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Routine Iron Supplementation and Screening for Iron Deficiency Anemia in Children Ages 6 to 24 Months: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: In 2006, the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to recommend for or against routine screening and supplementation for asymptomatic children ages 6 to 12 months at average risk for iron deficiency anemia but recommended routine iron supplementation for those at increased risk.

Purpose: To systematically update the prior USPSTF reviews on screening and supplementation for iron deficiency anemia in children ages 6 to 24 months.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE® (1996 to August 2014), and manually reviewed reference lists.

Study Selection: We included randomized, controlled trials and controlled observational studies of the effects of screening, treatment, and routine supplementation on clinical outcomes, prevalence of iron deficiency anemia and iron deficiency, hematological indexes and ferritin levels, and harms in children ages 6 to 24 months.

Data Extraction: One investigator abstracted details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF to rate the quality of each study. Discrepancies were resolved through a consensus process.

Results: No controlled trials of routine iron supplementation in children ages 6 to 24 months reported clinical outcomes related to diagnosis of neurodevelopmental delay, and five of six trials reporting growth found no benefit of supplementation. Although not clearly clinical outcomes, developmental test scores after 3- to 12-months' followup were reported in four trials, with mostly nonsignificant findings. The clinical significance of these findings is unclear. Ten trials assessing iron supplementation in children reported inconsistent findings for incidence of iron deficiency anemia, iron deficiency, and anemia, as well as hemoglobin and serum ferritin concentrations. One trial reported no difference in incidence of gastrointestinal adverse events in children receiving iron-fortified milk compared with nonfortified milk, and one trial reported no clinically significant adverse events attributable to study interventions. Other harms of supplementation were not reported. No studies assessed the benefits or harms of screening for or treatment of iron deficiency anemia in children ages 6 to 24 months. No studies assessed the association between change in iron status and clinical health outcomes, and three studies reported no difference between supplemented and unsupplemented infants in changes in iron status and measures of growth or developmental scale scores.

Limitations: Only English-language articles were included. Because there was limited evidence from randomized trials, we included nonrandomized trials.

Conclusions: More research is needed to assess the benefits and harms of routine iron supplementation to prevent iron deficiency anemia, and screening for and treatment of iron

deficiency anemia, in children ages 6 to 24 months. While some evidence is available showing improvements in hematological values, trials reporting clinical outcomes, including developmental outcomes, are lacking.

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Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report was commissioned by the U.S. Preventive Services Task Force (USPSTF) in order to update its 2006 recommendations on screening and supplementation for iron deficiency anemia in young children.[1]

The USPSTF previously concluded that the evidence was insufficient to recommend for or against routine screening for iron deficiency anemia in asymptomatic children ages 6 to 12 months (I statement) and that the evidence was insufficient to recommend for or against routine iron supplementation for asymptomatic children ages 6 to 12 months who are at average risk for iron deficiency anemia (I statement). These recommendations were based on a lack of evidence that screening results in improved health outcomes, and poor and conflicting evidence on the benefit of iron supplementation in children who are not at increased risk for iron deficiency anemia.

The USPSTF also previously recommended routine iron supplementation for asymptomatic children ages 6 to 12 months who are at increased risk for iron deficiency anemia (B recommendation). This recommendation was based on evidence that iron supplementation *may* improve neurodevelopmental outcomes in children who are at increased risk for iron deficiency anemia, a possible benefit that outweighed any potential harms.

Condition Definition

Iron is required in the production of hemoglobin, an essential protein found in red blood cells. Over time, iron is stored in the body for use in hemoglobin production. Iron deficiency occurs when the level of stored iron becomes depleted. Iron deficiency anemia occurs when iron levels are sufficiently depleted to produce anemia, characterized by hypochromic and microcytic red blood cells.[2]

For infants and children, iron deficiency anemia is defined as iron deficiency with hemoglobin levels less than 110 g/L.[3,4] When used alone, hemoglobin is not the most accurate test in this age group.[5] Hemoglobin is a sensitive test for iron deficiency anemia, but it has low specificity because iron deficiency anemia accounts for less than half of all cases of anemia in toddlers in the United States.[6] Serum ferritin—ideally assessed in the absence of infection or inflammatory disease and in combination with another hematological measure, such as C-reactive protein, transferritin saturation, or reticulocyte hemoglobin—is a useful laboratory measure of iron status, with a low value being diagnostic of iron deficiency.[6-8] Infants in the United States with iron deficiency are usually asymptomatic.

Prevalence

Iron deficiency among infants and toddlers in the United States has a prevalence of about 8 percent in the general population,[9-11] although estimates based on a model of body iron stores (as opposed to using the more conventional ferritin model) are much higher at 14 percent for children ages 1 to 2 years.[8] Only about one third of children who are iron deficient have associated anemia.[6,9,12] The prevalence of iron deficiency anemia in children ages 1 to 5 years is estimated to be about 1 to 2 percent in the United States.[6,13] Prevalence in children from low-income families is estimated to be slightly higher, around 3 percent for boys and 4 percent for girls, based on one study of 432 children ages 1 to 3 years residing in California.[11] Current evidence on the prevalence of iron deficiency anemia in infants younger than age 1 year in the United States is lacking, although estimates for low-risk infants in other developed countries range from 2 to 4 percent.[14,15]

Prevalence of iron deficiency anemia in the United States varies according to race/ethnicity. Based on National Health and Nutrition Examination Survey (NHANES) data from 1999–2002, rates of iron deficiency anemia among 1- to 3-year-olds were lowest in Mexican Americans (0.9%) and highest in non-Hispanic whites (2%), with rates for non-Hispanic blacks falling between the two (1.6%).[6] These data stand in contrast to older NHANES data (1988–1994), which found reversed prevalence trends in the same age group (Mexican Americans, 5.5%; blacks, 3.5%; and whites, 1.2%), although the overall prevalence of iron deficiency anemia (2.6%) was similar to the later data.[16] The reason for these differences is unclear. Definitions of iron deficiency anemia were the same at both timepoints; however, estimates of prevalence of iron deficiency anemia based on NHANES data have been noted to be statistically unreliable.[6,17]

Risk factors associated with iron deficiency anemia are discussed below in Contextual Question 1.

Burden of Disease/Illness

Iron deficiency anemia can present a significant burden of disease in infancy and childhood. A narrative review of 15 studies found that infants with iron deficiency anemia had cognitive test scores 6 to 15 points lower and motor test scores 9 to 15 points lower than iron-sufficient infants.[18] In addition, behavioral characteristics, such as diminished activity and social interaction levels, have consistently been observed in infants with iron deficiency anemia.[11,18]

The effect of iron deficiency anemia in infancy and childhood has been reported in few well-designed long-term controlled studies. As described in the 2006 USPSTF report, numerous cohort and case-control studies have reported a correlation between presence of iron deficiency with or without anemia and impaired neurodevelopment in older children.[17] However, many of these studies had methodological flaws; for example, the outcomes examined varied and were not clearly clinically important, and the effect of iron deficiency anemia in infancy and childhood has been reported in few well-designed long-term controlled studies. A more recent nonsystematic review of primarily observational studies determined that presence of iron deficiency anemia was consistently associated with cognitive and behavioral delays in children.[19]

This association was more pronounced when iron deficiency anemia was present in children younger than age 2 years than in those older than age 2 years, suggesting that the negative long-term effects of iron deficiency anemia may be more avoidable when it is identified and treated at a young age. However, the same review found that the evidence was insufficient to prove causation in these studies, primarily because of the difficulty in assessing the effect of potential confounders among the studies, including nutritional disparities between groups, socioeconomic factors, and clinical effects of anemia that are not directly related to cognitive function.

One of the longest and most frequently cited studies on the effect of iron deficiency anemia in infancy and long-term developmental outcomes followed 114 healthy and relatively well-nourished Costa Rican children from ages 12 to 23 months to age 19 years.[17,20-23] All children with iron deficiency anemia in this study received treatment in infancy, resulting in resolution of anemia within 3 months. Despite this, as noted in the prior USPSTF report, at ages 11 to 14 years the children who were treated for iron deficiency in infancy scored lower on intelligence tests (Wechsler Intelligence Scale for Children–Revised Verbal Intelligence Quotient, 101.8 ± 2.0 vs. 104.6 ± 1.3) and on a variety of cognitive function tests than children who were iron sufficient in infancy.[17,20] Previously iron-deficient children were also more likely to have repeated a grade in school (26% vs. 12%; p=0.04) and to have been referred for special education services (tutoring, 21% vs. 7%; p=0.02). Parents and teachers of children in the iron-deficient group were also more likely to report concerns regarding behavior compared with iron-sufficient children. Intelligence and cognitive test scores were adjusted for a number of potential confounders, including age, sex, and mother's Intelligence Quotient score. Longer followup of the same cohort, published since the 2006 USPSTF report, found that measures of cognitive function—using subscales of the Wechsler Intelligence Scale for Adults and measures of mathematic ability—remained lower in previously iron-deficient infants at age 19 years compared with previously iron-sufficient infants (mean score, 98.2 vs. 107.6 points; mean difference, 9.4 points [95% confidence interval (CI), 7.0 to 11.0 points]).[23] This effect was magnified in children from families with low socioeconomic status (mean score, 70.4 vs. 95.3 points; mean difference, 24.9 points [95% CI, 20.6 to 29.4 points]). Pattern recognition and other tests of neurocognitive function were also lower in the previously iron-deficient group at age 19 years.[24]

Presence of iron deficiency anemia has also been associated with ischemic stroke in otherwise healthy children in case reports.[25] A case-control study conducted in Canada found that among 15 cases of stroke in otherwise healthy children ages 12 to 38 months, eight had iron deficiency anemia (53%) compared with 13 of 143 (9%) matched healthy controls.[26] After controlling for platelet count, the adjusted odds ratio (OR) was 10 (95% CI, 3 to 33), suggesting that children with iron deficiency anemia may be at increased risk for stroke compared with similarly aged children without iron deficiency anemia.

Rationale for Screening/Screening Strategies

Screening young children for iron deficiency anemia may lead to earlier identification and therefore earlier treatment, which has the potential to prevent serious negative health outcomes. Strategies for screening can include either routine screening or targeted screening based on established risk factors or risk-assessment instruments and diagnostic tests. Routine screening for

all children could occur when they present for pediatric health visits.

Current Clinical Practice

Supplementation

Suggested prophylaxis for iron deficiency anemia in nonbreastfed infants is 1 to 2 mg elemental iron per kg per day, with a maximum of 15 mg elemental iron per day, in divided doses.[6] Infants who are not breastfeeding or partially breastfeeding are generally given an iron-supplemented formula in addition to an iron supplement. Supplementation generally continues until intake of iron through solid foods is adequate (e.g., two or more servings per day of iron-fortified cereals).

Treatment

Iron deficiency anemia in children is typically treated orally. For infants and young children, the recommended dose for treating iron deficiency anemia is 3 to 6 mg/kg elemental iron per day[27-29] in two to three divided doses, with dosing at the lower end for mild anemia and at the higher end for severe anemia. However, some studies have found that once-daily dosing results in similar improvement as dosing two or three times daily and does not significantly increase adverse effects.[30] Treatment for 4 weeks generally results in an increase of at least 1 g/dL and generally lasts for several months; the duration depends on the severity of anemia.

Adverse events are typically limited to gastrointestinal tract symptoms, such as constipation, thought to be directly related to the dose of elemental iron being taken. Slowly increasing the dose over several days, reducing the amount of elemental iron taken per dose or daily, or taking the iron with food may improve symptoms in many patients. These measures will likely mean that a longer duration of therapy is required. Urine and stool may be darker in color when taking iron, and liquid formulations can cause gray staining of teeth and gums; however, this is not permanent and can be ameliorated through the consumption of citrus juices. Iron can cause important interactions with several drugs and can be fatal in overdose in children.

The prior USPSTF report noted that accidental iron overdose can occur in children receiving treatment or supplementation with iron.[17] Specific data on iron overdose in children ages 6 to 24 months (the population included in this report) are lacking. However, according to 1988–1997 surveillance data from the American Association of Poison Control Centers, generally one to three children younger than age 6 years died each year from iron overdose, although some years, rates were substantially higher (five deaths in 1990 and 11 deaths in 1991).[31] To address the problem of iron overdose, in 1997 the Food and Drug Administration instituted the requirement that iron or supplements containing iron be packaged in unit-dose packaging. In the 5 years following this requirement, only one death due to iron overdose was reported, and the incidence of nonfatal iron overdose dropped from a high of 3.38 per 1,000 cases in 1992 to 1.76 per 1,000 cases in 2002. The unit-dose packaging requirement was removed in 2003 following a U.S. District Court decision.[32] From 2004 through 2011 (the most recent data available), there have been no reports of children younger than age 6 years dying from iron overdose in the United States.[33-36]

Recommendations of Other Groups

Screening

The American Academy of Pediatrics (AAP) recommends universal screening for anemia at age 12 months.[6] The Centers for Disease Control and Prevention (CDC)[4] and the Institute of Medicine (IOM)[37] recommend screening high-risk children at varying ages. Specifically, the CDC recommends screening children who are at risk for anemia at ages 9 to 12 months and then 6 months later (at ages 15 to 18 months). The IOM guidelines specify screening term infants not receiving iron-fortified formula or who are breastfeeding at age 9 months; preterm infants not receiving formula before age 3 months; and at age 15 or 18 months in infants who were previously anemic. The IOM also recommends against routinely screening children who were not anemic during prior screenings unless other risk factors exist. Bright Futures cites the CDC and AAP recommendations.[38] The American Academy of Family Physicians[39] follows the 2006 USPSTF recommendation,[1] concluding that the evidence is insufficient to recommend for or against screening for iron deficiency anemia in asymptomatic children ages 6 to 12 months. The Canadian Task Force on Preventive Health Care does not have a current screening recommendation.

Routine Supplementation

The IOM[37] and AAP[6] recommend that exclusively and partially breastfed infants should receive an iron supplement of 1 mg/kg per day through liquid, formula, or food starting at age 4 months. The CDC recommends the same starting between ages 4 and 6 months.[4] All three organizations state that formula-fed infants receive their iron needs through the first 12 months via iron-fortified formulas and that whole milk (i.e., cow's, goat's, or soy milk) should not be used before age 12 months. For preterm infants, all three organizations recommend iron supplementation of 2 mg/kg per day through oral drops, iron-fortified formula, or complementary food by age 1 month, continuing through age 12 months.

Contextual Question 1. What Risk Factors Are Associated With Iron Deficiency Anemia, and How Well Do Risk-Assessment Tools Identify Children at Increased Risk for Iron Deficiency Anemia?

The CDC has identified children from families with low socioeconomic status (including migrant workers and recent immigrants to the United States) as having a high risk for developing iron deficiency anemia.[4] Prematurity or low birthweight also increases risk for developing iron deficiency anemia, as does use of nonfortified formula in the first year of life (unlikely to occur in the United States), exclusive breastfeeding with no or erratic iron supplementation after age 6 months, and the introduction of cow's milk before the age of 1 year.[17] As with the prior report, we found no studies reporting quantified data on these risk factors and their association with iron deficiency anemia.[17] One small study of 68 children younger than age 3 years found that those

with food insecurity were more likely than food-secure children to have iron deficiency anemia (19% [12/65] vs. 10% [56/561]; adjusted OR, 2.4 [95% CI, 1.1 to 5.2]).[40]

The relationship between specific risk factors and presence of iron deficiency can be estimated based on several analyses of NHANES data on children ages 1 to 3 years[10,16,41] and one study[42] of similarly aged, low-income, primarily Hispanic children (**Table 1**). Based on these data, weight for height at or greater than the 95th percentile was consistently associated with presence of iron deficiency, although the risk estimate was not significant in one study. Bottle-feeding beyond the first year of life, having a mother who is currently pregnant, and residence in an urban area were also all significantly associated with increased iron deficiency risk based on one study. Hispanic ethnicity was a significant predictor of iron deficiency in two studies, but two others found no significant association. Results from two studies were also mixed on the association between risk for iron deficiency and male sex. Birthweight less than 2,500 g and family income below the Federal poverty level were associated with a nonsignificant trend toward presence of iron deficiency in these studies.

Risk for anemia was reported separately in one study.[42] Having a mother who is pregnant was a significant predictor of anemia in this population (OR, 3.5 [95% CI, 1.4 to 8.9]). Hispanic children had moderately increased risk for anemia compared with non-Hispanic children (OR, 1.3), although the result was not statistically significant (95% CI, 0.3 to 5.9). Children who participated in the Women, Infants, and Children Special Supplemental Nutrition Program (WIC) were less likely to be anemic than children who did not participate (adjusted OR, 0.34 [95% CI, 0.1 to 0.9]). Children with a higher rate of weight gain were also marginally less likely to be anemic than slower growing children (adjusted OR, 0.995 [95% CI, 0.990 to 0.999]). There was no significant association between either age or sex and increased risk for anemia.

We identified no studies that assessed how well risk-assessment tools identify children at increased risk for iron deficiency anemia.

Chapter 2. Methods

Key Questions and Analytic Frameworks

Using the methods developed by the USPSTF,[43] we collaborated with the USPSTF and the Agency for Healthcare Research and Quality to determine the scope and Key Questions for this review to update the prior reports.[17,44] Investigators created analytic frameworks with the Key Questions for the patient populations, interventions, and outcomes reviewed. The target population was asymptomatic children ages 6 to 24 months representative of children in the United States with respect to rates of malnutrition, hemoparasite burden, and general socioeconomic status.

The Key Questions are presented as two separate analytic frameworks: one for routine iron supplementation (**Figure 1**) and one for screening for iron deficiency anemia (**Figure 2**).

Routine Iron Supplementation in Children

1. What are the benefits of routine iron supplementation in children ages 6 to 24 months on child health outcomes?
2. What are the harms of routine iron supplementation in children ages 6 to 24 months?

Screening for Iron Deficiency Anemia in Children

1. What are the benefits of screening for iron deficiency anemia in asymptomatic children ages 6 to 24 months on child health outcomes?
2. What are the harms of screening for iron deficiency anemia in children ages 6 to 24 months?
3. What are benefits of treatment of iron deficiency anemia in children ages 6 to 24 months on child health outcomes?
4. What are the harms of iron treatment in children ages 6 to 24 months?
5. What is the association between change in iron status and improvement in child health outcomes in U.S.-relevant populations?

We also addressed a Contextual Question requested by the USPSTF to help inform the report. Contextual Questions address background areas deemed important by the USPSTF for informing its recommendations. Contextual Questions are not reviewed using systematic review methodology but rather summarize the evidence from key informative studies.

Contextual Question

1. What risk factors are associated with iron deficiency anemia, and how well do risk-assessment tools identify children at increased risk for iron deficiency anemia?

For the screening framework, Key Questions 1 and 2 focus on direct evidence on the effectiveness and harms of screening for iron deficiency anemia in asymptomatic children ages 6

to 24 months compared with not screening. Such direct evidence on the effectiveness of screening interventions may be limited. Therefore, the remainder of the analytic framework (Key Questions 3 through 5) evaluates the chain of indirect evidence needed to link screening with improvement in important health outcomes. Links in the chain of indirect evidence include the accuracy of screening in identifying children with iron deficiency anemia or at risk for iron deficiency anemia, the effectiveness of interventions in reducing the incidence of iron deficiency anemia and associated complications, the association between improvements in intermediate outcomes and clinical health outcomes, and harms associated with preventive treatments. Implicit in the indirect chain of evidence is that, to understand the benefits and harms of screening, it is necessary but not sufficient to show that children at risk for iron deficiency anemia can be identified; it is also necessary to show that there are effective treatments for those identified. Not all of the indirect links are included in this update, as some of the links (e.g., test accuracy) have been considered to be established.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE® (1996 to August 2014) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed the prior USPSTF reports, reference lists of relevant articles, and related systematic reviews. Based on feedback from the USPSTF, and because the 2006 review focused on systematic reviews and key studies of treatment of iron deficiency anemia, we also searched the reference lists of systematic reviews to identify relevant additional studies published prior to 1996.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies published since 1996 to update the prior systematic evidence reviews[17,44] on the basis of inclusion and exclusion criteria developed for each Key Question (**Appendix A2**). Since the scope of the 1996 and 2006 reviews differed somewhat from the scope of this update, we also included studies published before 1996 that had not been included in either of those reports.

Articles were selected for full review if they were about iron deficiency anemia in children who received intervention between the ages of 6 and 24 months, were relevant to a Key Question, and met the predefined inclusion criteria. We restricted inclusion to English-language articles and excluded studies published only as abstracts. Studies of nonhuman subjects were also excluded, and studies had to report original data. For supplementation Key Questions 1 and 2 and screening Key Questions 1 through 4, we excluded studies conducted in resource-poor populations, including nutritionally-deficient populations in developing countries and populations in areas considered to have high prevalence of hemoparasites. We included studies conducted in countries listed as having “high” or “very high” human development based on the United Nations International Human Development Index as a guide.[45] For screening Key Questions 3 and 4, we focused on studies that used iron supplementation and treatment regimens commonly used in clinical practice in the United States. For screening Key Question 5, we included studies conducted in any country but prioritized those conducted in countries with high or very high

human development ratings.

Included clinical outcomes were morbidity (including cognitive, psychomotor, and neurodevelopmental outcomes and diagnosis of developmental delay), growth, mortality, and quality of life. Harms outcomes included accidental overdose, study discontinuations, and other harms related to screening, supplementation, or treatment. Included intermediate outcomes were incidence of iron deficiency anemia, iron deficiency, and anemia, as well as hematological indexes (including ferritin levels). We included randomized, controlled trials (RCTs); nonrandomized controlled clinical trials; and controlled cohort studies for supplementation Key Questions 1 and 2 and screening Key Questions 1 through 4, and longitudinal studies for screening Key Question 5. **Appendix A3** shows the results of our literature search and selection process and **Appendix A4** lists excluded studies pulled at the full-text level with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. When otherwise not reported and where possible, we calculated relative risks (RRs) and 95 percent CIs or p-values. Two investigators independently applied criteria developed by the USPSTF[43] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process. Studies deemed poor quality were not synthesized with higher-quality evidence and not reported in evidence tables but are cited in the report for transparency.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each Key Question (good, fair, or poor) using methods developed by the USPSTF,[43] based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence. Meta-analysis was not attempted because of the limited number of studies for each Key Question and differences among studies in design, population, and outcomes.

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners, and revised prior to finalization.

Chapter 3. Results

Routine Iron Supplementation in Children

Key Question 1. What Are the Benefits of Routine Iron Supplementation in Children Ages 6 to 24 Months on Child Health Outcomes?

Summary

In the current review, six placebo-controlled trials of routine iron supplementation in children ages 6 to 24 months reported growth outcomes, with most studies finding no effect of supplementation on weight, length, or head circumference. Other clinical outcomes, such as diagnosis of psychomotor or neurodevelopmental delay or quality of life, were not reported in any trial. Although not clearly clinical outcomes, developmental test scores were reported in four trials after 3- to 12-month followup periods, with mostly nonsignificant findings. The clinical significance of these findings is unclear.

Ten trials that assessed iron supplementation in children reported inconsistent findings for incidence of iron deficiency anemia, iron deficiency, and anemia, as well as hemoglobin and serum ferritin concentrations. Iron deficiency anemia was reported in five studies, one of which reported a significant benefit (RR, 0.14 [95% CI, 0.09 to 0.20]). This same study reported a significant benefit of supplementation on iron deficiency (RR, 0.52 [95% CI, 0.45 to 0.59]). Another study, in which 6 percent of children received iron-fortified formula, 22 percent received nonfortified formula, and 43 percent received cow's milk, also reported a significant benefit of supplementation on iron deficiency, but the RR was not calculable because the authors reported percentages that do not correspond to whole numbers of participants according to group sizes. Two studies reported results suggesting a benefit but failed to reach significance, and two other studies found no difference between groups. Two of six studies reporting anemia found a significant benefit of iron supplementation (RR, 0.14 [95% CI, 0.09 to 0.20] and 0.07 [95% CI, 0.01 to 0.48]), although both trials had methodological shortcomings. Hemoglobin concentration was reported in eight studies and ferritin concentration was reported in nine studies, with conflicting results.

The USPSTF recommendation from 1996[44] found adequate evidence that iron supplementation resulted in reduced incidence of iron deficiency and iron deficiency anemia but found little evidence focused on clinical outcomes. The 2006 USPSTF review[17] did not assess the effect of supplementation on hematological indexes or incidence of iron deficiency and iron deficiency anemia, and found mixed evidence supporting the benefit of iron supplementation on neurodevelopmental test scores.

Evidence

Ten trials (in 11 publications) were included (**Tables 2** and **3**; **Appendix B1**) (two poor-quality

trials were omitted from tables).[46-58] Studies were conducted in primary care and community settings in the United States (one study), United Kingdom (four studies), Canada (one study), New Zealand (one study), Chile (one study), Australia (one study), Sweden (one study), and Turkey (one study). Children were generally enrolled at ages between 6 and 9 months, with one study enrolling children with a mean age of approximately 10 months[52] and another study at approximately 17 months.[53] Iron supplementation was administered for durations ranging from 3 to 18 months. Supplementation was provided as oral iron drops in three studies;[48,54,56] iron-fortified formula in four studies;[46,47,49,50,52] and iron-fortified milk, foods, or meat in three studies.[51,53,55] Control groups were given a non–iron-containing formula or supplement or a weaning diet in four trials;[48,49,51,56] cow's milk in four trials;[47,49,52,53] and no treatment, instructions, or supplement in three trials.[50,54,55] Race or ethnicity was not reported in seven studies,[49-52,54-56] was predominately white in two studies,[46,47,53] and approximately half black in one study conducted in the United States.[48] Studies enrolled nearly equal proportions of males and females (proportion of females ranged from 43% to 58%). Most studies excluded children born prematurely and those with conditions likely to affect iron absorption, growth, or development. Enrolled sample sizes ranged from 24 to 493 except for one larger study of 1,798 children, and many studies analyzed fewer numbers because of loss to followup or refusal to undergo venipuncture. Only one study analyzed children on an intention-to-treat basis;[53] the proportion of the sample available for analysis at the end of the other studies ranged from 53 to 92 percent.

These studies mostly represent children at average risk for iron deficiency anemia because all enrolled healthy children and most excluded children born preterm (except for one study) or with low birthweight (eight of 10 studies). One of the studies conducted in the United Kingdom[47] considered its population to be at higher risk for iron deficiency anemia because it included children from a socioeconomically deprived neighborhood. Information on race or ethnicity was poorly reported; six of nine studies did not report race or ethnicity distributions and none analyzed results by these characteristics. Other risk factors (which are more fully described in Contextual Question 1), such as having a pregnant mother, having a low rate of weight gain, and consuming cow's milk as the main source of nutrition, were not reported in any trial. Cow's milk was used as a comparator in four studies, and while it is unclear whether it was the primary source of nutrition for these children, as noted above, the control groups may have been at higher risk for iron deficiency anemia than the intervention or other control groups (e.g., receiving nonfortified formula). The IOM, AAP, and CDC advise against giving infants cow's milk before age 12 months because of potential issues with digestion, irritation of the stomach and intestine lining, and risk for illness, and because it may even cause iron deficiency anemia.[59]

One study was rated good-quality,[53] seven fair-quality,[46-52,56] and two poor-quality[54,55] (**Appendix B2**). Methodological shortcomings included unclear methods of randomization and allocation concealment,[49-51,54-56] lack of or unclear methods of blinding,[46,47,49,51,54,55] and high or differential loss to followup.[48,51,52,54,55]

One study, conducted in Chile by Lozoff et al,[50] initially randomized children to low- or high-iron supplementation, but the low-iron intervention was replaced with a noniron intervention partway through the study, in part because interim analysis suggested that the low-iron intervention was sufficient to prevent iron deficiency anemia. For analysis, the authors combined

all children who received any iron supplementation and compared them with children who did not receive supplementation, essentially breaking randomization and leading to baseline differences between the groups. Because randomization was broken, we considered the results to be comparable with those of a fair-quality comparative observational study.

Seven studies (including one poor-quality trial[55]) reported power or sample size calculations.[48,50-53,55,56] Two studies were powered to detect effects on developmental outcomes, with one sufficient to detect a 5-point difference on the Bayley Scale[52] and one sufficient to detect a 2.5-point difference in developmental scores (no specific scale cited).[50] One study was powered to detect a 50 percent reduction in the rate of iron deficiency anemia.[48] One was powered to detect mean reductions of 6 g/L for hemoglobin and 18 µg/L for ferritin,[51] and another was powered to detect a difference in hemoglobin of 5 g/L.[56] A good-quality study was powered to detect a reduction in iron deficiency prevalence of 20 percent (decrease from 30% to 10%) for one group only (red meat diet) but powered to detect an increase in ferritin of at least 5 µg/L for the other groups (fortified milk and control).[53]

Because of the heterogeneity of the studies in supplementation method, dose, duration, timing of initiation, and timing of followup, we did not pool results. In addition, risk factors were largely not reported, and no studies stratified results by risk groups.

Clinical Outcomes

Similar to the prior USPSTF reviews,[17,44] no trials assessed the long-term effects of routine iron supplementation compared with placebo in children ages 6 to 24 months on clinical outcomes aside from growth. In the current review, six trials reported growth outcomes, with most studies reporting no differences between groups, but no placebo-controlled trials of routine iron supplementation in children ages 6 to 24 months reported on diagnosis of psychomotor or neurodevelopmental delay or quality of life. Four trials reported developmental test scores (not diagnosis of delay) after 3- to 12-month followup periods, with mostly nonsignificant findings. The clinical significance of these findings is unclear.

Growth. Growth parameters were reported in six studies,[46,49,50,52,53,56] with only one study reporting significant differences. One reported no difference between groups in weight (8.9 vs. 8.9 kg),[56] two reported no differences in weight (11.1 vs. 11.1 vs. 11.3 kg[49] and 11.4 vs. 11.3 vs. 11.4 kg[52]) or length (78.9 vs. 79.1 vs. 80.3 cm[49] and 82.3 vs. 82.3 vs. 82.6 cm[52]), and two studies reported no differences in growth parameters, without showing data.[46,53] The study by Lozoff et al[50] reported small but significant differences in length (74.7 vs. 75.1 cm; $p<0.001$; length-for-age z-score, $p<0.01$) and head circumference (46.7 vs. 47.0 cm; $p<0.001$). While the study reported a significant difference in absolute weight at the endpoint (9,958 vs. 10,082 g; $p<0.05$), no difference was found in weight-for-age z-scores. These results should be interpreted with caution, as the groups differed by weight and length at baseline (7,984 vs. 8,092 g and 66.6 vs. 66.9 cm, respectively; both $p<0.01$).

Developmental scale scores. Four trials reported scores on developmental tests, with mixed results depending on the scale or method used for assessment. Three of the studies were rated fair-quality,[47,50,52] one was rated poor-quality,[54] and none of the trials were conducted in the

United States.

The best evidence on developmental outcomes comes from two fair-quality trials of children at average risk for iron deficiency anemia, which found no difference between groups on the Bayley Scale of Infant Development (between-group differences ranged from 0.6 to 0.7 for mental development and 0.2 to 0.7 for psychomotor development scores) (**Table 2**).[50,52] A Cochrane meta-analysis of older studies from any country was included in the 2006 report and was recently updated. This review reported no statistically significant differences on the Bayley Scale indexes.[60]

One fair-quality trial of children potentially at higher risk for iron deficiency anemia used the Griffiths scale to measure psychomotor development and reported that scores declined in both groups over the course of the study but declined somewhat less in the iron-supplemented group after 24 months (general quotient score at 24 months, −9.3 vs. −14.7; p=0.04).[47] The clinical meaning of this difference (5.4) is unclear, particularly because both groups' scores at 24 months were within normal limits.

Other developmental measures. In addition to measuring the Bayley Scale, the Lozoff study reported that children in the intervention group began crawling earlier than children in the control group (298 vs. 303 days; p<0.01).[50] Using a method that involved measuring the amount of time children spent looking at pairs of novel and familiar pictures, children in the intervention group spent a significantly shorter time than children in the control group (1.39 vs. 1.46 seconds; p<0.01). Although these differences are statistically significant, it is not clear that crawling 5 days earlier or a difference of 0.07 seconds viewing time are clinically important differences. This study also reported that unsupplemented children were more likely than supplemented children to be rated as showing no positive affect, making no attempt to interact socially, and making no bids for help. They were also more likely to be rated as "adaptable," and a greater proportion could not be soothed by words or objects when distressed. However, the trial had methodological flaws, which are detailed above, and the clinical significance of these findings is unclear.

The prior USPSTF report cited a meta-analysis of 17 trials of iron supplementation, which found no significant differences between groups on individual mental and motor development tests.[61] While the review found a small but significant benefit in a composite mental development score, derived from a variety of mental development tests, subgroup analysis attributed this difference to trials in children age 7 years and older that were conducted in developing countries.

Intermediate Outcomes

Ten trials (in 11 publications) reported the incidence of iron deficiency anemia, iron deficiency, or anemia and hematological parameters in children ages 6 to 24 months receiving iron supplementation compared with no supplementation (**Table 3**).[46-56] All trials except one[47] were of children at average risk for iron deficiency anemia.

One study was rated good-quality,[53] seven fair-quality,[46-52,56] and two poor-quality,[54,55] with only one conducted in the United States.[48] It should be noted that the trial by Lozoff et al,[50] with the

methodological issues described above, also reported hematological outcomes.

The 1996 USPSTF review[44] found that supplementation reduced the incidence of iron deficiency and iron deficiency anemia based on older studies conducted in developing and developed countries. The 2006 USPSTF review[17] did not reassess these outcomes.

Iron deficiency anemia. Five trials (one good-quality[53] and four fair-quality[48,50,51,56]) reported incidence of iron deficiency anemia, with ranges of 0 to 8 percent for those in the supplementation group and 0 to 22.6 percent in the placebo group. Iron deficiency anemia was variably defined as hemoglobin level less than 110 g/L and two of three abnormal iron measures (specifically ferritin, mean cell volume, and zinc protoporphyrin),[48,53,56] hemoglobin level less than 100 g/L and two or more abnormal iron measures,[50] or hemoglobin level less than 105 g/L and ferritin level less than 10 µg/L.[51] Four studies found no difference between groups in incidence of iron deficiency anemia, including one good-quality trial conducted in New Zealand (data represented in a figure in the article),[53] one study conducted in the United States (n=282) that reported that 8 percent of children in both groups (iron supplement and placebo) were anemic and had two other abnormal hematological values (RR, 1.04 [95% CI, 0.47 to 2.33]),[48] one study in Sweden that reported no effect of iron supplementation on rates of iron deficiency anemia (numbers not reported),[56] and one small study in Australia that reported no instances of iron deficiency anemia in either group.[51] The study by Lozoff et al, conducted in Chile, found that children receiving iron supplementation were significantly less likely to have iron deficiency anemia than untreated children (3.1% [34/1,114] vs. 22.6% [116/514]; RR, 0.14 [95% CI, 0.09 to 0.20]).[50] Incidence in the control group in this study (22.6%) was very high compared with the other studies (control group rates, 0% to 8%) and higher than estimated prevalence rates in the United States, suggesting that an effect may be evident in populations with higher baseline risk. However, known risk factors for iron deficiency anemia (e.g., proportion of control group using nonfortified cow's milk as the primary nutrition source) in included populations were not reported in these studies, so further analysis of this stratification could not be undertaken.

Iron deficiency. Five studies (four fair-quality and one poor-quality[54]) reported measures of iron deficiency, with incidence ranging from 3.9 to 78 percent for children in the supplementation group and 7.7 to 84 percent in the placebo group; only one study was conducted in the United States.[48-51,54] The fair-quality study conducted in the United States found no difference in the incidence of iron deficiency, defined as the presence of two abnormal iron measures, with supplementation.[48] Forty-eight percent (66/138) of those receiving oral iron drops and 51 percent (73/144) of those receiving placebo drops had two abnormal hematological values indicative of iron deficiency (i.e., zinc protoporphyrin, mean corpuscular volume, red cell distribution width, ferritin, transferritin saturation, and reticulocyte hemoglobin content) (RR, 0.94 [95% CI, 0.74 to 1.20]). This study provided iron supplementation for 3 months. A small fair-quality study also did not find statistically significant differences between groups, with serum ferritin concentration less than 10 µg/L in 3.9 percent (5/36) of children in the iron group and 7.7 percent (2/26) in the control group (RR, 1.81 [95% CI, 0.38 to 8.60]).[51] Two studies, however, reported a significant benefit of iron supplementation on incidence of iron deficiency.[49,50] A fair-quality study that compared iron-fortified formula with nonfortified formula and cow's milk reported a benefit of iron supplementation on incidence of iron deficiency (6% vs. 22% vs. 43%; RR not calculable based on data reported), defined as serum ferritin concentration less than 10 µg/L.[49] The study by

Lozoff et al found a beneficial effect of iron supplementation on incidence of iron deficiency (26.5% [286/1,081] vs. 51.3% [273/532]; RR, 0.52 [95% CI, 0.45 to 0.59]), defined as two of three abnormal iron measures (serum ferritin concentration <12 µg/L, mean cell volume <70 fL, and erythrocyte protoporphyrin >100 µg/dL red blood cells).[50] Finally, a poor-quality study[54] found no difference in incidence of iron deficiency (defined as serum ferritin concentration <10 µg/L), likely due to lack of statistical power.

Partly because of the variation in methods used to identify and define iron deficiency, incidence rates in control groups varied widely across these studies, ranging from 7.7 to 84 percent. Additional factors may have contributed to this variability, such as known risk factors in the included population that were not reported or analyzed. For these reasons, the inconsistencies in this evidence cannot be resolved.

Anemia. Six trials, including one study of children at higher risk for iron deficiency anemia[47] and one poor-quality trial,[54] reported incidence of anemia, ranging from 0 to 22 percent in the supplementation group and 13 to 33 percent in the placebo group. Iron deficiency anemia was variably defined as venous hemoglobin concentration less than 110 g/L,[46-49,54] less than 105 g/L,[51] or less than 100 g/L.[50]

Two fair-quality studies found very similar rates of anemia across supplemented and nonsupplemented groups. A fair-quality study conducted in the United States reported that 22 percent (31/138) of treated patients and 19 percent (27/144) of patients receiving placebo were anemic after 3 months (RR, 1.20 [95% CI, 0.76 to 1.90]).[48] Similarly, a study from the United Kingdom found no difference in incidence of anemia in children given iron-fortified formula and nonfortified formula (11% vs. 13%; RR not calculable based on data reported).[49]

Three other studies found a benefit of supplementation on the incidence of anemia. One small study from Australia found no cases of anemia in the supplemented group compared with 19.2 percent (5/26) of children in the unsupplemented group (RR, 0.07 [95% CI, 0.00 to 1.15]).[51] The study by Lozoff et al found that after 6 months of treatment, anemia was present in 3 percent (34/1,114) of children in the intervention group compared with 23 percent (116/514) in the control group (RR, 0.14 [95% CI, 0.09 to 0.20]).[50] One U.K. trial of iron-fortified formula compared with unmodified cow's milk in children at higher risk for iron deficiency anemia, also found a benefit after 12 months' followup, reporting rates of anemia of 2 percent (1/46) in the intervention group versus 33 percent (15/46) in the control group (RR, 0.07 [95% CI, 0.01 to 0.48]).[46,47]

Lastly, a very small poor-quality trial of oral iron drops reported that no treated patients (0/9) and 22 percent of untreated patients (2/9) were anemic.[54]

Variability in the definitions of anemia, the unknown mixture of baseline risk in enrolled children, and the variation in control group rates across these studies limit the interpretability of the findings for U.S. populations. For example, while prevalence rates of iron deficiency among infants and toddlers in the United States are currently estimated at 8 percent, control group rates in these studies ranged from 13 to 33 percent. Studies finding a benefit generally had higher rates of iron deficiency in the control group than studies that did not find a benefit, suggesting that

baseline risk is important in determining who will benefit from supplementation in terms of preventing iron deficiency.

Hemoglobin levels. Mean hemoglobin concentration was reported in eight studies, including one poor-quality study,[54] ranging from 116 to 126 g/L for children in the supplementation group and 111 to 120 g/L in the placebo group.[48-54,56] Five studies (one good-quality,[53] one poor-quality,[54] and three fair-quality[48,51,56]) reported no significant difference in hemoglobin values between groups. In contrast, three fair-quality studies reported significantly higher values in the iron-treated group.[49,50,52] Control group rates again varied widely, from 111 to 120.2 g/L across all studies. The most relevant evidence in this group of studies comes from the only study conducted in the United States (117 g/L in both groups)[48] and from the only good-quality study (118.6 vs. 120.2 g/L),[53] both of which found no significant difference between groups.

Serum ferritin levels. Serum ferritin concentrations were reported in nine trials, including one study of children at higher risk for iron deficiency anemia[47] and one poor-quality study,[54] ranging from 14 to 47.3 µg/L for children in the supplementation group and 8.7 to 35 µg/L in the placebo group at followup of 3 to 12 months.[46-54,56] Six of these studies, including a good-quality study, found significantly higher values in the treated group.[46,49,50,52,53,56] Studies finding a difference compared iron-fortified cow's milk, fortified formula, or iron drops with nonfortified milk or formula, placebo, or no specific intervention.

A good-quality study compared children eating two or more portions of red meat daily with children receiving iron-fortified milk and a control group of children receiving cow's milk, reporting median ferritin values after 20 weeks of 43.5 versus 32.8 versus 29.9 µg/L (effect size in fortified milk group, 1.68 [95% CI, 1.27 to 2.24]).[53] A trial of higher-risk children compared iron-supplemented formula with cow's milk and reported median ferritin concentrations of 30.5 µg/L in the treated group versus 15.9 µg/L in the control group (p=0.001). A second study of iron-fortified formula versus cow's milk in an average-risk population reported values of 21.7 versus 13.1 µg/L for iron-fortified formula versus cow's milk (p<0.001) and 21.7 versus 14.3 µg/L for iron-fortified versus nonfortified formula (p<0.001).[52] A study of children receiving iron-fortified versus nonfortified formula reported values of 25.1 versus 15.3 µg/L (p<0.001).[49] A study of iron drops reported mean ferritin values of 47.3 µg/L in the supplementation group and 22.9 µg/L in the placebo group (p<0.001).[56] Finally, Lozoff et al reported values of 14.0 µg/L in children supplemented with iron-fortified formula versus a low mean value of 8.7 µg/L in unsupplemented children (p<0.001).[50]

In contrast, two studies, including one conducted in the United States, found no difference between groups.[48,51] These studies reported ferritin values of 32.0 µg/L in children receiving oral multivitamin drops with 10 mg iron compared with 29.2 µg/L in children receiving multivitamin drops without iron, and 26 µg/L in children receiving a high-iron weaning diet compared with 35 µg/L in children receiving a control weaning diet.[48,51] The poor-quality study was very small and also found no difference between groups.[54]

In studies finding a significant difference, ferritin levels in the control groups ranged from 8.7 µg/L (study in Chile) to 29.9 µg/L (study in New Zealand), and in studies not finding a difference, they ranged from 29.2 to 35 µg/L. Additionally, three of the six studies finding a

difference used nonfortified cow's milk (a known risk factor for iron deficiency) as the control.

Key Question 2. What Are the Harms of Routine Iron Supplementation in Children Ages 6 to 24 Months?

Summary

Harms associated with routine iron supplementation were not well reported; the limited evidence indicates few adverse events, with no differences between treatment and placebo groups. No serious adverse events, including accidental overdose, were reported.

Evidence

Incidence of serious harms, including accidental overdose, was not reported in studies of iron supplementation (**Appendix B1**). One fair-quality trial stated that no clinically significant adverse events thought to be related to study interventions were reported.[49]

No study reported comparative evidence on withdrawals due to adverse events, although one study noted that a child consuming two or more meals of red meat per day discontinued because of dislike of the study-provided meals.[53] One good-quality study[53] and two fair-quality[48,52] studies reported rates of intervention adherence, which we considered a surrogate marker of discontinuation rates in the absence of data on withdrawals due to adverse events. A wide range of nonadherence was reported across the studies (9% to 59% in supplementation groups and 4% to 59% in control groups). Some between-group differences were observed, but the differences appear to be based on the type of supplement/control rather than the iron content. One study found that infants and toddlers given iron-fortified or nonfortified formula had significantly higher rates of nonadherence compared with those consuming regular cow's milk (22% [36/162] vs. 4% [7/166]; RR, 5.3 [95% CI, 2.42 to 11.5] and 23% [38/165] vs. 4% [7/166]; RR, 5.46 [95% CI, 2.52 to 11.88]).[52] In a second study, toddlers eating two or more meals of red meat per day were more likely to be nonadherent than children in the control group drinking nonfortified powdered cow's milk (30% [26/87] vs. 11% [9/85]; RR, 2.82 [95% CI, 1.41 to 5.66]). In the same study, there was no significant difference in nonadherence between those using fortified and nonfortified powdered cow's milk (19% [8/43] vs. 11% [9/85]; RR, 1.76 [95% CI, 0.73 to 4.23]).[53] There was also no significant difference in nonadherence between groups in a third study comparing multivitamin drops with or without iron supplementation, although nonadherence was higher in both the supplementation and control groups compared with the other two studies (41% vs. 41%; RR, 1.01 [95% CI, 0.83 to 1.22]).[48] There was no significant difference between supplementation and control groups in nonadherence in two poor-quality studies.[54,55]

One good-quality trial reported no difference in rates of gastrointestinal adverse events in toddlers consuming iron-fortified versus nonfortified milk (2% vs. 2%; RR, 1.0 [95% CI, 0.9 to 11]).[53] No other studies reported incidence of gastrointestinal adverse events. The prior USPSTF report[17,44] included evidence from a meta-analysis of 28 studies (published and unpublished RCTs and cohort studies) that found a slightly increased risk for diarrhea with iron supplementation (RR, 1.1 [95% CI, 1.0 to 1.2]).[62] The majority of studies included in this meta-

analysis were conducted in developing countries, and the age of the populations ranged from 2 days to 14 years.[31]

A recently published study provides some contextual evidence on the long-term harms of iron supplementation.[63] The study randomized 835 healthy Chilean infants without iron deficiency anemia to supplementation with low-iron formula (mean, 2.3 mg/L) or high-iron formula (mean, 12.7 mg/L, similar to levels in current iron-fortified formulas in the United States). It was not eligible for inclusion for this report because of the lack of a placebo/untreated control group. At 10 years' followup of 473 study participants (57%), those randomized to receive high-iron formula (particularly those with a hemoglobin level >12.8 g/L) scored lower on multiple developmental outcomes, including measures of visual and motor skills and mathematical ability, than those who had received low-iron formula, suggesting that supplementation of iron-replete children may unnecessarily expose children to harm. In most cases, the score differences between the low- and high-iron groups were small and not statistically significant. The generalizability of these study results to current populations in the United States is not clear.

Screening for Iron Deficiency Anemia in Children

Key Question 1. What Are the Benefits of Screening for Iron Deficiency Anemia in Asymptomatic Children Ages 6 to 24 Months on Child Health Outcomes?

No studies that evaluated screening programs for iron deficiency anemia in asymptomatic children ages 6 to 24 months were found, as was the case in the prior reviews.[17,44]

Key Question 2. What Are the Harms of Screening for Iron Deficiency Anemia in Children Ages 6 to 24 Months?

No studies that evaluated screening programs for iron deficiency anemia or harms of screening in asymptomatic children ages 6 to 24 months were found, as was the case in the prior reviews.[17,44]

Key Question 3. What Are the Benefits of Treatment of Iron Deficiency Anemia in Children Ages 6 to 24 Months on Child Health Outcomes?

No new studies of treatment of iron deficiency anemia with oral iron in infants and children ages 6 to 24 months were found.

The 2006 review included seven older trials of iron therapy, five of which used oral formulations.[21,22,64-66] These studies were conducted in England (one study), Chile (two studies), Guatemala (one study), and Indonesia (one study). The study most applicable to the U.S. population is the study conducted in England, which was rated poor-quality. It compared treatment for only 1 week with placebo and found no differences in psychomotor development outcomes using the Denver scale but improved hemoglobin and ferritin levels and growth

velocity in the treatment group.[64] No growth outcomes were reported.

Searches of other systematic reviews of treatment of iron deficiency anemia did not identify additional trials published prior to 1996 that were eligible for the current review.[60,67,68] Studies included in these reviews either were included in the prior report,[21,22,64-66] used injectable iron formulations,[69-71] were conducted in older children,[72] or were studies of supplementation of nonanemic children.[73]

Key Question 4. What Are the Harms of Iron Treatment in Children Ages 6 to 24 Months?

No newly published studies that reported harms of iron treatment in children ages 6 to 24 months were found.

One older RCT (n=334), published in 1991 and not included in the prior USPSTF review,[74] compared oral iron with placebo in children already receiving iron-fortified formula. This study reported no differences between iron- and placebo-treated children in incidence of overall or specific adverse events, including gastrointestinal events. Based on small short-term trials conducted in countries other than the United States, prior USPSTF reports concluded that there was no evidence on the relative harms of treatment.

Key Question 5. What Is the Association Between Change in Iron Status and Improvement in Child Health Outcomes in U.S.-Relevant Populations?

Summary

To answer this question, studies were required to include infants ages 6 to 24 months who were iron deficient (with or without anemia) at baseline and to report growth or neurodevelopmental outcomes for those children whose iron status did and did not improve over time. This design would allow for detection of any association between improvement in iron status and child health outcomes. We did not find any studies meeting these criteria. The only evidence found to indirectly answer this question were studies of iron supplementation in iron-sufficient children. One poor-quality study and two fair-quality studies found no difference between iron-supplemented and nonsupplemented infants in changes in iron status and measures of growth or development scale scores.

Evidence

Growth. Searches identified no studies directly meeting eligibility criteria for this Key Question that reported growth outcomes.

The best evidence available is indirect evidence from studies of iron supplementation in children ages 6 to 24 months. Three studies reported iron status and measures of growth at baseline and at followup (**Table 4**).[46,49,54] These studies are also included in Key Question 1.

Two studies were rated fair-quality and the other poor-quality (**Appendix B2**). The studies enrolled infants at age 6 months, with duration of followup ranging from 3 to 18 months. The two fair-quality studies compared iron-fortified formula with cow's milk and/or nonfortified formula, while the poor-quality study compared ferrous sulfate with placebo, with only 3 months' followup. While differences in iron status measures were reported in these studies, no differences in growth parameters were found between groups.

The largest study (n=406) randomized 6-month-old infants to iron-fortified formula (n=264), nonfortified formula (n=85), or cow's milk (n=57).[49] Baseline serum ferritin levels were 41.6, 42.3, and 31.9 μg/L, respectively, and corresponding hemoglobin levels were 118.9, 116.6, and 114.4 g/L, indicating that the infants enrolled in this study were iron replete at baseline. Although all groups had a significant decrease in ferritin levels in the first 3 months, both hemoglobin and ferritin levels were higher in the supplemented group after 9 months' followup (at age 15 months), particularly compared with the cow's milk group. Comparing the iron-supplemented group and the cow's milk group allows comparison of the largest differences in iron status and the corresponding change in growth. The supplemented group had better iron status measures at followup than the cow's milk group, but weight and length changes were not significantly different between groups (p-value not reported). The supplemented group's hemoglobin level increased by a mean of 2.6 g/L (range, 118.9 to 121.5 g/L) compared with a decrease of 3.0 g/L in the cow's milk group. Mean serum ferritin level decreased by 16.6 μg/L in the supplemented group versus 20.9 μg/L in the cow's milk group. Mean weight change in the supplemented group was 3.2 kg compared with 3.0 kg in the cow's milk group, and mean length change was 11.3 cm in the supplemented group compared with 12.2 cm in the cow's milk group.

The second fair-quality trial was smaller (n=84) and also compared iron-fortified formula with cow's milk.[46] At 18 months, mean changes in hemoglobin level were 5 versus −2 g/L and mean changes in serum ferritin level were 0.8 versus −19.7 μg/L in the supplemented and nonsupplemented groups, respectively. The study reported no difference in z-scores for measures of growth (e.g., weight for height, weight for age) but no data or p-values were reported.

The poor-quality study was very small (n=24) and reported differences favoring supplementation between groups in transferrin saturation and serum iron level but not hemoglobin or serum ferritin levels, and no difference between groups in measures of growth.[54]

Developmental scale scores. Only the small poor-quality study described above reported neurodevelopmental outcomes. As noted above, the study reported differences favoring supplementation between groups in transferrin saturation and serum iron level but not hemoglobin or serum ferritin levels. No difference between groups was found on the Bayley Scale mental or motor scores.[54]

Chapter 4. Discussion

Summary of Review Findings

Table 5 summarizes the evidence reviewed for this update.

As in the prior reviews, no trials assessed the effects of routine iron supplementation compared with placebo in children ages 6 to 24 months on diagnosis of psychomotor or neurodevelopmental delay or quality of life, and five of six trials reporting growth outcomes found no benefit of supplementation. Although not clearly clinical outcomes, developmental test scores after 3- to 12-month followup periods were reported in four trials, with mostly nonsignificant findings (**Table 2**; **Appendix B1**).[47,50,52,54] The clinical significance of these findings is unclear. These findings are similar to those in the prior reviews,[17,44] which also included evidence from developing countries. Several studies[46,49,50,52,53,56] (including two poor-quality studies[54,55]) reported growth outcomes, such as weight, length, and head circumference. All but the study by Lozoff et al[50] (in which the groups differed by weight and length at baseline) found no significant differences between groups. Similarly, a recent systematic review and meta-analysis of 21 RCTs showed no effects of iron intervention on growth parameters.[67]

Ten trials (in 11 publications) that assessed routine iron supplementation versus placebo or other control interventions in children reported inconsistent findings for incidence of iron deficiency anemia, iron deficiency, and anemia, as well as venous hemoglobin and serum ferritin concentrations.[46-56] Iron deficiency anemia was reported in five studies; of these, one good-quality study and two fair-quality studies in the United States found no differences between groups. One large study with a very high rate of iron deficiency anemia in the control group reported a significant benefit (RR, 0.14 [95% CI, 0.09 to 0.20]).[50] This same study and another fair-quality study[49] reported a significant benefit of supplementation on iron deficiency (RR, 0.52 [95% CI, 0.45 to 0.59]), with deficiency found in 6 percent of supplemented children versus 22 percent of unsupplemented children (RR not calculable from data reported). Two other studies, including one in the United States, found no difference between groups (RR, 0.94 [95% CI, 0.74 to 1.20] and 1.81 [95% CI, 0.38 to 8.60], respectively). Two of six studies reporting iron deficiency anemia found a significant benefit of iron supplementation (RR, 0.14 [95% CI, 0.09 to 0.20] and 0.07 [95% CI, 0.01 to 0.48]), although both trials had methodological shortcomings.[46, 47,50] Hemoglobin concentration was reported in eight studies and ferritin concentration was reported in nine studies, with conflicting results.[47-54,56]

Partly because of the variation in methods used to identify and define iron deficiency anemia, iron deficiency, and anemia, incidence rates in control groups varied widely across these studies. Additional factors may have contributed to this variability, such as the unknown mixture of baseline risk in enrolled children (e.g., proportion of control group using nonfortified cow's milk as the primary nutrition source), which were rarely reported and not analyzed, so further analysis with risk stratification could not be undertaken. As mentioned, children receiving cow's milk may be a flawed comparison group, as cow's milk is considered a risk factor for iron deficiency anemia, and its consumption is advised against before age 12 months by IOM, AAP, and CDC. For these reasons, the inconsistencies in this evidence cannot be resolved and the interpretability

of these findings for populations in the United States is somewhat limited. Sample sizes were not calculated a priori in some cases, and some studies were not powered to detect differences for specific outcomes.

Harms of routine iron supplementation in children were rarely reported. No studies reported accidental overdose. One good-quality trial reported no difference in rates of gastrointestinal adverse events in toddlers consuming iron-fortified milk and those consuming nonfortified milk (2% vs. 2%; RR, 1.0 [95% CI, 0.9 to 11]),[53] and one other trial reported no clinically significant adverse events that investigators judged to be due to study interventions. Other harms were not reported. This result was similar to findings in the prior USPSTF reports,[17,44] which included evidence from a meta-analysis of 28 studies (published and unpublished RCTs and cohort studies) and found a slightly increased risk for diarrhea with iron supplementation (RR, 1.1 [95% CI, 1.0 to 1.2]).[62] The majority of studies included in this meta-analysis were conducted in developing countries, and the age of the populations ranged from 2 days to 14 years.

As in the prior USPSTF reports, no trials were identified to address the Key Questions on the benefits or harms of screening for iron deficiency anemia in children ages 6 to 24 months. No new trials addressed treatment of iron deficiency anemia in children ages 6 to 24 months. The prior USPSTF reviews included trials of treatment conducted in mostly developing countries; the only study conducted in a country directly generalizable to the United States (England) was rated poor-quality.[64] This study compared treatment for 1 week versus placebo and found no differences in psychomotor development outcomes but improved hemoglobin and ferritin levels and growth velocity in the treatment group. Finally, no new studies reported harms of treatment of iron deficiency anemia, although we identified an older trial[74] that reported no differences between iron- and placebo-treated children in incidence of overall or specific adverse events, including gastrointestinal events. Based on small short-term trials conducted in countries other than the United States, prior USPSTF reports concluded that there was no evidence on the relative harms of treatment.

No studies that assessed an association between change in iron-deficient status and differences in growth or development were found. Indirect evidence from three studies of infants who were iron replete at baseline but showed increased iron status with supplementation did not find an association between this change and growth or developmental outcomes.

Limitations

Limitations of our report include restricting inclusion to studies published in English, RCTs and controlled observational studies, and studies conducted in developed countries or developing countries where the enrolled population was similar to the U.S. population, particularly in terms of rates of malnutrition, hemoparasite burden, and general socioeconomic status. Numerous studies of iron supplementation and treatment that were conducted in developing countries were excluded.[75-81] Malnourishment, very low socioeconomic status, and/or presence of parasitic endemic diseases were common in included populations in these studies. We also excluded studies of iron supplementation that enrolled children younger than age 6 months, as this population was determined to be outside the scope of this review.[82-85]

Limitations of the evidence are described throughout the report and can be summarized as lack of adequate sample sizes, inconsistency in method and timing of outcome measurement, and lack of reporting of clinical outcomes.

Emerging Issues

We did not identify ongoing studies or emerging issues relevant to a U.S.-applicable population.

Relevance for Priority Populations

Race or ethnicity was not reported in most studies. It was predominately white in two studies[46,47,53] and approximately half black in one study conducted in the United States.[48] This provides limited ability to extrapolate on any racial or ethnic issues.

Future Research

Good-quality RCTs of routine supplementation and screening programs for iron deficiency anemia in children ages 6 to 24 months that have adequate sample sizes are needed. Such trials should more clearly report baseline characteristics of enrolled children and details of interventions and harms, in addition to examining longer-term benefits, especially clinical and developmental outcomes using appropriate neurodevelopmental tests. The clinical significance of developmental test scores is unclear.

Conclusions

More research is needed to assess the benefits and harms of routine iron supplementation to prevent iron deficiency anemia, and screening for and treatment of iron deficiency anemia, in children ages 6 to 24 months. While some evidence is available showing improvements in hematological values, trials reporting clinical outcomes, including developmental outcomes, are lacking.

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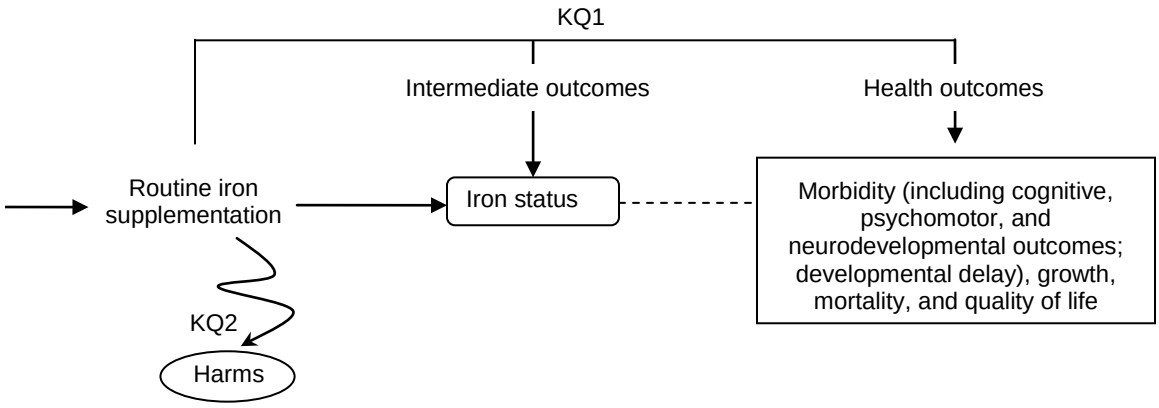
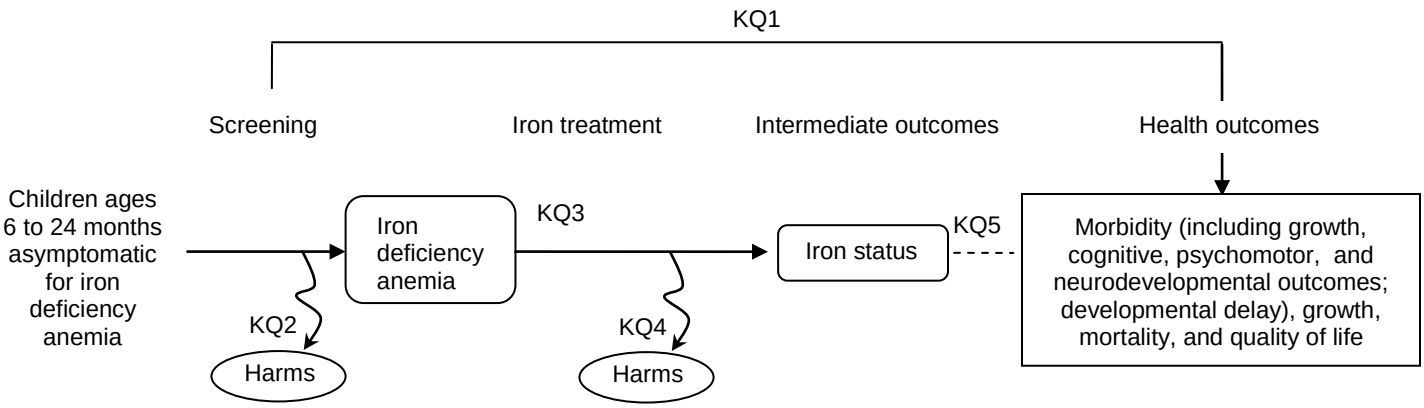
Figure 1. Analytic Framework for Routine Iron Supplementation in Children



Key Questions

1. What are the benefits of routine iron supplementation in children ages 6 to 24 months on child health outcomes?
2. What are the harms of routine iron supplementation in children ages 6 to 24 months?

Figure 2. Analytic Framework for Screening for Iron Deficiency Anemia in Children



Key Questions

1. What are the benefits of screening for iron deficiency anemia in asymptomatic children ages 6 to 24 months on child health outcomes?
2. What are the harms of screening for iron deficiency anemia in children ages 6 to 24 months?
3. What are the benefits of treatment of iron deficiency anemia in children ages 6 to 24 months on child health outcomes?
4. What are the harms of iron treatment in children ages 6 to 24 months?
5. What is the association between change in iron deficiency anemia status and improvement in child health outcomes in U.S.-relevant populations?

Contextual Question (not systematically reviewed)

1. How well does risk assessment identify children who are at increased risk for iron deficiency anemia?

Table 1. Association Between Demographic Characteristics and Iron Deficiency

	Data Source			
Demographic Characteristic	**NHANES, 1988–1994[16]**	**NHANES, 1976–2002[10]**	**NHANES, 1999–2002[41]**	**California WIC Applicants/Participants, 2000–2002[42]**
	Adjusted Odds Ratio (95% CI)[a]			
Hispanic ethnicity Reference: white or non-Hispanic	2.9 (1.5 to 5.6)	1.7 (1.02 to 2.9)	0.94 (0.36 to 2.45)	3.0 (0.6 to 14)[b]
Weight/height ratio ≥95th percentile Reference: <85th percentile	2.0 (0.98 to 3.9)	2.8 (1.7 to 4.3)	3.34 (1.1 to 10)	
Income <Federal poverty level Reference: >Federal poverty level	1.5 (0.6 to 3.9)	1.4 (0.97 to 1.9)		
Birth weight <2,500 g Reference: ≥2,500 g	1.3 (0.6 to 3.2)	1.6 (0.9 to 2.6)		
Male sex Reference: female sex	0.9 (0.5 to 1.4)			2.0 (1.05 to 3.7)
Bottle feeding >1 year Bottle feeding >2 years Reference: bottle feeding <1 year	2.1 (1.0 to 4.4) 2.8 (1.3 to 6.0)			
Pregnant mother Reference: Nonpregnant mother				2.5 (1.04 to 6.0)
Mother participating in WIC during pregnancy Reference: no WIC participation during pregnancy				0.4 (0.2 to 0.8)
Residence in an urban area Reference: residence in a rural area				2.1 (1.1 to 3.9)

Abbreviations: CI=confidence interval; NHANES=National Health and Nutrition Examination Survey; WIC=Women, Infants, and Children Special Supplementation Nutrition Program.

[a]All studies conducted multivariate analyses adjusting for potential confounders.
[b]94% of study participants were Hispanic.

Table 2. Child Bayley Scale Outcomes in Iron Supplementation Studies

				Supplementation vs. Control	
Study, Year Country n Quality	**Duration**	**Risk Factors Reported**	**Interventions and Comparator**	**Mental Development Index**	**Psychomotor Development Index**
Lozoff, 2003[50] Chile n=1,657 Fair	6 months	Race: NR Preterm and low birth weight infants excluded	A. Multiple interventions with varying iron concentrations B. No iron supplementation	103.9 vs. 104.6; p=NS	96.7 vs. 97.5; p=NS
Morley, 1999[52] United Kingdom n=428 Fair	9 months	Race: NR Preterm and low birth weight infants excluded	A. Iron-fortified formula, 1.2 mg iron/L B. Unfortified formula, 0.9 mg iron/L C. Cow's milk	93.9 vs. 94.5 vs. 96.2; p=NS	94.8 vs. 94.6 vs. 93.6; p=NS

Abbreviations: NR=not reported; NS=not significant.

Note 1: Cutoffs used for Bayley Scale Mental and Psychomotor Development Index scores vary, but several authors suggest that scores <85 represent moderate developmental delay, while scores <70 represent severe delay.[57,58]
Note 2: One additional fair-quality study conducted in the United Kingdom (n=92) reported developmental test scores using the Griffiths scale.[47] Scores declined in both groups over the course of the study but declined somewhat less in the iron-supplemented group (general quotient score at 24 months, −9.3 vs. −14.7; p=0.04). The clinical meaning of this difference (5.4) is unclear, particularly because both group's scores at 24 months were within normal limits.
Note 3: One trial omitted from table due to poor-quality rating (Yalcin, 2000[54]).

Table 3. Good- and Fair-Quality Trials of Iron Supplementation in Children Ages 6 to 24 Months on Hematological Outcomes

			Supplementation vs. Control				
Study, Year Country n Duration Quality	**Risk Factors Reported**	**Interventions and Comparator**	**Hemoglobin**	**Serum Ferritin**	**Iron Deficiency[a]**	**Anemia (Hb <110 g/L)**	**Iron Deficiency Anemia (Hb <110 g/L and Iron Deficiency[a])**
Domellof, 2001[56] Sweden n=70 3 months Fair	Race: NR Preterm and low birth weight infants excluded	A. Placebo from 4 to 6 months and iron supplement from 6 to 9 months (n=34) B. Placebo from 4 to 9 months (n=36)	117.1 vs. 114.4 g/L; p=NS	47.3 vs. 22.9 µg/L; p<0.001			No effect (numbers NR)
Geltman, 2004[48] United States n=284 3 months Fair	Race: 55% vs. 48% black Preterm and low birth weight infants excluded	A. Oral multivitamin drops, 10 mg iron/day B. Multivitamin drops without iron	117 vs. 117 g/L; p=NS	32.0 vs. 29.2 µg/L; p=NS	78% (108/138) vs. 84% (121/144) had 1 abnormal hematological value indicative of iron deficiency; RR, 0.93, (95% CI, 0.83 to 1.04)	22% (31/138) vs. 19% (27/144); RR, 1.20 (95% CI, 0.76 to 1.90)	8% (11/138) vs. 8% (11/144) anemic and had 2 other abnormal hematological values; RR, 1.04 (95% CI, 0.47 to 2.33)
Gill, 1997[49] United Kingdom and Ireland n=302 11 months Fair	Race: NR Preterm and low birth weight infants excluded	A. Iron-fortified formula B. Unfortified formula C. Cow's milk	121.5 vs. 117.7 vs. 111.4 g/L[b]; p=0.006	25.1 vs. 15.3 vs. 11.0 µg/L; p<0.001	6% vs. 22% vs. 43%[c]	11% vs. 13% vs. 33%[c]	
Lozoff, 2003[50] Chile n=1,657 6 months Fair	Race: NR Preterm and low birth weight infants excluded	A. Multiple interventions with varying iron concentrations B. No iron supplementation	123.6 vs. 115.6 g/L; p<0.001	14.0 vs. 8.7 µg/L; p<0.001	26.5% (286/1081) vs. 51.3% (273/532); RR, 0.52 (95% CI, 0.45 to 0.59)	4.3% (48/1123) vs. 25.8% (138/534); RR, 0.17 (95% CI, 0.12 to 0.23)	3.1% (34/1114) vs. 22.6% (116/514); RR, 0.14 (95% CI, 0.09 to 0.20)
Makrides, 1998[51] Australia n=62 6 months Fair	Race: NR Preterm and low birth weight infants excluded	A. High-iron weaning diet B. Control weaning diet	120 vs. 115 g/L; p=NS	26 vs. 35 µg/L; p=NS	3.9% (5/36) vs. 7.7% (2/26); RR, 1.81 (95% CI, 0.38 to 8.60)	0 vs. 19.2% (5/26); RR, 0.07 (95% CI, 0.00 to 1.15)	0 vs. 0
Morley, 1999[52] United Kingdom n=428 9 months Fair	Race: NR Preterm and low birth weight infants excluded	A. Iron-fortified formula, 1.2 mg iron/L B. Unfortified formula, 0.9 mg iron/L C. Cow's milk	126 vs. 120 vs. 119 g/L; p<0.01 for A vs. C, p<0.05 for A vs. B	21.7 vs. 13.1 vs. 14.3 µg/L; p<0.0001 for A vs. B and A vs. C			

Table 3. Good- and Fair-Quality Trials of Iron Supplementation in Children Ages 6 to 24 Months on Hematological Outcomes

			Supplementation vs. Control				
Study, Year Country n Duration Quality	**Risk Factors Reported**	**Interventions and Comparator**	**Hemoglobin**	**Serum Ferritin**	**Iron Deficiency[a]**	**Anemia (Hb <110 g/L)**	**Iron Deficiency Anemia (Hb <110 g/L and Iron Deficiency[a])**
Szymlek-Gay, 2009[53] New Zealand n=225 5 months Good	Race: 76% vs. 84% vs. 78% white	A. ≥2 portions of red meat, 1.3 mg iron per portion B. Iron-fortified milk, 1.5 mg iron/100 g C. Cow's milk	121.5 vs. 118.6 vs. 120.2 g/L; p=NS	43.5 vs. 32.8 vs. 29.9 µg/L; effect size in fortified milk group, 1.68 (95% CI, 1.27 to 2.24)			No difference between groups (data only reported in a figure)
Williams, 1999[47] Other publication: Daly, 1996[46] United Kingdom n=92 10 to 12 months Fair	Race: 74% white, 24% black, 2% Asian Receiving income support: 59% Preterm and low birth weight infants excluded	A. Iron-supplemented formula, 1.2 mg iron/100 mL B. Cow's milk		30.5 vs. 15.9 µg/L; p=0.001		At age 18 months: 2% (1/46) vs. 33% (15/46); RR, 0.07 (95% CI, 0.01 to 0.48)	

Abbreviations: CI=confidence interval; Hb=hemoglobin; NR=not reported; NS=not significant; RR=relative risk.

[a]Iron deficiency was defined variably as serum ferritin <10,[49,51,54] <15,[48] or <12 µg/L in addition to 1 of 2 other hematological indicators.[50]
[b]Groups differed significantly at baseline.
[c]RR not calculable based on data reported.

Note: Two trials omitted from table due to poor-quality rating (Yalcon, 2000[54] and Yeung, 2000[55]).

Table 4. Association Between Change in Iron Status and Health Outcomes

Study, Year Country n Quality	Duration	Intervention Groups	Baseline Iron Status	Follow-Up Iron Status	Mean Change in Iron Status	Health Outcomes
Daly, 1996[46] United Kingdom n=84 Fair	18 months	A. Iron-fortified formula (n=41) B. Cow's milk (n=43)	A vs. B Hemoglobin: 119 vs. 120 g/L Serum ferritin: 33.2 vs. 34.6 µg/L	A vs. B Hemoglobin: 124 vs. 118 g/L Serum ferritin: 32.4 vs. 14.9 µg/L	A vs. B Hemoglobin: 5.0 vs. −2.0 g/L (p<0.0001) Serum ferritin: 0.8 vs. −19.7 µg/L (p<0.0001)	A vs. B No difference between groups in weight for age, weight for height, or height for age (data not shown)
Gill, 1997[49] United Kingdom and Ireland n=406 Fair	9 months	A. Iron-fortified formula (n=264) B. Unfortified formula (n=85) C. Cow's milk (n=57)	A vs. B vs. C Hemoglobin: 118.9 vs. 116.6 vs. 114.4 µg/L Serum ferritin: 41.6 vs. 42.3 vs. 31.9 µg/L Serum iron: 14.9 vs. 13.9 vs. 12.5 mmol/L Total iron binding capacity: 61.1 vs. 59.0 vs. 64.9 mmol/L	A vs. B vs. C Hemoglobin: 121.5 vs. 117.7 vs. 111.4 µg/L Serum ferritin: 25.1 vs. 15.3 vs. 11.0 µg/L Serum iron: 14.4 vs. 12.9 vs. 10.0 mmol/L Total iron binding capacity: 63.0 vs. 70.3 vs. 73.2 mmol/L	A vs. B vs. C Hemoglobin: 2.6 vs. 1.1 vs. −3.0 µg/L (A vs. B and C; p<0.01) Serum ferritin: −16.5 vs. −27.0 vs. −20.9 µg/L (A vs. B and C, p<0.001) Serum iron: −0.5 vs. −1.0 vs. −2.5 mmol/L (A vs. B and C; p=0.04) Total iron binding capacity: 1.9 vs. 11.3 vs. 8.3 mmol/L (A vs. B and C; p=0.05)	A vs. B vs. C Weight, mean change from baseline: 11.1 (3.2) vs. 11.1 (3.1) vs. 11.3 (3.0) kg (p=NS for all comparisons) Length, mean change from baseline: 79.1 (11.3) vs. 78.9 (11.5) vs. 80.3 (12.2) cm (p=NS for all comparisons)

Abbreviation: NS=not significant.

Note: Poor-quality trial omitted from table (Yalcin, 2000[54]).

Table 5. Summary of Evidence

Routine Iron Supplementation in Children

Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 1. What are the benefits of routine iron supplementation in children ages 6 to 24 months on child health outcomes?						
Clinical outcomes						
No evidence on clinical outcomes. Mixed results were found on the effect of iron supplementation on child developmental test scores in developing and developed countries	Growth: 6 trials Developmental test scores: 4 trials	No trials reported developmental diagnoses or other clinical outcomes; the clinical implications of test scores are unclear	Growth: consistent Developmental test scores: inconsistent	1 trial was conducted in Turkey and 1 in Chile	Evidence from 5 of 6 trials found no difference in short-term growth parameters between supplemented and nonsupplemented groups. The sixth trial was methodologically flawed, with important differences at baseline. None of the 3 studies that used the Bayley Scale of Infant Development reported significant differences in developmental test scores between groups. Another trial found that scores on the Griffiths scale, a measure of psychomotor development, declined in both groups over the course of the study but declined somewhat less in the iron-supplemented group after 24 months (p=0.04). No trials assessed the effect of routine iron supplementation on other clinical outcomes.	Growth: Fair Developmental test scores: Poor
Intermediate outcomes						
Older studies of supplementation found reduced incidence of iron deficiency and iron deficiency anemia based on evidence in developing and developed countries. These studies were not reassessed in the 2006 update	10 trials	Interventions were widely variable, some studies were conducted in developing countries, and many studies had high attrition or exclusion from analysis	Inconsistent	1 trial was conducted in Turkey and 1 in Chile. Others in U.S. or countries with similar economic profile	A significant benefit of supplementation was reported in 1 of 5 trials reporting iron deficiency anemia (RR, 0.14 [95% CI, 0.09 to 0.20]); 2 of 5 trials reporting iron deficiency (RR, 0.52 [95% CI, 0.45 to 0.59]) and 6% of supplemented children vs. 22% of unsupplemented children (RR not calculable); and 2 of 6 trials reporting anemia (RR, 0.14 [95% CI, 0.09 to 0.20] and RR, 0.07 [95% CI, 0.01 to 0.48]). 1 trial, which had methodological flaws, found beneficial effects for all 3 outcomes.	Fair

Table 5. Summary of Evidence

Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 2. What are the harms of routine iron supplementation in children ages 6 to 24 months?						
Harms included were gastrointestinal symptoms and fatal overdose, though evidence from controlled trials was lacking. 1 meta-analysis reported an 11% increase in risk for diarrhea.	2 trials	Harms were rarely reported	Consistent	1 study conducted in New Zealand used a nonstandard intervention (red meat)	1 trial reported no difference in rates of gastrointestinal adverse events between toddlers receiving iron-fortified milk and those consuming unfortified milk (RR, 1.0 [95% CI, 0.9 to 11]), while another trial stated that no clinically significant adverse events were judged by investigators to be attributable to study interventions. Some between-group differences were observed in nonadherence; however, the differences appear to be based on the type of supplement/control rather than the iron content. Other harms were not reported.	Poor

Screening for Iron Deficiency Anemia in Children

Main findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 1. What are the benefits of screening for iron deficiency anemia in asymptomatic children ages 6 to 24 months on child health outcomes?						
No controlled trials evaluated screening for iron deficiency anemia	No studies	No studies	N/A	N/A	No evidence	N/A
Key Question 2. What are the harms of screening for iron deficiency anemia in children ages 6 to 24 months?						
No studies evaluated harms of screening for iron deficiency anemia	No studies	No studies	N/A	N/A	No evidence	N/A
Key Question 3. What are the benefits of treatment of iron deficiency anemia in children ages 6 to 24 months on child health outcomes?						
7 trials of treatment for iron deficiency anemia reported few benefits of treatment on psychomotor development outcomes in mostly developing countries	No studies	No studies	N/A	N/A	No evidence	N/A
Key Question 4. What are the harms of iron treatment in children ages 6 to 24 months?						
Harms of iron treatment were considered to be similar to harms of iron supplementation and were not directly assessed	No studies	No studies	N/A	N/A	No evidence	N/A
Key Question 5. What is the association between a change in iron status and improvement in child-health outcomes in U.S.-relevant populations?						
Not assessed	No studies	No studies	N/A	N/A	No evidence	N/A

Abbreviations: CI=confidence interval; N/A= not applicable; RR=relative risk.

[a]"Overall quality" is based on new evidence identified for this update plus previously reviewed evidence.

Appendix A1. Search Strategies

Supplementation: Key Questions 1 and 2

Database: Ovid MEDLINE(R) without Revisions
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
5 pc.fs.
6 Dietary Supplements/
7 Iron/
8 6 and 7
9 (iron adj2 supplemen$).mp.
10 Iron, Dietary/ad [Administration & Dosage]
11 or/8-10
12 4 and 5
13 4 and 11
14 12 or 13
15 limit 14 to humans
16 limit 15 to english language
17 limit 15 to abstracts
18 (infan$ or pediatr$ or neonate$ or newborn or child$ or offspring).mp.
19 17 and 18

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 pc.fs.
6 Dietary Supplements/
7 Iron/
8 6 and 7
9 (iron adj2 supplemen$).mp.
10 Iron, Dietary
11 or/8-10
12 4 and 5
13 4 and 11
14 12 or 13
15 (infan$ or pediatr$ or neonate$ or newborn or child$ or offspring).mp.
19 14 and 15

Screening: Key Questions 1 and 2

Database: Ovid MEDLINE(R) without Revisions
1. exp Anemia, Iron-Deficiency/
2. "iron deficiency anemia".mp.
3. ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4. or/1-3
5. exp Mass Screening/
6. screen$.mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to "all infant (birth to 23 months)"
10. limit 9 to humans
11. limit 10 to english language
12. limit 10 to abstracts

13. 11 or 12

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 exp Mass Screening/
6 screen$.mp.
7 5 or 6 (12598)
8 4 and 7 (25)

Treatment: Key Questions 3 and 4

Database: Ovid MEDLINE(R) without Revisions
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 Infant Formula/
6 Iron, Dietary/
7 (de or dt or th).fs.
8 4 and 7
9 4 and (5 or 6)
10 8 or 9
11 (infan$ or neonate$ or newborn or child$ or offspring).mp.
12 10 and 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 Infant Formula/
6 Iron, Dietary
7 (de or dt or th).fs.
8 4 and 7
9 4 and (5 or 6)
10 8 or 9
11 (infan$ or neonate$ or newborn or child$ or offspring).mp.
12 10 and 11

Association: Key Question 5

Database: Ovid MEDLINE(R) without Revisions
1 Iron/
2 Iron, Dietary/
3 Anemia, Iron-Deficiency/
4 1 or 2
5 4 and (anemia or anemic or deficiency or deficient).mp.
6 3 or 5
7 Treatment Outcome/
8 6 and 7
9 6 and association.mp.
10 8 or 9

11 limit 10 to humans
12 limit 11 to english language

Systematic Reviews: All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 iron deficiency anemia.mp.
2 ("iron deficiency" adj2 anemia).mp.
3 1 or 2

Iron Deficiency Without Anemia: All Key Questions

Database: Ovid MEDLINE(R) without Revisions
1 Iron/df [Deficiency]
2 limit 1 to "all infant (birth to 23 months)"
3 (infan$ or neonate$ or newborn or child$ or offspring).mp
4 1 and 3
5 2 or 4
6 limit 5 to humans
7 limit 6 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Iron/df [Deficiency]
2 limit 1 to "all infant (birth to 23 months)"
3 (infan$ or neonate$ or newborn or child$ or offspring).mp
4 1 and 3
5 2 or 4

Appendix A2. Inclusion and Exclusion Criteria

Routine Iron Supplementation in Children

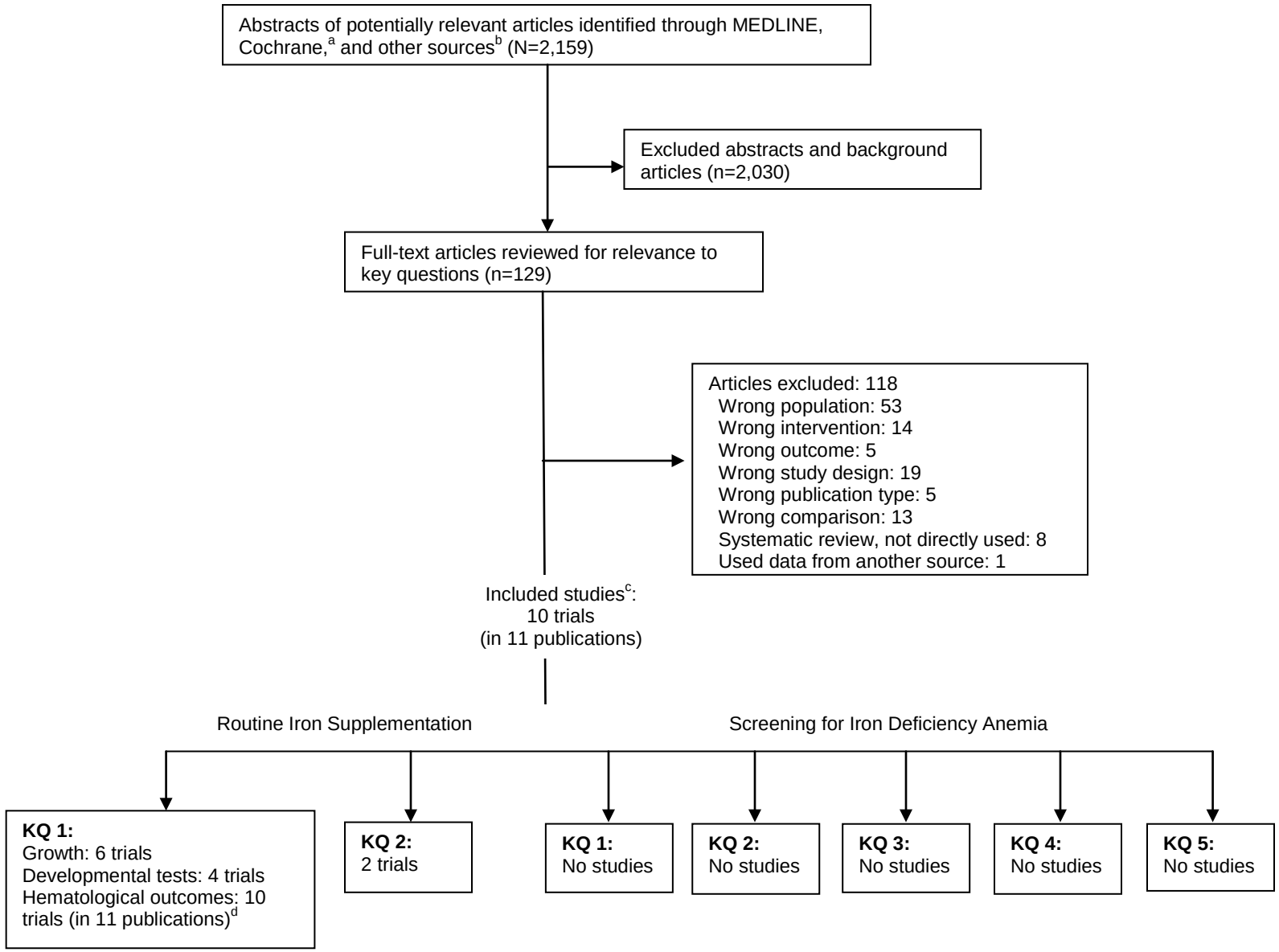
	Include	Exclude
Populations	Children ages 6 to 24 months	Severely malnourished children who are not representative of those in the United States
Interventions	Oral iron supplementation; iron-fortified formulas and foods	Injectable forms of iron
Comparators	No supplementation	
Outcomes	**KQ 1:** Morbidity (including cognitive, psychomotor, and neurodevelopmental outcomes; developmental delay), growth, mortality, quality of life; incidence of iron deficiency anemia; incidence of iron deficiency; hematological indices and ferritin levels **KQ 2:** More serious harms; discontinuations; accidental overdose	
Settings	Primary care relevant	
Timing	**KQ 1:** Long term **KQ 2:** Short or long term	
Study Designs	**KQ 1:** Randomized, controlled trials; controlled cohort studies and other controlled observational studies (KQ1) **KQ 2:** Studies from KQ 1 and large uncontrolled observational studies	**KQ 1:** Uncontrolled studies

Screening for Iron Deficiency Anemia in Children

	Include	Exclude
Populations	**KQs 1, 2:** Asymptomatic children ages 6 to 24 months **KQs 3, 4:** Children ages 6 to 24 months with iron deficiency anemia **KQ 5:** Children with iron deficiency, with or without anemia	• Severely malnourished children who are not representative of those in the United States • Children who are symptomatic for iron deficiency anemia • Children ages <6 or >24 months
Interventions	**KQs 1, 2:** Screening for iron deficiency anemia **KQs 3, 4:** Oral iron treatment; iron-fortified formulas and foods	Injectable forms of iron
Comparators	**KQs 1, 2:** No screening for iron deficiency anemia **KQs 3, 4:** No treatment **KQ 5:** Change in iron deficiency and/or iron deficiency anemia status	
Outcomes	**KQs 1, 3, 5:** Morbidity (including growth, cognitive, psychomotor, and neurodevelopmental outcomes; developmental delay), growth, mortality, quality of life **KQ 2:** Overdiagnosis, anxiety, labeling **KQ 3:** Incidence of iron deficiency anemia; incidence of iron deficiency; hematological indices and ferritin levels **KQ 4:** More serious harms; discontinuations and overtreatment	
Settings	U.S. primary care relevant	
Timing	**KQs 1, 3:** Long term **KQs 2, 4, 5:** Short or long term	
Study Designs	**KQs 1, 3:** Randomized, controlled trials; controlled cohort studies and other controlled observational studies **KQs 2, 4:** Studies included from other KQs and large uncontrolled observational studies **KQ 5:** Longitudinal studies	**KQs 1, 3:** Uncontrolled studies **KQ 5:** Case-control and cross-sectional studies

Abbreviation: KQ=key question.

Appendix A3. Literature Flow Diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
[b] Other sources include prior reports, reference lists of relevant articles, and systematic reviews
[c] Some studies are included for more than one key question.
[d] Including 2 poor-quality studies.

Appendix A4. Excluded Studies

Wrong Population

Abdelrazik N, Al-Haggar M, Al-Marsafawy H, et al. Impact of long-term oral iron supplementation in breast-fed infants. *Indian J Pediatr*. 2007;74(8):739-45.

Adetifa I, Okomo U. Iron supplementation for reducing morbidity and mortality in children with HIV. *Cochrane Database Syst Rev*. 2009(1):CD006736.

Aranda N, Ribot B, Garcia E, et al. Pre-pregnancy iron reserves, iron supplementation during pregnancy, and birth weight. *Early Hum Dev*. 2011;87(12):791-7.

Arvas A, Elgormus Y, Gur E, et al. Iron status in breast-fed full-term infants. *Turk J Pediatr*. 2000;42(1):22-6.

Berger J, Ninh N, Khan N, et al. Efficacy of combined iron and zinc supplementation on micronutrient status and growth in vietnamese infants. *Eur J Clin Nutr*. 2006;60(4):443-54.

Berglund S, Westrup B, Domellof M. Iron supplements reduce the risk of iron deficiency anemia in marginally low birth weight infants. *Pediatrics*. 2010;126(4):e874-83.

Black MM, Baqui AH, Zaman K, et al. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. *Am J Clin Nutr*. 2004;80(4):903-10.

Capozzi L, Russo R, Bertocco F, et al. Effect on haematological and anthropometric parameters of iron supplementation in the first 2 years of life. Risks and benefits. *Hematol*. 2011;16(5):261-4.

Casanueva E, Viteri FE, Mares-Galindo M, et al. Weekly iron as a safe alternative to daily supplementation for nonanemic pregnant women. *Arch Med Res*. 2006;37(5):674-82.

de Silva A, Atukorala S, Weerasinghe I, et al. Iron supplementation improves iron status and reduces morbidity in children with or without upper respiratory tract infections: a randomized controlled study in Colombo, Sri Lanka. *Am J Clin Nutr*. 2003;77(1):234-41.

Dijkhuizen MA, Wieringa FT, West CE, et al. Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. *J Nutr*. 2001;131(11):2860-5.

Eickmann SH, Brito CM, Lira PI, et al. Effectiveness of weekly iron supplementation on hemoglobin concentration, nutritional status and development of infants of public daycare centers in Recife, Pernambuco State, Brazil [Spanish]. *Cad Saude Publica*. 2008;24(Suppl 2):S303-11.

Engstrom EM, Castro IR, Portela M, et al. Effectiveness of daily and weekly iron supplementation in the prevention of anemia in infants. *Revista de Saude Publica*. 2008;42(5):786-95.

Ermis B, Demirel F, Demircan N, et al. Effects of three different iron supplementations in term healthy infants after 5 months of life. *J Trop Pediatr*. 2002;48(5):280-4.

Finkelstein Y, Wahl MS, Bentur Y, et al. Universal versus selective iron supplementation for infants and the risk of unintentional poisoning in young children: a comparative study of two populations. *Ann Pharmacother*. 2007;41(3):414-9.

Fischer Walker CL, Baqui AH, Ahmed S, et al. Low-dose weekly supplementation of iron and/or zinc does not affect growth among Bangladeshi infants. *Eur J Clin Nutr*. 2009;63(1):87-92.

Franco E, Hertrampf E, Hazbun J, et al. Iron supplementation in Chilean Mapuche infants of the Cautin Province, Chile [Spanish]. *Arch Latinoam Nutr*. 1996;46(2):118-21.

Friel JK, Aziz K, Andrews WL, et al. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. *J Pediatr*. 2003;143(5):582-6.

Ghorashi Z, Nezami N, Ghalehgolab Behbahan A, et al. Supplemental food may not prevent iron-deficiency anemia in infants. *Indian J Pediatr*. 2008;75(11):1121-4.

Gupta SK, Bansal D, Malhi P, et al. Developmental profile in children with iron deficiency anemia and its changes after therapeutic iron supplementation. *Indian J Pediatr*. 2010;77(4):375-9.

Halterman JS, Kaczorowski JM, Aligne CA, et al. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics*. 2001;107(6):1381-6.

Appendix A4. Excluded Studies

Huang SC, Yang YJ, Cheng CN, et al. The etiology and treatment outcome of iron deficiency and iron deficiency anemia in children. *J Pediatr Hematol Oncol*. 2010;32(4):282-5.

Idjradinata P, Watkins WE, Pollitt E. Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet*. 1994;343(8908):1252-4.

Kapur D, Sharma S, Agarwal KN. Effectiveness of nutrition education, iron supplementation or both on iron status in children. *Indian Pediatr*. 2003;40(12):1131-44.

Kordas K, Stoltzfus RJ, Lopez P, et al. Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *J Pediatr*. 2005;147(5):632-9.

Lind T, Lonnerdal B, Stenlund H, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: interactions between iron and zinc. *Am J Clin Nutr*. 2003;77(4):883-90.

Lind T, Lönnerdal B, Stenlund H, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. *Am J Clin Nutr*. 2004;80(3):729-36.

Lind T, Seswandhana R, Persson LA, et al. Iron supplementation of iron-replete Indonesian infants is associated with reduced weight-for-age. *Acta Paediatrica*. 2008; 97(6):770-5.

Lopez de Romana G, Cusirramos S, Lopez de Romana D, et al. Efficacy of multiple micronutrient supplementation for improving anemia, micronutrient status, growth, and morbidity of Peruvian infants. *J Nutr*. 2005;135(3):646S-52.

Lozoff B, Brittenham GM, Viteri FE, et al. The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants. *J Pediatr*. 1982;100(3):351-7.

Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*. 2000;105(4):E51.

Lukowski AF, Koss M, Burden MJ, et al. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. *Nutr Neurosci*. 2010;13(2):54-70.

Majumdar I, Paul P, Talib VH, et al. The effect of iron therapy on the growth of iron-replete and iron-deplete children. *J Trop Pediatr*. 2003;49(2):84-8.

Nagpal J, Sachdev HP, Singh T, et al. A randomized placebo-controlled trial of iron supplementation in breastfed young infants initiated on complementary feeding: effect on haematological status. *J Health Popul Nutr*. 2004;22(2):203-11.

Nogueira Arcanjo FP, Santos PR, Costa Arcanjo CP, et al. Daily and weekly iron supplementations are effective in increasing hemoglobin and reducing anemia in infants. *J Trop Pediatr*. 2013;59(3):175-9.

Olney DK, Pollitt E, Kariger PK, et al. Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old. *J Nutr*. 2006;136(9):2427-34.

Pinsk V, Levy J, Moser A, et al. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr Med Assoc J*. 2008;10(5):335-8.

Pollitt E, Saco-Pollitt C, Jahari A, et al. Effects of an energy and micronutrient supplement on mental development and behavior under natural conditions in undernourished children in Indonesia. *Eur J Clin Nutr*. 2000;54(Suppl 2):S80-90.

Rosado JL, López P, Muñoz E, et al. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *Am J Clin Nutr*. 1997;65(1):13-9.

Sanad M, Osman M, Gharib A. Obesity modulate serum hepcidin and treatment outcome of iron deficiency anemia in children: a case control study. *Ital J Pediatr*. 2011;37:34.

Sankar MJ, Saxena R, Mani K, et al. Early iron supplementation in very low birth weight infants--a randomized controlled trial. *Acta Paediatr*. 2009;98(6):953-8.

Sankaranarayanan S, Untoro J, Erhardt J, et al. Daily iron alone but not in combination with multimicronutrients increases plasma ferritin concentrations in Indonesian infants with inflammation. *J Nutr*. 2004;134(8):1916-22.

Appendix A4. Excluded Studies

Smuts CM, Lombard CJ, Benadé AJ, et al. Efficacy of a foodlet-based multiple micronutrient supplement for preventing growth faltering, anemia, and micronutrient deficiency of infants: the four country IRIS trial pooled data analysis. *J Nutr*. 2005;135(3):631S-8.

Soliman AT, Al Dabbagh MM, Habboub AH, et al. Linear growth in children with iron deficiency anemia before and after treatment. *J Trop Pediatr*. 2009;55(5):324-7.

Thorisdottir AV, Gunnarsdottir I, Palsson GI, et al. Iron status and developmental scores in 6-year-olds highlights ongoing need to tackle iron deficiency in infants. *Acta Paediatr*. 2013;102(9):914-9.

Tielsch JM, Khatry SK, Stoltzfus RJ, et al. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet*. 2006;367(9505):144-52.

Walter T, De Andraca I, Chadud P, et al. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*. 1989;84(1):7-17.

Yalcin SS, Tezel B, Yurdakok K, et al. A community-based iron supplementation program, "Iron-Like Turkey," and the following prevalence of anemia among infants aged 12-23 months. *Turk J Pediatr*. 2013;55(1):16-28.

Yurdakok K, Temiz F, Yalcin SS, et al. Efficacy of daily and weekly iron supplementation on iron status in exclusively breast-fed infants. *J Pediatr Hematol Oncol*. 2004;26(5):284-8.

Ziegler EE, Nelson SE, Jeter JM. Iron status of breastfed infants is improved equally by medicinal iron and iron-fortified cereal. *Am J Clin Nutr*. 2009;90(1):76-87.

Ziegler EE, Nelson SE, Jeter JM. Iron supplementation of breastfed infants from an early age. *Am J Clin Nutr*. 2009;89(2):525-32.

Zlotkin S, Antwi KY, Schauer C, et al. Use of microencapsulated iron(II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk. *Bull World Health Organ*. 2003;81(2):108-15.

Zlotkin S, Arthur P, Schauer C, et al. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. *J Nutr*. 2003;133(4):1075-80.

Wrong Intervention

Borigato EV, Martinez FE. Iron nutritional status is improved in Brazilian preterm infants fed food cooked in iron pots. *J Nutr*. 1998;128(5):855-9.

Chang S, Wang L, Wang Y, et al. Iron-deficiency anemia in infancy and social emotional development in preschool-aged Chinese children. *Pediatrics*. 2011;127(4):e927-33.

Christofides A, Schauer C, Sharieff W, et al. Acceptability of micronutrient sprinkles: a new food-based approach for delivering iron to First Nations and Inuit children in northern Canada. *Chronic Dis Can*. 2005;26(4):114-20.

Driva A, Kafatos A, Solman M. Iron deficiency and the cognitive and psychomotor development of children: a pilot study with institutionalised children. *Early Child Dev Care*. 1985;22(1):73-82.

Faber M, Kvalsvig JD, Lombard CJ, et al. Effect of a fortified maize-meal porridge on anemia, micronutrient status, and motor development of infants. *Am J Clin Nutr*. 2005;82(5):1032-9.

Geltman PL, Meyers AF, Bauchner H. Daily multivitamins with iron to prevent anemia in infancy: a randomized clinical trial. *Clin Pediatr*. 2001;40(10):549-54.

Gera T, Sachdev HP, Nestel P. Effect of combining multiple micronutrients with iron supplementation on Hb response in children: systematic review of randomized controlled trials. *Public Health Nutr*. 2009;12(6):756-73.

Honig AS, Oski FA. Developmental scores of iron deficient infants and the effects of therapy. *Infant Behav Dev*. 1978;1:168-76.

Jack SJ, Ou K, Chea M, et al. Effect of micronutrient sprinkles on reducing anemia: a cluster-randomized effectiveness trial. *Arch Pediatr Adolesc Med*. 2012;166(9):842-50.

Kimmons G, Moffatt M, Lonstaffe S, et al. Short term effects of intramuscular iron on the behavior of iron-deficient children: a clinical trial. In: Martins S, ed.

Appendix A4. Excluded Studies

Oski FA, Honig AS. The effects of therapy on the developmental scores of iron-deficient infants. *J Pediatr*. 1978;92(1):21-5.

Oski FA, Honig AS, Helu B, et al. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. *Pediatrics*. 1983;71(6):877-80.

Power HM, Heese HD, Beatty DW, et al. Iron fortification of infant milk formula: the effect on iron status and immune function. *Ann Trop Paediatr*. 1991;11(1):57-66.

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Wrong Outcome

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Appendix A4. Excluded Studies

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Appendix A4. Excluded Studies

Systematic Review, Not Directly Used

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Criteria for Assessing Internal Validity of Individual Studies

The USPSTF Methods Workgroup developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria that relate to internal validity, and the associated definitions of quality categories, at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria; comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention

to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Case-Control Studies

Criteria:
- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on criteria above:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate ≥80%; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables

Fair: Recent, relevant, without major apparent selection or diagnostic workup bias but with response rate <80 %or attention to some but not all important confounding variables

Poor: Major selection or diagnostic workup biases, response rates <50%, or inattention to confounding variables

Systematic Reviews

Criteria:
- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important

Appendix A5. USPSTF Quality Rating Criteria

Definition of ratings from above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Source: U.S. Preventive Services Task Force Procedure Manual. Available at: http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual

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Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Domellof, 2001[56] (Results from Sweden and group supplement at ages 6–9 months vs. placebo)	RCT	Single center Sweden	A. Placebo from 4 to 6 months and iron supplement from 6 to 9 months (n=34) B. Placebo from 4 to 9 months (n=36)	Treatment duration: 3 months (ages 6–9 months)	A vs. B Mean age: NR Female sex: 50% vs. 58% Race: NR Mean hemoglobin at 4 months: 118.5 vs. 117.4 g/L Mean hemoglobin at 6 months: 119.3 vs. 117.7 g/L Mean ferritin at 4 months: 110 vs. 114 µg/L Mean ferritin at 6 months: 56.2 vs. 56.4 µg/L	Infants born at ≥37 weeks' gestation, birth weight ≥2,500 g, without chronic illness, to mothers age ≥16 years, exclusively breastfed at 4 months and intended to be exclusively breastfed until 6 months and partially breastfed to at least 9 months	NR
Geltman 2004[48]	RCT	3 primary care sites United States	A. Multivitamin drops including iron, providing 10 mg iron/day (n=138) B. Multivitamin drops without iron (n=146)	Treatment duration: 3 months	A vs. B Mean age: 185 vs. 183 days Female sex: 47% vs. 50% Race: 55% vs. 48% black Received WIC during pregnancy: 90% vs. 88%	Infants attending study sites for 6-month well-child visit	Premature birth (<37 weeks); low birth weight (<2,500 g); major medical, hematological, or gastrointestinal conditions; previous supplement use
Gill 1997[49]	RCT	21 centers United Kingdom and Ireland	A. Iron-fortified formula, providing 12.3 mg iron/L (n=264) B. Unfortified formula, providing 1.4 mg iron/L (n=85) C. Cow's milk, providing 0.5 mg iron/L (n=57)	Treatment duration: 11 months	A vs. B vs. C Mean age: 6.1 vs. 6.2 vs. 6.6 months Female sex: 48% vs. 51% vs. 32% Race: NR	Healthy children age 6 months; full-term birth; product of a normal delivery; receiving formula or cow's milk at study entry	Children who were totally or partially breastfed; received iron supplementation or blood transfusion; suffering from severe or chronic disease, hematological disorders, malnutrition, or congenital abnormalities that interfere with growth or feeding; iron deficient or anemic; or <2,500 g at birth

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Lozoff 2003[50]	Controlled observational study	Community setting Chile	A. Iron-supplemented formula (n=1,123) B. No iron supplementation (n=534)	Treatment duration: 6 months Followup: 10 years	A vs. B Mean age: NR Female sex: 45.5% vs. 48.2% Race: NR	Healthy children age 6 months without iron deficiency anemia, birth weight ≥3.0 kg, singleton term birth, routine vaginal delivery, no major congenital abnormalities or perinatal complications, no phototherapy, no hospitalizations longer than 5 days, no chronic illness, and no iron therapy	Children residing outside of the neighborhood, another infant age <12 months in the household, infant in child care, illiterate or psychotic caregiver or no stable caregiver, and (until mid-1994 only) receiving <250 mL cow's milk or formula per day
Makrides 1998[51]	RCT	Single center Australia	A. High-iron weaning diet (n=36) B. Control weaning diet (n=26)	Treatment duration: 6 months	A vs. B Mean age: NR Female sex: 47% vs. 54% Race: NR	Healthy children age 6 months; full-term birth; birth weight >2,500 g; solely breastfed	Children with chronic disease; who ceased breastfeeding before age 9 monthse; or had received iron supplementation
Morley 1999[52]	RCT	3 centers United Kingdom	A. Fortified formula, providing 1.2 mg iron/L (n=162) B. Unfortified formula, providing 0.9 mg iron/L (n=165) C. Cow's milk, providing 0.05 mg iron/L (n=166)	Treatment duration: 9 months	A vs. B vs. C Mean age: 40.9 vs. 40.9 vs. 41.0 weeks Female sex: 50% vs. 50% vs. 43% Race: NR	Healthy infants born after ≥36 weeks' gestation, weighing >2,500 g, and either singleton or sole survivor from a multiple pregnancy, enrolled at age 9 months	Children with a disease known to affect growth or development, developmental or neurosensory impairment, history of transfusion or iron supplementation, or first language other than English

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Szymlek-Gay 2009[53]	RCT	Community setting New Zealand	A. ≥2 portions of red meat, with a mean of 1.3 mg iron/portion (n=90) B. Iron-fortified milk, with 1.5 mg iron/100 g prepared milk (n=45) C. Nonfortified milk, with 0.01 mg iron/100 g prepared milk (n=90)	Treatment duration: 5 months	A vs. B vs. C Mean age: 16.8 vs. 17.6 vs. 16.8 months Female sex: 46% vs. 40% vs. 47% Race: 76% vs. 84% vs. 78% white Hemoglobin: 118.7 vs. 118.5 vs. 120.1 g/L	Healthy children ages 12 to 20 months	Children with health problems or taking medication likely to affect iron absorption, baseline hemoglobin <105 g/L or <110 g/L and ferritin ≤12 µg/L, taking supplements containing iron, given iron-fortified milk, or whose parents were unwilling to offer study foods to child and refrain from giving supplements or iron-fortified milk during study
Williams 1999[47]	RCT	Single center United Kingdom	A. Iron-supplemented formula for 12 months, with 1.2 mg iron/100 mL (n=46) B. Unmodified cow's milk (n=46)	Study duration: 10–18 months (mean or median NR) Treatment duration: 10–12 months	Mean age: 7.8 months Female sex: 53% Race: 75% white, 24% black, 2% Asian Receiving income support: 59% Hemoglobin <110 g/L at baseline: 16% vs. 13%	Infants ages 6–8 months whose mothers had changed the infant's diet to unmodified cow's milk	Preterm infants
Other publication to Williams 1999[47]: Daly 1996[46]	RCT	Single center United Kingdom	A. Iron-supplemented formula for 18 months, with 1.2 mg iron/100 mL (n=41) B. Unmodified cow's milk (n=43)	Study duration: 10–18 months (mean or median NR) Treatment duration: 10–12 months	Mean age: 7.8 months Female sex: 53% Race: 74% white, 24% black, 2% Asian Receiving income support: 59% Hemoglobin <110 g/L at baseline: 16% vs. 13%	Infants ages 6-8 months whose mothers had changed the infant's diet to unmodified cow's milk	Preterm infants

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Loss to Followup (Number, %)	Outcome Results	Adverse Events	Quality Rating	Funding Source
Domellof, 2001[56] (Results from Sweden and group supplement from 6–9 months vs. placebo)	Sweden site overall (including 4–9 month supplemented group) Screened: 1,100 Eligible: 400 Enrolled: 121 Analyzed: 96 **A vs. B** Loss to followup: 26.5% (9/34) vs. 8.3% (3/36); RR, 3.18 (95% CI, 0.94 to 10.76)	**A vs. B** Mean hemoglobin at 9 months: 117.1 vs. 114.4 g/L; p=0.12 Mean ferritin at 9 months: 47.3 vs. 22.9 µg/L; p<0.001 Weight at 9 months: 8.9 vs. 8.9 kg (p=NS) *No effect on proportion of IDA at 9 months (numbers NR)	NR	Fair	U.S. Department of Agriculture; Thrasher Research Fund; Stiftelsen Oskarfonden; Swedish Nutrition Foundation; Stiftelsen Samariten; Swedish Medical Research Council
Geltman 2004[48]	Screened: 585 Eligible: 459 Enrolled: 376 Analyzed: 284 **A vs. B** Loss to followup: 22.9% (41/179) vs. 25.9% (51/197)	**A vs. B** Mean hemoglobin: 11.7 vs. 11.7 g/dL Median ferritin: 32.0 vs. 29.2 µg/L 1 abnormal hematological value indicative of iron deficiency: 78% (108/138) vs. 84% (121/144); RR, 0.93 (95% CI, 0.83 to 1.04) 2 abnormal hematological values indicative of iron deficiency: 48% (66/138) vs. 51% (73/144); RR, 0.94 (95% CI, 0.74 to 1.20) Hb <11.0 g/dL: 22% (31/138) vs. 19% (27/144); RR, 1.20 (95% CI, 0.76 to 1.90) Hb <11.0 g/dL and 2 other abnormal hematological values: 8% (11/138) vs. 8% (11/144); RR, 1.04 (95% CI, 0.47 to 2.33)	**A vs. B** Nonadherence: 41% (56/138) vs. 41% (60/146); RR, 1.01 (95% CI, 0.83 to 1.22)	Fair	Gerber Foundation; National Institute of Child Health and Human Development
Gill 1997[49]	Screened: NR Eligible: NR Enrolled: 406 Analyzed: 302 **A vs. B vs. C** Withdrawal: 27.3% (72/264) vs. 29.4% (25/85) vs. 12.3% (7/57)	**A vs. B vs. C** Mean hemoglobin: 121.5 vs. 117.7 vs. 111.4 g/L; p=0.006 Geometric mean ferritin: 25.1 vs. 15.3 vs. 11.0 µg/L; p<0.001 Iron deficiency: 6% vs. 22% vs. 43% (proportions NR) Anemia: 11% vs. 13% vs. 33% (proportions NR) Weight: 11.1 vs. 11.1 vs. 11.3 kg (p=NS) Length: 78.9 vs. 79.1 vs. 80.3 cm (p=NS)	No clinically significant adverse events thought to be related to interventions were reported	Fair	SMA Nutrition

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Loss to Followup (Number, %)	Outcome Results	Adverse Events	Quality Rating	Funding Source
Lozoff 2003[50]	Screened: 6,280 Eligible: 1,798 Enrolled: 1,798 Analyzed: 1,657 Attrition: 7.8% (NR by group)	**A vs. B** Iron deficiency anemia: 3.1% (34/1114) vs. 22.6% (116/514); RR, 0.14 (95% CI, 0.09 to 0.20) Iron deficiency without anemia: 26.5% (286/1081) vs. 51.3% (273/532); RR, 0.52 (95% CI, 0.45 to 0.59) Anemia: 4.3% (48/1123) vs. 25.8% (138/534); RR, 0.17 (95% CI, 0.12 to 0.23) Mean hemoglobin: 123.6 vs. 115.6 g/L Mean ferritin: 14.0 vs. 8.7 µg/L Bayley Scale MDI: 103.9 vs. 104.6 Bayley Scale PDI: 96.7 vs. 97.5 Fagan Test novelty preference: 62.3% vs. 62.7% Fagan Test mean looking time: 1.39 vs. 1.46 seconds; p<0.01 Fagan Test age of crawling: 297.7 vs. 303.0 days; p<0.01 Behavioral Rating Scale Factor 1: 0.04 vs. −0.03 Behavioral Rating Scale Factor 2: 0.06 vs. −0.01 Behavioral Rating Scale Factor 3: 0.12 vs. −0.05 Behavioral Rating Scale Factor 4: −0.21 vs. 0.05 Weight: 10.0 vs. 10.1 kg (p<0.05) Weight for age (z score): 0.05 vs. 0.13 (p=NS) Length: 74.7 vs. 75.1 cm (p<0.001) Length for age (z score): −0.27 vs. −0.15 (p<0.01) Head circumference: 46.7 vs. 47.0 cm (p<0.001)	NR	Fair	National Institutes of Health; Abbott-Ross Laboratories
Makrides 1998[51]	Screened: NR Eligible: 79 Enrolled: 72 Analyzed: 62 **A vs. B** Withdrawal: 10% (4/40) vs. 33% (13/39); RR, 0.30 (95% CI, 0.11 to 0.84)	**A vs. B** Mean hemoglobin: 120 vs. 115 g/L Median ferritin: 26 vs. 35 µg/L Iron deficiency: 13.9% (5/36) vs. 7.7% (2/26); RR, 1.81 (95% CI, 0.38 to 8.60) Anemia: 0.0 vs. 19.2% (5/26); RR, 0.07 (95% CI, 0.00 to 1.15) Iron deficiency anemia: 0 vs. 0	NR	Fair	Channel 7 Children's Medical Research Foundation; Gerber International

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Loss to Followup (Number, %)	Outcome Results	Adverse Events	Quality Rating	Funding Source
Morley 1999[52]	Screened: 2,043 Eligible: 592 Enrolled: 493 Analyzed: 428 (261 consented to blood test) **A vs. B vs. C** Loss to followup: 17.9% (29/162) vs. 18.2% (30/165) vs. 3.6% (6/166)	**A vs. B vs. C** Mean hemoglobin at 18 months: 126 vs. 120 vs. 119 g/L; p<0.01 for A vs. C; p<0.05 for A vs. B Mean ferritin at 18 months: 21.7 vs. 13.1 vs. 14.3 µg/L; p<0.0001 for A vs. B and A vs. C Bayley MDI: 93.9 vs. 94.5 vs. 96.2 Bayley PDI: 94.8 vs. 94.6 vs. 93.6 Weight: 11.4 vs. 11.3 vs. 11.4 kg (p=NS) Length: 82.3 vs. 82.3 vs. 82.6 cm (p=NS)	**A vs. B vs. C** Nonadherence: 22% (36/162) vs. 23% (38/165) vs. 4% (7/166); A vs. C: RR, 5.30 (95% CI, 2.42 to 11.50) B vs. C: RR, 5.46 (95% CI, 2.52 to 11.88)	Fair	Wyeth Laboratories
Szymlek-Gay 2009[53]	Screened: 486 Eligible: NR Enrolled: 225 Analyzed: 225 **A vs. B vs. C** Loss to followup: 5.5% (5/90) vs. 3.3% (3/90) vs. 4.4% (2/45)	**A vs. B vs. C** <u>20 weeks</u> Mean hemoglobin: 121.5 vs. 118.6 vs. 120.2 g/L Ferritin: 43.5 vs. 32.8 vs. 29.9 µg/L; effect size in fortified milk group, 1.68 (95% CI, 1.27 to 2.24) *No effect on growth	**A vs. B vs. C** Gastric events thought by parents to be associated with treatment: 0% vs. 2.4% vs. 2.3% Nonadherence: 30% (26/87) vs. 19% (8/43) vs. 11% (9/85); A vs. C: RR, 2.82 (95% CI, 1.41 to 5.66); B vs. C: RR, 1.76 (95% CI, 0.73 to 4.23)	Good	Health Research Council of New Zealand; Meat and Livestock, Australia; Meat and Wool, New Zealand; University of Otago; Heinz Wattie New Zealand; Fonterra New Zealand; Canpac International; Fisher and Paykel Appliances; Bristol-Myers Squibb Metabolic Kitchen
Williams 1999[47]	Screened: 567 Eligible: 116 Enrolled: 100 Analyzed: 92 **A vs. B** Post-randomization loss: 8% (4/50) vs. 8% (4/50) Loss between 18- and 24-month followup: 11% (5/46) vs. 4% (2/46)	**A vs. B** Hemoglobin <110 g/L at 18 months: 2% (1/46) vs. 33% (15/46); RR, 0.07 (95% CI, 0.01 to 0.48) Mean difference in Griffiths general quotient score at 18 months: −6.7 vs. −8.3; p=0.66 Mean difference in Griffiths general quotient score at 24 months: −9.3 vs. −14.7; p=0.04	NR	Fair	Farley Health Products

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Loss to Followup (Number, %)	Outcome Results	Adverse Events	Quality Rating	Funding Source
Other publication to Williams 1999[47]: Daly 1996[46]	Screened: 567 Eligible: 116 Enrolled: 100 Analyzed: 92 **A vs. B** Loss to followup: 18% (9/50) vs. 14% (7/50)	**A vs. B** Hemoglobin <110 g/L at 12 months: 3% vs. 31% (proportions NR) Mean ferritin concentration at 18 months: 30.5 vs. 15.9 µg/L; p=0.001 Mean ferritin concentration at 24 months: 32.4 vs. 14.9 µg/L; p=0.016 *No effect on growth (data not shown)	NR	Fair	Farley Health Products

Abbreviations: CI=confidence interval; MDI=Mental Development Index; NR=not reported; NS=not significant; PDI=Psychomotor Development Index; RCT=randomized, controlled trial; RR=relative risk; WIC=Women, Infants, and Children Special Supplemental Nutrition Program.

Note: Two poor-quality trials were omitted.[54,55]

Appendix B2. Quality Assessment of Trials of Routine Iron Supplementation in Children Ages 6 to 24 Months

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup Differential/ High?	Subjects Analyzed in the Groups to Which They Were Randomized?	Quality Rating
Domellof, 2001[56]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
Geltman, 2004[48]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	Fair
Gill, 1997[49]	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	No	Fair
Lozoff, 2003[50]	No; resulted in many between-group differences	Unclear	No	Yes; however, changed during study	No	Yes	Yes	Yes	No/No	No	Fair
Makrides, 1998[51]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No/Yes	Yes	Fair
Morley, 1999[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	Fair
Szymlek-Gay, 2009[53]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes; only milk groups	Yes	No/No	Yes	Good
Williams, 1999[47] Other publication: Daly, 1996[46]	Yes	No	Yes	Yes	No	No	No	Yes	No/No	Yes	Fair

Note: Two poor-quality trials were omitted.[54,55]