical test shown). Rosado et al. found no significant difference in number of episodes of fever between iron-supplemented children and controls (iron supplemented versus controls: 60 vs 48; iron and zinc supplemented versus zinc alone: 43 vs 53). Smith et al. reported a similar number of febrile episodes per health worker visit in children receiving iron versus control (35 vs 32). Mitra et al. and Rosado et al. reported the number of episodes of diarrheal and respiratory illnesses per child per year. There was no significant difference between treatment and control (diarrheal episodes: MD = 0.3, \( P = .13 \).
Iron increased risk of fever related to malaria parasitemia (fever and ≥10 positive fields per 100 high power fields: 12/700 health worker visits in iron supplemented vs 2/682 in controls, P < .025; fever and ≥50 positive fields per 100 high power fields: 9/700 health worker visits in iron supplemented vs 0/682 in controls, P < .01). Children with malaria were screened for malaria 2 weeks before the end of the study and referred if clinical malaria was detected. Nwanyanwu et al reported outcomes for malaria treatment with sulphadoxine-pyrimethamine and found that iron-treated subjects were more likely to be parasitemic at the completion of treatment (22/77 in iron supplemented vs 14/75 in control; no statistical analysis presented). Children with parasitemia were treated.

### DISCUSSION

This systematic review confirms that iron supplementation increases Hb and ferritin levels. Surprisingly, there were negligible data evaluating the impact of iron supplementation on anemia, ID, or IDA. Limited evidence suggests a beneficial effect from iron on children's cognitive development. Daily iron supplementation does not appear to improve or impair physical growth, and there was no evidence to suggest iron increases morbidity from diarrhea or respiratory infection. Table 2 presents a summary of findings and an evaluation of the quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) approach.

Our study is the first meta-analysis and systematic review to specifically evaluate the effects of iron supplementation administered daily to 2- to 5-year-old children. Previous systematic reviews evaluating the effects and safety of iron administered in various forms to children of various ages have addressed outcomes including hematology, infectious disease, cognitive development, mental and motor development, physical growth, and physical performance in children <18 years of age. Our review extends the literature because previous reviews have not specifically studied 2 to 5 year olds or addressed the effects of daily oral iron supplementation, which is the therapy most often used by clinicians. We also identified several studies that were not included in the previous reviews.

Iron supplementation clearly increased Hb and ferritin. Significant heterogeneity in the effect on Hb may be explained by subgroup differences, particularly in baseline iron and Hb status. Children who were initially iron replete or nonanemic responded less well compared with those who were anemic/iron deficient at baseline. Iron-replete individuals absorb less iron than deficient individuals. However, subjects enrolled in studies where baseline anemia or iron status had not been determined still benefited from iron. Accordingly, where facilities to screen for anemia or iron status are available, directed intervention with iron given exclusively to anemic/iron deficient children is likely to achieve the optimal benefit. However, where such testing facilities are unavailable or too costly, routine iron supplementation to all children in the population should achieve an improvement in Hb concentration, especially where the majority of individuals are known to be anemic.

Gera et al reported that iron delivered through various forms improved Hb by 7.4 g/L, similar to our result. The authors also found that iron reduced anemia prevalence by between 37.9% and 62.3% in non–malaria-endemic areas and by between 5.8% and 31.8% in malaria-endemic areas. Our review highlights the lack of data regarding the impact of iron supplementation on anemia, ID, or IDA.
daily oral iron on anemia in this population. Physiology would suggest a reduction in the prevalence of anemia remains a likely outcome from an approach of daily iron supplementation, but the expected population benefit of this intervention remains unproven.

Identification of the most effective dose and duration of treatment is critical to management of ID and has important public health implications. Although the reliability of subgroup analysis is limited by small numbers of studies, the analysis suggests Hb improvement may be optimal with a course of iron of 12.6 to 30 mg daily over a treatment period of 1 to 3 months. No additional benefit to Hb with total elemental iron doses >2500 mg was seen. However, for maximal improvement in ferritin, a higher dose or longer treatment period (or both) may be required. The need for additional iron replacement reflects clinical experience that the prescribed duration of supplementation should be sufficient to replenish both hemoglobin (often achieved early) and iron stores. Additional data on adherence may have provided more insight into the ideal dose and duration.

ID has been considered a cause of cognitive impairment in children, but the effects of iron supplementation on cognitive development have been uncertain. Our meta-analysis revealed that there are only limited data from randomized controlled trials on the effects of iron on cognitive development in 2 to 5 year olds. We observed that 3 of the 4 studies undertaken in this age group suggested benefit from iron on cognitive development, but only 2 of these demonstrated statistical significance. Unfortunately, data from only 2 of these studies were extractable for meta-analysis, and we combined different measures of cognitive development. Taken together with the 2 other studies that were not included in the meta-analysis, our data suggest that iron may improve cognitive development among children in this age group. A 2001 Cochrane Review evaluating the effects of iron therapy on psychomotor and cognitive development in ID children under 3 years of age concluded that evidence of iron depletion on children’s development was unclear, although given that the numbers of children in the trials were small, data were “compatible with substantial beneficial effects of iron therapy.” Sachdev et al meta-analyzed the effects of iron on mental development in 15 studies and reported a small significant benefit from iron chiefly attributable to an improvement in IQ scores in older, but not young, children. The authors concluded that iron marginally improves children’s mental development. More recently, Szajewska et al performed a meta-analysis of the effects of iron given as supplements or formula to nonanemic children and found a significant improvement in psychomotor development by 12 months of age in iron-treated children. Falkingham et al reviewed the effects of iron on cognition in older children and adults and found evidence that iron supplementation improved attention and concentration. Our data thus support previous findings that iron supplementation may benefit cognitive performance.

---

**TABLE 2 Summary of Findings**

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>MD (95% CI)</th>
<th>No of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>6.97 (4.21–9.72)</td>
<td>1680 (8)</td>
<td><strong>AA</strong></td>
<td>Only 1 randomized controlled trial has reported on this outcome in this population; no evidence of benefit on anemia reduction was demonstrated.</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>11.64 (6.02–17.25)</td>
<td>944 (5)</td>
<td><strong>AA</strong></td>
<td>No randomized controlled trial has reported on this outcome in this population.</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>0.25 (0.06–0.45)</td>
<td>394 (2)</td>
<td><strong>AA</strong></td>
<td>On the basis of meta-analysis of different outcomes; 2 further randomized controlled trials also found evidence of benefit but cannot be included in meta-analysis because of limitations in reporting.</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>End point: 0.19 (‐1.33 to 0.94)</td>
<td>End point: 634 (3)</td>
<td><strong>AA</strong></td>
<td>All studies at high risk of bias.</td>
</tr>
<tr>
<td>Change from baseline: 0.26 (‐0.48 to 1.01)</td>
<td>Change from baseline: 633 (4)</td>
<td>Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>End point: 0.15 (‐0.22 to 0.51)</td>
<td>End point: 634 (3)</td>
<td><strong>AA</strong></td>
<td>All studies at high risk of bias.</td>
</tr>
<tr>
<td>Change from baseline: ‐0.06 (‐0.14 to 0.02)</td>
<td>Change from baseline: 633 (4)</td>
<td>Very low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE:** Working Group grades of evidence. High quality, additional research is very unlikely to change our confidence in the estimate of effect; Moderate quality, additional research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality, additional research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality, we are very uncertain about the estimate.
We found no evidence that daily iron supplementation affects physical growth in children. The meta-analysis had a power of 0.59 and 0.55 to detect differences in height and weight, respectively, at the end point, based on the approach recommended by Borenstein et al.\textsuperscript{54} Sachdev et al\textsuperscript{45} similarly found no evidence of benefit from iron on growth and suggested an adverse effect of iron on growth in children living in developed settings. The latter finding was not indicated by our data.

Reporting of morbidity in included trials was limited, with no documentation of important adverse effects that may impair adherence such as vomiting, nausea, or constipation. Studies reporting morbidity provided data in different formats, preventing meta-analysis. We could find no convincing evidence that daily iron supplementation increases risk of diarrhea or respiratory infection. Reported effects of iron on clinical malaria and parasitemia were conflicting. A recent Cochrane review of trials giving iron in malaria-endemic areas found that the risk of clinical malaria was higher with iron in trials where services did not provide for malaria surveillance and treatment.\textsuperscript{55} Information on malaria surveillance and treatment was not available from the included studies. Gera and Sachdev\textsuperscript{45} reported in a meta-analysis that iron in various forms given to children may slightly increase the risk of diarrhea. The safety of iron supplementation in the field requires additional study.

The findings of this study should be considered within the context of its limitations. There were limitations in the number and quality of eligible studies. No eligible studies were at low risk of bias. Studies gave little or no information on random sequence generation or allocation concealment. There was no evidence of imbalanced attrition between children randomized to iron or control, although only 8 studies reported on losses to follow-up. There was a surprising lack of studies measuring outcomes of anemia, ID, or IDA. The lack of studies impaired the capacity of this review to define the reduction in the burden of these outcomes that might be achieved by implementation of daily iron supplementation. There were few data evaluating the impact of iron supplementation on development. Only four outcomes contained sufficient trials to enable subgroup analysis, and techniques such as meta-regression could not be used because of the paucity of studies.

The studies included in this systematic review were undertaken in a broad range of settings, but most were performed in developing settings; therefore, our findings are relevant in lower- and middle-income countries where the burden of anemia and ID is highest.

**CONCLUSIONS**

This systematic review and meta-analysis confirm the benefit of daily iron supplementation on Hb and iron stores in 2- to 5-year-old children. A small benefit from iron on cognitive parameters is suggested, although the number of studies is small, and the combination of the different scales limits the validity of meta-analysis. Our study highlights a concerning lack of data on the effect of iron supplementation on the clinically important outcomes of anemia, ID, IDA, and cognitive development in the important preschool age group. Additional research is needed to address the operational challenges associated with delivering iron supplementation programs in the field. There remains a need for well conducted and clearly reported interventional studies in this age group that evaluate important clinical and functional outcomes, side effects, and adherence.

**APPENDIX: SEARCH STRATEGIES FOR ELECTRONIC DATABASES**

#1 ((TITLE-ABS-KEY(iron OR ferric* OR ferrous* OR ifa)) AND (TITLE-ABS-KEY (infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*)) OR ((TITLE-ABS-KEY(iron OR ferric* OR ferrous* OR ifa)) AND (TITLE-ABS-KEY (infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*)) AND (TITLE-ABS-KEY (trace element* OR micro*nutrient*)) AND NOT (((TITLE-ABS-KEY(iron OR ferric* OR ferrous* OR ifa)) AND (TITLE-ABS-KEY (infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY(random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*))))

#2 ((TITLE-ABS-KEY(infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY(random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*)) AND (TITLE-ABS-KEY (trace element* OR micro*nutrient*)) AND NOT (((TITLE-ABS-KEY(iron OR ferric* OR ferrous* OR ifa)) AND (TITLE-ABS-KEY (infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY(random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*))))

#3 ((TITLE-ABS-KEY(infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY(random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*)) AND (TITLE-ABS-KEY (trace element* OR micro*nutrient*)) AND NOT (((TITLE-ABS-KEY(iron OR ferric* OR ferrous* OR ifa)) AND (TITLE-ABS-KEY (infant* OR child* OR baby OR babies OR newborn* OR toddler* OR preschool* OR pre-school*)) AND (TITLE-ABS-KEY(random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial*))))

#4 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#5 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#6 (trace element* OR micro*nutrient*)

#7 (iron OR ferric* OR ferrous* OR ifa)

#8 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#9 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#10 (trace element* OR micro*nutrient*)

#11 (iron OR ferric* OR ferrous* OR ifa)

#12 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#13 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#14 (trace element* OR micro*nutrient*)

#15 (iron OR ferric* OR ferrous* OR ifa)

#16 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#17 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#18 (trace element* OR micro*nutrient*)

#19 (iron OR ferric* OR ferrous* OR ifa)

#20 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#21 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#22 (trace element* OR micro*nutrient*)

#23 (iron OR ferric* OR ferrous* OR ifa)

#24 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#25 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#26 (trace element* OR micro*nutrient*)

#27 (iron OR ferric* OR ferrous* OR ifa)

#28 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#29 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#30 (trace element* OR micro*nutrient*)

#31 (iron OR ferric* OR ferrous* OR ifa)

#32 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#33 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#34 (trace element* OR micro*nutrient*)

#35 (iron OR ferric* OR ferrous* OR ifa)

#36 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#37 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#38 (trace element* OR micro*nutrient*)

#39 (iron OR ferric* OR ferrous* OR ifa)

#40 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#41 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#42 (trace element* OR micro*nutrient*)

#43 (iron OR ferric* OR ferrous* OR ifa)

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#45 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#46 (trace element* OR micro*nutrient*)

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#48 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#49 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#50 (trace element* OR micro*nutrient*)

#51 (iron OR ferric* OR ferrous* OR ifa)

#52 (infant* OR child* OR baby OR babies OR newborn OR toddler OR preschool OR pre-school)

#53 (random* OR rct OR drug therap* OR diet* therap* OR placebo* OR trial)

#54 (trace element* OR micro*nutrient*)

#55 (iron OR ferric* OR ferrous* OR ifa)
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