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Iron supplementation in early childhood: health benefits and risks[1,2,3]

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Abstract

The prevalence of iron deficiency among infants and young children living in developing countries is high. Because of its chemical properties—namely, its oxidative potential—iron functions in several biological systems that are crucial to human health. Iron, which is not easily eliminated from the body, can also cause harm through oxidative stress, interference with the absorption or metabolism of other nutrients, and suppression of critical enzymatic activities. We reviewed 26 randomized controlled trials of preventive, oral iron supplementation in young children (aged 0–59 mo) living in developing countries to ascertain the associated health benefits and risks. The outcomes investigated were anemia, development, growth, morbidity, and mortality. Initial hemoglobin concentrations and iron status were considered as effect modifiers, although few studies included such subgroup analyses. Among iron-deficient or anemic children, hemoglobin concentrations were improved with iron supplementation. Reductions in cognitive and motor development deficits were observed in iron-deficient or anemic children, particularly with longer-duration, lower-dose regimens. With iron supplementation, weight gains were adversely affected in iron-replete children; the effects on height were inconclusive. Most studies found no effect on morbidity, although few had sample sizes or study designs that were adequate for drawing conclusions. In a malaria-endemic population of Zanzibar, significant increases in serious adverse events were associated with iron supplementation, whereas, in Nepal, no effects on mortality in young children were found. More research is needed in populations affected by HIV and tuberculosis. Iron supplementation in preventive programs may need to be targeted through identification of iron-deficient children.

Keywords

Iron; supplementation; children; development; growth; infection

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INTRODUCTION

Iron deficiency has been considered an important risk factor for ill health (1) and is estimated to affect 2 billion people worldwide (2). Concerns have been raised about the effects of iron deficiency in children on their health and development, which have led to recommendations for supplementation of all children of certain ages in populations with a high prevalence of anemia (2). This recommendation for a preventive iron intervention will reach both children in need of additional iron and children without that need. This nondiscrimination may be acceptable if no harm is done by the iron supplementation, especially in those children who receive no benefit. Although some studies suggest risks with iron supplementation, it is important to determine whether these risks are generally supported by available evidence and whether they can be mitigated with altered recommendations regarding iron supplementation. The focus of this review was to examine the evidence for the health benefits and risks of preventive iron supplementation in children aged <5 y in developing countries.

Iron is essential for all tissues in a young child's developing body. Iron is present in the brain from very early in life, when it participates in the neural myelination processes. Other roles that would affect growth and immune function have been postulated (3). Iron, which is essential to both the host and invading pathogens, must be carefully regulated to promote optimal conditions that preserve the health of young children. Furthermore, iron can interfere with the absorption of other nutrients and, in excess, can generate free radicals that impair cellular functions and suppress enzymatic activity (4, 5).

Iron supplementation for children <5 y old is recommended on the basis of anemia prevalence (Table 1). Low-birth-weight infants are at high risk of iron deficiency, and the current recommendation is that they receive supplementation from 2 mo through 2 y of age. Anemia prevalence, determined by hemoglobin status, is used as a practical indicator because of the relative difficulty in collecting additional markers of iron deficiency. The consumption of iron-poor complementary diets (lacking iron-fortified foods or heme iron) is also used to justify supplementation in infants and preschool-aged children. Complementary foods, even with continued breastfeeding, must contribute nearly 100% of dietary iron for young children because breast milk contains little iron (6). Other prevention and control approaches for iron deficiency—such as food fortification, dietary improvements, and treatment of hookworm and other helminth infections—were not considered in this review.

The objective of this review was to evaluate the health benefits and risks of iron supplementation as a strategy to prevent iron deficiency in children 0–4 y old. Evidence (primarily) from randomized placebo-controlled trials (RCTs) provided the basis for this assessment because these designs allow causal inference that is not possible with cross-sectional or quasi-experimental designs.

We conducted a literature review in PubMed (National Library of Medicine, Bethesda, MD) to identify studies meeting several criteria. The review was limited to RCTs published after 1980 and targeting young children 0–59 mo of age who were living in developing countries. Oral iron supplementation, as prevention and not therapy, was the intervention examined in comparison with placebo and, in a few studies, in comparison with other micronutrients. Trials of iron fortification or parenteral iron were excluded. In certain circumstances when data were scarce, as in the case of iron supplementation and HIV infection or tuberculosis, some observational studies were reviewed to suggest possible relations that should be further investigated with RCTs.

Twenty-six RCTs were identified for this review. If recent meta-analyses of RCTs have been performed, results are given, even though selection criteria such as the age of the

children may have differed slightly. The outcomes examined in these iron supplementation trials were grouped into the following categories: anemia and iron status, development (including cognition, motor skills, and language), growth, morbidity, and mortality. To highlight particular findings, these outcome categories were then placed within the sections of the review as either benefits or risks. However, findings were not consistent across many of these outcomes, and this variability deserves careful consideration when policy is made for programs in countries throughout the world.

BENEFITS OF IRON SUPPLEMENTATION IN EARLY CHILDHOOD

Possible beneficial effects of iron supplementation in young children are primarily in the realms of anemia prevention and improvements in developmental outcomes.

Anemia

Anemia may be due to iron deficiency (inadequate iron intake, poor iron absorption, or excess iron losses), insufficient hematopoiesis (eg, from vitamin B-12 deficiency), loss of blood (hemorrhagic anemia), premature red blood cell plasma membrane rupture (hemolytic anemia), deficient or abnormal synthesis of hemoglobin (eg, thalassemia), or destruction of bone marrow (aplastic anemia) (7). In developing countries, the prevalence of anemia among preschool-aged children is 42%, and the regions most affected regions are Southeast Asia, Central and East Africa, and the Eastern Mediterranean (8). Hemoglobin concentrations are most often used for anemia screening. In children 6–59 mo old, anemia is defined as hemoglobin <110 g/L or hematocrit <6.83 mmol/L or 0.33 L/L (9).

Evidence of the effect of iron supplementation on anemia outcomes is widely available. Studies usually incorporate iron status indicators, such as serum ferritin or transferrin saturation. One meta-analysis of 21 data sets from iron supplementation RCTs in children ranging in age from 0 to 12 y found a significant difference in the mean change in hemoglobin concentrations between treatment and control groups of 7.8 g/L, or an effect size of 1.49 (95% CI: 0.46, 2.51) (10).

Of the studies we examined for development, growth, and infectious disease outcomes (Tables 2, 3, and 4), 13 reported significantly increased hemoglobin concentrations and reduced anemia prevalence associated with iron supplementation of young children (11–15, 19, 23, 30, 31). Eleven studies showed improvements in other iron status indicators: serum iron, serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin (11, 13, 15, 16, 19, 20, 23, 24, 30–32). Of the 5 studies reporting no significant effect on hemoglobin concentrations in the entire sample or particular strata (11, 16, 17, 24, 32), 4 showed improvements in iron status markers (11, 16, 24, 32). This inconsistent effect on hemoglobin concentrations may be indicative of the varied causes of anemia in these study populations. Sustained significant ($P = 0.022$) improvements in hemoglobin concentrations 7 mo after a 3-mo treatment period were found in one study (21), whereas another study found that only serum ferritin concentrations remained significantly higher in the treatment group 6 mo after cessation of supplementation (31). Hemoglobin improvements appeared to be related to baseline status (11, 17) and to exposure to anemia risk factors in addition to iron deficiency (ie, residence in malarial endemic regions) (16, 32).

Development

Iron supplementation has been hypothesized to have benefits in children that prevent possible detrimental effects of iron deficiency during development. The pace of neurologic development in young children aged 0–4 y is rapid, including critical periods of neural circuit formation and myelination occurring in the brain. Iron's role in the brain is likely to be multifaceted and has not been fully elucidated. Iron in oligodendrocytes is required for

proper myelination of the neurons used in sensory systems (visual, auditory) and learning and interacting behaviors (38). Dopaminergic neurotransmitter systems related to behavioral development (eg, inhibition, affect, attention processing, and extraneous motor movements) are sensitive to changes in iron status. Iron is also a cofactor for enzymes that synthesize neurotransmitters such as tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine, dopamine) (39). Iron deficiency has been linked to changes in neuronal metabolism in the hippocampus and prefrontal projections where memory processing occurs (40).

Lead and other neurotoxic metals that impair early childhood development have been shown to be absorbed during iron deficiency (41). Iron is recognized as sharing the divalent metal transporter 1 (DMT1) with both lead and cadmium (42). No studies investigating reduced lead absorption as an outcome of iron supplementation met the criteria for this review. One RCT in Mexican school-age children, 51% of whom had blood lead concentrations ≥10 μg/dL, found no effect of a 6-mo regimen of iron supplementation on cognitive performance (43) or parent or teacher ratings of behavior (44).

A meta-analysis of RCTs examining iron in relation to development in children included trials of oral iron supplementation, fortified milks and cereals, and parenteral iron. Significant beneficial effects on mental development for children who were anemic or iron deficient at baseline and for all children >7 y old were reported (45) The standardized mean difference (SMD) for the mental development score, a composite of different tests assessing the same aspect of mental development, was 0.30 (95% CI: 0.15, 0.46; P <0.001). This is a modest effect, equivalent to 1.5 to 2 Intelligence Quotient points. In younger children (aged <27 mo), no effect of iron supplementation on mental development was detected. Motor development was not found to be improved through iron supplementation (SMD: 0.09; 95% CI: −0.08, 0.26, P = 0.28) (35).

Of the 8 RCTs identified for this review that addressed developmental outcomes, 5 found some possible benefits of iron supplementation (11, 13, 16–18), but the importance of many of these effects on later academic performance is unknown (Table 2). One study in Bangladesh found that a weekly dose of 20 mg ferrous sulfate over 6 mo significantly reduced developmental losses in orientation engagement (exploration), whereas placebo did not affect the losses with age (17). A study in Indonesia found that iron supplementation for 4 mo resulted in higher motor and mental development scores on the Bayley Scales for Infant Development II (BSID) in children with iron deficiency anemia, but not in children who were iron deficient without anemia or who were iron replete (11). In contrast, a trial in Guatemala that provided supplementation for only 1 wk found no benefit of iron supplements when testing with the BSID was used (12). In Chile, another trial of short-term (10 d) iron supplementation also found no benefit when testing by BSID was used (14). The third study that found no developmental effects of iron treatment was conducted in Costa Rica and was of longer duration but had a smaller sample than the other 2 studies had (15). Two Indonesian studies with longer supplementation periods (6 and 2 mo, respectively) indicated positive development outcomes: one related to motor development as assessed by BSID in all children (18), and the other related to visual attention and concept acquisition only in children with iron deficiency anemia (13). A Zanzibar study found that iron supplementation given for 12 mo was associated with more rapid achievement of language milestones in all children and motor milestones in the more anemic children (16).

The BSID is probably the most well standardized, widely used assessment of infant development in the world, and it has been sensitive to deviations in early development associated with iron status. However, the BSID is a global assessment that may obscure subtle differences in neurobehavioral development. Evidence for developmental continuity

in cognitive functioning suggests the importance of variability in early processing skills, such as those associated with iron deficiency, and of the modifying effects of the home environment and the family's socioeconomic status (46). Thus, estimates of the effects of iron status during infancy on school-age measures of academic performance may be enhanced by the combination of a well-standardized assessment of development such as the BSID, measures of specific neurobehavioral processes thought to be sensitive to iron deficiency, and consideration of the home and family environment.

RISKS OF IRON SUPPLEMENTATION IN EARLY CHILDHOOD

Because iron is not easily eliminated from the body, attention has been paid to circumstances in which excess iron may be absorbed or used inappropriately. An overabundance of iron may catalyze the generation of hydroxyl radicals through the Fenton reaction (47). Chronic iron overload has been studied in the context of hemochromatosis (48), and these studies may provide insight into the mechanisms and clinical manifestations of excess iron. Tissue injury, in particular that to the liver, may result from the generation of free radicals, but evidence also exists of intracellular damage. Extensive studies and reviews have looked at oxidative damage to DNA, proteins, and lipids (49, 50).

Excess iron may be detrimental to cognitive, motor, and behavioral development, although this detrimental effect is likely limited to cases of genetically susceptible children. Children with mutations in the gene encoding pantothenate kinase 2 (PANK2) have neuronal brain iron accumulation that is manifest in dystonia, dysarthria, rigidity, and early death (51). Animal models have shown potential neurologic dysfunctions associated with dietary iron overload early in life (53); evidence for these effects in humans is less clear.

From the murine model, it is known that iron supplementation can result in the generation of free radicals (49) and will increase intestinal susceptibility to peroxidative damage in an iron-deficient state (53). Known defense systems in the body protect against free radical damage. In young children, lactoferrin from breast milk may be used for iron chelation, although this process is largely thought to produce mostly antiinfective properties. Antioxidants such as selenium or glutathione also are known to protect against free radical damage. Malnourished children with kwashiorkor or marasmus may be deficient in antioxidants, which leaves them susceptible to potential harm due to excess iron (54, 55). Other mechanisms besides the generation of free radicals have been postulated for the observed negative effects of iron supplementation, including potential interference with absorption of other essential nutrients (5, 56), the growth and proliferation of invading pathogens, and the suppression of enzyme activity in host defense (3).

Growth

In the early months and years of life, infants and young children pass through a crucial period of growth that may not be regained later in life. Results from trials of iron supplementation overall have not found significant growth effects, even in anemic children, though some studies have shown an adverse effect, especially in iron-replete children. Dietary iron may inhibit the absorption of other essential growth-promoting nutrients such as zinc, although a recent review of trials found no conclusive evidence of this association (56). Iron supplementation may lead to increased morbidity and, consequently, to reduced dietary intakes, poor nutrient absorption, and negative energy balance (57).

A meta-analysis of RCTs examining vitamin A, iron, and multimicronutrient interventions in children aged <18 y found that, in the 21 iron-supplementation RCTs identified, no significant effect on growth was reported (10). The overall effect size was 0.09 (95% CI: −0.07, 0.24) for height and 0.13 (95% CI: −0.05, 0.30) for weight, and negligible

differences in height gain (0.007 cm) and weight gain (0.012 kg) were found between treatment and controls. When the studies were stratified for baseline hemoglobin status, the lack of significant differences remained, although the effect size for height gain was greater in subjects who were anemic at baseline (0.21; 95% CI: −0.14, 0.56) than in those who were not anemic (0.02; 95% CI: −0.14, 0.18) (10).

The International Research on Infant Supplementation (IRIS) analysis is a recent pooled-data analysis that compared the findings from RCTs of supplementation in infants aged 6–12 mo in Indonesia, Peru, South Africa, and Vietnam. The 4 supplementation groups were daily iron supplementation, daily multiple micronutrients, weekly multiple micronutrients, and placebo. As compared with placebo, iron treatment had no significantly different effect on weight or height gains over the course of the 6-mo trials. Changes in hemoglobin and plasma ferritin concentrations were significantly larger in the iron group than in the placebo group (58).

In the current review, the 10 identified studies had varied results (Table 3). In 2 studies, iron supplementation had a significant positive effect on height or length gains and height-forage *z* score (19, 25), and low baseline hemoglobin and iron deficiency appeared to be associated with this effect in both studies. The study in Indonesia adjusted for dietary intake in the assessment of the effect on growth and concluded that a decrease in morbidity in the supplementation group may have mediated the growth effect (19). In India, iron supplements were randomized within iron-replete and iron-deficient strata of children. Monthly weight gain and linear growth increased significantly (both: $P < 0.001$) in iron-deficient children but not in iron-replete children (25). This study was the only 1 of the 10 to find improvements in weight gain associated with iron supplementation.

Three of the 10 studies, including one described above that found improvements in iron-deficient children (25), reported significant reductions in weight gains in the iron treatment groups (25–27); 2 of these studies also found reductions in linear growth in those groups (25, 26). The study in Honduras found that, in infants aged 4–6 mo with baseline hemoglobin ≥110 g/L, length gains were less than those in infants who received placebo (26). This study also examined iron treatment effects in a population of breastfed infants in Sweden and found lower gains in length and head circumference in supplemented infants aged 4–9 mo. Infection did not appear to influence growth outcomes. Similarly, the study in India found an adverse effect of iron supplementation on weight gain and linear growth in iron-replete children aged 6–24 mo (25). In Indonesia, the negative effect was seen only on weight, and no effect was found on length or arm circumference (27). In the remaining 6 reviewed studies, no effect of iron supplementation was reported for either weight or height (18, 20–22, 24, 28).

From the available literature, it appears that iron supplementation may be of limited or no benefit for growth; the few studies that showed a benefit found it primarily in the children with iron deficiency at baseline. Evidence suggests that iron supplementation in young children without iron deficiency may jeopardize optimal height and weight gains.

Morbidity due to infectious disease

Growing concern about the effect of iron supplementation on increased susceptibility to infection has prompted several studies to examine this relation. The physiologic process most commonly implicated is that of the enhanced growth of pathogens from available iron in tissues. Iron is an important nutrient both for host requirements and for the metabolism of invading pathogens. Nutritional immunity involves iron-withholding defense systems that include hypoferremia, a condition in which the amount of iron available for parasites and other organisms is reduced by the activity of iron-binding proteins (59). Another pathway

proposed in defense against parasitic infection in particular is one in which iron inhibits the expression of inducible nitric oxide synthase (iNOS), which subsequently down-regulates the formation of nitric oxide in macrophages. Nitric oxide appears to be critical to macrophage defense against *Plasmodium falciparum* (60).

The influence of iron supplementation on infection may be differentiated by such variables as increased incidence, duration, or severity of infection. One meta-analysis of 28 RCTs examining iron (oral, parenteral, and fortified foods or beverages) found that the pooled estimate of the incidence rate ratio for all infectious illnesses, including respiratory tract infection, diarrhea, malaria, and other infections, was not elevated in iron-supplemented children (61). A higher risk of diarrhea (incidence rate ratio: 1.11; 95% CI: 1.01, 1.23; $P = 0.04$) was found, however, in those given iron than in those given placebo. A nonsignificant increase in malaria was also observed in the iron-supplemented group (incidence rate ratio: 1.06; 95% CI: 0.94, 1.24). Interpretation of these findings should consider that several of the studies screened for and included only anemic children. Moreover, the trials used forms of iron administration other than supplements, including parenteral iron (3 studies) and fortified beverages or foods (5 studies). The age of the study participants also varied from 2 d to 14 y, and the inclusion and exclusion criteria were heterogeneous.

Our review identified 16 RCTs of oral iron supplementation for infants and young children in developing countries with infectious disease outcomes (Table 4) (16, 18, 19, 22, 24, 26, 27, 29–37). The methods applied to measure morbidity varied greatly across studies. Five studies used clinical measures, 4 studies used blood or stool samples for assessment, and the remaining 7 combined these approaches. Of the 4 studies finding an association between iron supplementation and infection, 3 used the combined approach, with both blood and clinical measures of morbidity.

Four studies in our review reported adverse outcomes related to iron supplementation. In Bangladesh, in children aged <12 mo, iron supplementation resulted in a 49% increase ($P = 0.03$) in the number of episodes of dysentery (34). An earlier study in the Gambia that included only children who were anemic at baseline (hemoglobin <3rd percentile of reference population) found that iron treatment was associated with an increase in fever-associated severe malaria (37). Although 2 small studies in Tanzania found no infection-related adverse effects with iron supplements (29, 32), a third study from Tanazania found, in children with severe anemia (hemoglobin ≤ 5.0 g/L), a significant increase in morbidity from infectious causes and a significantly higher incidence of pneumonia in the iron group (both: $P = 0.004$) (35).

A large trial conducted in Zanzibar, Tanzania ($n = 24\,076$) found a 12% (95% CI: 2%, 23%) greater risk of severe illness leading to hospitalization or death and a 16% (95% CI: 2%, 32%) greater risk of adverse events due to malaria associated with iron and folic acid supplementation (36). To further examine the effects of supplementation on hematologic and zinc status and morbidity, a substudy in Zanzibar ($n = 2413$) was also carried out. In this analysis, supplement effect was assessed by iron and anemia status. Children with iron-deficiency anemia who were being treated for malaria and other infections had a significantly ($P = 0.006$) lower risk of adverse events (eg, hospitalization or death) (RR: 0.51; 95% CI: 0.31, 0.83) associated with concomitant treatment with iron and folic acid than did those given placebo. Those who were iron replete (with or without anemia) showed a trend toward a greater risk of adverse events when they were iron supplemented, but the substudy sample size lacked sufficient power to detect statistically significant differences. In addition, any apparent adverse effects of iron supplementation in the iron-replete groups may have been mitigated by the more extensive diagnosis and treatment services provided by the sub-study than by the routine government services in the larger study.

Only one study in Indonesia (n = 76) found a positive effect for reduced frequency of fever, respiratory infection, and diarrhea associated with iron supplementation in children aged 2–5 y (19). In infants with hemoglobin <110 g/L at baseline in Honduras, a trend toward a lower risk of diarrhea was seen in the iron-supplemented group (OR: 0.11; 95% CI: 0.01, 1.08; P = 0.06), but no similar reverse trend was seen in infants with hemoglobin ≥110 g/L (26). In the current study, however, the combined analysis, which included Swedish infants randomly assigned to iron supplementation and placebo, found a significant protective effect against diarrhea with iron supplementation in infants with hemoglobin <110 g/L (OR: 0.21; 95% CI: 0.04, 0.95; P = 0.04) and an adverse effect among those with hemoglobin ≥110 g/L (OR: 2.4; 95% CI: 1.0, 5.8; P = 0.05). The remaining 10 studies of the review found no effect on morbidity associated with iron supplementation of young children.

Malaria

Malarial infection contributes to the development and severity of anemia through the destruction of parasitized red blood cells, through immune mechanisms including the destruction of unparasitized red cells, and through dyserthropoiesis (7). Its relation to iron status is less well characterized. Other studies have found that additional risks may be associated with malarial infection and iron supplementation in children, which has increased the attention the public is directing toward this association. Of the 7 studies identified in our review, 5 (29, 31–33, 35) showed no significantly greater risk in the iron supplementation groups and 2 (36, 37) indicated a greater risk of adverse events due to malaria. Only 3 of these studies did not use anemia as an enrollment criteria (24, 30, 36); one of these studies, the trial in Zanzibar, was the only study of malarial outcomes with adequate power to detect serious adverse events or mortality (36). That study found a 16% (95% CI: 2%, 32%; P =0.02) greater risk of serious adverse events due to clinical malaria in the treatment groups that received iron (iron + folic acid and iron + folic acid + zinc groups) than in the placebo groups. More specifically, this group had an elevated risk of illnesses with clinical signs of cerebral malaria and a malaria-positive blood film (RR: 1.22; 95% CI: 1.02, 1.46; P = 0.03). Cerebral malaria as a cause of death was increased by 70% (RR: 1.70; 95% CI: 1.08, 2.68; P = 0.02) in the iron + folic acid treatment group.

HIV

The risks and benefits of iron supplementation in HIV-positive children have not been extensively studied. No RCTs were identified in this age category. Globally, 2.2 million children aged <15 y are living with HIV/AIDS; most of them live in sub-Saharan Africa and South and Southeast Asia (36). Numerous risk factors for compromised health, that may be either diminished or exacerbated by iron supplementation are present in children born to HIV-positive mothers. Evidence from a review of observational studies suggests that infants born to HIV-positive mothers are at greater risk of low birth weight (63); low-birth-weight infants are currently recommended to receive iron supplementation from 2 to 23 mo of age. Moreover, infants born to HIV-positive mothers may have compromised iron nutriture (64) and, conversely, may be susceptible to iron overload through antioxidant deficiencies (65).

Before highly active antiretroviral therapy (HAART), which remains largely unavailable in developing countries, iron loading was observed in various tissues of HIV-positive adults, including bone marrow, brain, muscle, liver, and spleen (66). Evidence from a study of HIV-positive, iron-deficient pregnant women in Africa found no relation between the severity of HIV disease and iron status indicators (ie, hemoglobin, ferritin, transferrin receptor, HIV load, and $CD4^+$ lymphocyte count) (67). One RCT in a small group of HIV-infected adults (n = 45) in Kenya found no differences in viral load between the placebo and the iron-supplemented groups after 4 mo of follow-up (68). Further research is needed in developing

countries, especially in young children (infected or noninfected) and those born to HIV-positive mothers.

Tuberculosis

Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, the pathogen that causes tuberculosis. The incidence of tuberculosis has increased dramatically with the HIV/AIDS epidemic (69). Whereas we found no RCTs examining the effect of iron supplementation on tuberculosis in young children, this research may be necessary. Iron has been shown to enhance the growth of *M. tuberculosis* growth in mice (70). The loading of iron in macrophages where this bacterium grows may both facilitate its acquisition of iron and inhibit cellular defense systems (71). However, in a study of anemia in adult males with pulmonary tuberculosis, no differences were found in the recovery rates between iron-supplemented and placebo groups (72). Another study examined retrospective exposure to dietary iron and found a significant increase in the odds of tuberculosis with high iron, after adjustment for HIV status and liver function (71). These studies highlight the need for more investigation, particularly in young children.

Overall mortality

Two additional RCTs that investigated infection outcomes examined the risk of mortality related to oral iron supplementation. As stated above, the study in Tanzania found a trend toward a greater risk of mortality in the iron + folic acid treatment groups, which is consistent with the increase in hospitalization for severe infectious diseases (36). Serious adverse events were mainly attributed to malaria. In Nepal, no effect was found for total mortality (30). In "other infections" (including sepsis, hepatitis, meningitis, and gastrointestinal infections) category of cause-specific mortality, a significant increase was seen in the relative risk in the iron + folic acid treatment group compared with placebo group. Cautious interpretation of these findings is warranted given the limited reliability of cause of death data. A 70% reduction in severe anemia was seen with iron supplementation, but it did not lead to a reduction in mortality.

CONCLUSIONS: BALANCE OF BENEFITS AND RISKS

Twenty-six studies were assessed in this review; they reported various effects associated with preventive iron supplementation in children aged 0–4 y. The outcomes of anemia, development, growth, infectious disease morbidity, and mortality were considered, and the following conclusions were drawn.

For anemia, hemoglobin concentrations were consistently increased in iron-supplemented children who were anemic or had iron-deficient anemia at baseline. Improvements or increases in iron status indicators were also associated with iron supplementation in both iron-deficient and iron-replete children at baseline, although the response was less in the latter group. Iron supplementation may have had some positive effects on a number of developmental outcomes, primarily through reducing preexisting deficits or preventing losses over time in cognitive and motor skill development among preschool-aged children who were iron deficient or anemic before supplementation. Treatment at lower doses for 2–12 mo appeared to be more beneficial than very short courses of supplementation. The variations in developmental responses to iron supplementation, combined with the poor or unknown correlations of the measured outcomes with longer-term cognition, make interpretation or quantification of the possible benefits difficult.

In terms of growth, we found evidence from trials of various sizes for significant adverse effects on weight gains in iron-replete subgroups of young children. For height or linear

growth, results varied. Two studies found a positive effect of iron supplementation on height increases in iron-deficient children, but 2 found a negative effect and 2 found no effect on height or length in iron-replete children.

With respect to infectious disease morbidity and mortality outcomes, our review found mixed evidence for increased incidence, duration, or severity of all infections in association with iron supplementation. Nearly all of the studies to date have been too small to enable examination of severe disease events or deaths. The only trials of sufficient size for these outcomes are those in Nepal and Zanzibar. In Nepal, no benefit or adverse effect of iron + folic acid supplements on mortality was found in young children. In Zanzibar, clear evidence shows that iron + folic acid supplementation, in a population of children with high rates of malaria and other infectious diseases and with limited access to disease-control programs, results in a significant increase in serious adverse events, including deaths. Additional evidence from this setting suggests that the degree of infectious-disease treatment and the child's baseline iron status are critical determinants of who benefits and who is harmed in terms of serious infectious-disease outcomes when the population is provided low-dose oral iron supplements. Insufficient data are available on iron supplementation in relation to HIV or tuberculosis outcomes for conclusions to be drawn about possible benefits or risks.

One general conclusion that may be drawn from this analysis is that baseline hemoglobin and iron status indicators appear to be important determinants of these outcomes (Table 5). Our review found this through results from 12 trials screening for and including children according to hemoglobin or iron status at baseline (11–15, 19, 25, 29, 32, 33, 35, 37) and 8 trials that later stratified or adjusted for hemoglobin and iron status parameters in analyses associating supplementation with various outcomes (16–18, 21, 22, 26, 28, 36). In the first case of screening or restriction design, the ability to generalize to the larger population may be absent, although several studies showed effects with screening in all outcome categories. Larger, well-designed RCTs were among those finding differential effects of baseline hemoglobin and iron status markers on development, growth, and morbidity outcomes that support this conclusion. Only 2 studies reported an interaction between iron supplementation and initial hemoglobin concentration: significant findings for development outcomes were reported from Zanzibar (16), and marginal significance for morbidity outcomes was found in Honduras (26). Studies from industrialized countries may also suggest the potential for interaction. A trial in Greek preschoolers aged 3–4 y (n = 49) found a significant interaction with cognitive performance (choice reaction time) for baseline iron status and treatment group (73). Additional analyses of the interaction of anemia and iron status at baseline for iron supplementation are needed.

In the substudy of the Zanzibar trial in which substantial malaria treatment was provided, in contrast with the larger trial, children with iron deficiency anemia had a reduction in adverse events. However, an elevated rate of adverse events was observed in those without iron deficiency. Detection and treatment of iron deficiency anemia at an individual level may be required to provide the best overall balance of health benefits and risks. Particular caution is advised in areas with high rates of malaria and other serious infections. Futhermore, there may be irregularities in both iron absorption and metabolism when particular genetic polymorphisms—ie, those that may also be associated with infection variables—are present. A study in Zimbabwe found a significant interaction effect with ferroportin Q248H mutation and elevated C-reactive protein (CRP) for higher ferritin concentrations (74). More research is needed in this area. Ultimately, in the consideration of supplementation of young children with low doses of oral iron, an assessment of the balance of risks and benefits should be integral to the decision-making process.

We recognize that the realities of nutrition and disease-control programs may be vastly different from those of the controlled environment of these trials. The availability of resources, both financial and staffing, may be a problem if screening for iron deficiency and targeting treatment regimens are necessary to avoid causing harm to some children in the population. At the individual level, problems of compliance have often been cited with respect to implementing effective iron-supplementation programs. Alternative prevention and control strategies such as diet-based approaches may be preferred, if vulnerable population groups have access to foods, because those groups may be able to avoid the adverse effects associated with supplementation.

The need to address the problem of iron deficiency and the related consequences affecting millions worldwide is undisputed. Finding the appropriate response, however, particularly for young children living in developing countries, is a more difficult endeavor. This review presents the available evidence from carefully designed trials and offers context and individual-specific results with respect to a variety of outcomes. Further research is warranted, especially with respect to populations affected by malaria, HIV, and tuberculosis. In the short term, these findings suggest that the current recommendations regarding preventive iron supplementation should be reexamined.

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TABLE 1

Dosage schedule for iron supplementation[1]

Age group	Indications for supplementation	Dosage schedule[2]	Duration
Low-birthweight infants (2–23 mo old)	Universal supplementation	2 mg · kg body wt^{-1} · d^{-1}	From age 2 mo to 23 mo
Children 6–23 mo old	Diet does not include foods fortified with iron; anemia prevalence >40%	2 mg · kg body wt^{-1} · d^{-1}	From age 6 mo to 23 mo
Children 24–59 mo old	Anemia prevalence >40%	2 mg · kg body wt^{-1} · d^{-1} (up to 30 mg)	3 mo

[1] Adapted from reference 2.

[2] Recommended forms for children: liquid, powder, or crushable tablet. Recommended iron compounds: ferrous fumarate; ferrous gluconate; ferrous sulfate ($7H_2O$); ferrous sulfate, anhydrous; ferrous sulfate, exsiccated (1 H_2O).

TABLE 2

Development and iron supplementation[1]

Study and location	Age group	Sample size by supplement	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Black et al, Bangladesh (17)	6–12 mo old	Total: 221 Iron group: 49 Zinc group: 49 Iron + zinc group: 43 Multivitamin group: 35 Riboflavin group: 45	Ferrous sulfate (20 mg) + riboflavin (1 mg) Zinc acetate (20 mg) + riboflavin (1 mg) Iron (20 mg) + zinc (20 mg) + riboflavin (1 mg) Multivitamins (with iron and zinc) Riboflavin Weekly dose 6-mo duration	Age 6 mo; not receiving formula; MUAC ≥110 mm; hemoglobin ≥90 g/L; no obvious neurologic disorders, physical disabilities, or chronic illness	Iron: 10.3 ± 0.8 Zinc: 10.5 ± 1.0 Iron ± zinc: 10.5 ± 1.0 Multivitamin: 10.5 ± 0.8 Riboflavin: 10.8 ± 1.4	BSID II; HOME scale	Significantly smaller decrease in orientation engagement (exploration) scores in iron and iron + zinc groups than in placebo group ($P < 0.05$); PDI scores from 6 mo to 12 mo of age decreased less for iron + zinc and multivitamins ($P < 0.05$); hemoglobin at baseline and change in hemoglobin not associated with development outcomes
Idjradinata and Pollitt, Indonesia (11)	12–18 mo old	Total: 126 IDA group: 50 Iron-deficient, nonanemic group: 29 Iron-sufficient group: 47	IDA group: ferrous sulfate (3 mg · kg^{-1} · d^{-1}) or placebo Iron-deficient, nonanemic group: ferrous sulfate (3 mg · kg^{-1} · d^{-1}) or placebo 4-mo duration	Attending clinic at Padjadjaran University; birth weight >2500 g; singleton; no major congenital anomalies or perinatal complications; no jaundice treated with phototherapy; no hospital admission or supplementation with micronutrients during the 6 mo before enrollment; no clinically identified neuromotor delay; no chronic illness or folic acid deficiency; hemoglobin >80 g/L; no abnormal hemoglobin or thalassemia; weight, length, and head circumference within 2 SD of reference standards	IDA group: hemoglobin ≤105 g/L, TS ≤10%, serum ferritin ≤12 μg/L Iron-deficient, nonanemic group: hemoglobin ≥120 g/L, TS ≤10%, serum ferritin ≤12 μg/L Iron-sufficient group: hemoglobin ≥120 g/L, TS > 10%, serum ferritin >12 μg/L	MDI; PDI	Significant changes in mean mental development and psychomotor scores of IDA infants, but not in other groups; developmental delay reversed after 4 mo of treatment
Lind et al, Indonesia (18)	6 mo old	Total: 666 Iron group: 166 Iron + zinc group: 164	Iron (10 mg/d) Zinc (10 mg/d) Iron (10 mg) + zinc (10 mg)	Resident in Purworejo, Central Java; singleton infants; age < 6 mo	Hemoglobin 114 g/L (hemoglobin <110 g/L observed in 41%,	Anthropometric indexes; developmental indexes (BSID); morbidity	Iron improved BSID psychomotor development index significantly more

Study and location	Age group	Sample size by supplement	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
		Zinc group: 167 Placebo group: 169	Placebo 6-mo duration	Exclusions: metabolic or neurologic disorders; handicaps affecting development, feeding, or activity; severe or protracted illness: hemoglobin < 90 g/L	hemoglobin <110 g/L and ferritin < 12 μg/L in 8%) Weight-for-age *z* score = −0.42; height-for-age *z* score = −0.57; weight-for-height *z* score = −0.02		than did placebo; no effect on morbidity; no effect of iron alone on growth, but iron + zinc significantly improved knee-heel length compared with placebo; no confounding or interaction found according to initial iron status
Lozoff et al, Costa Rica (15)	12–23 mo old	Total: 86 IDA iron-supplemented group: 32 Nonanemic iron-supplemented group: 27 Nonanemic group: 27	Oral iron (3 mg/kg twice a day) 6-mo duration	Resident of periurban area Desamparados; birth weight ≥2500 g; singleton birth; free of acute or chronic medical conditions IDA group: hemoglobin ≤100 g/L plus 2 of 3 iron measures indicating deficiency: serum ferritin ≤12 mg/L, erythrocyte protoporphyrin >100 mg/dL, or transferrin saturation ≤10% Nonanemic group: hemoglobin ≥125 g/L	Anemic group: hemoglobin 94 ± 6 g/L; free erythrocyte protoporphyrin 335.3 ± 173.6 μg/dL; packed RBC ferritin 4.4 ± 4.7 μg/L; TS 8.4 ± 2.6% Nonanemic group: hemoglobin 132 ± 5 g/L; free erythrocyte protoporphyrin 59.6 ± 24.1 μg/dL; packed RBC ferritin 13.0 ± 17.1 μg/L; TS 16.8 ± 1.9%	Bayley MDI; Bayley PDI	No significant differences in mental or motor test scores; mental test scores in both IDA and nonanemic groups declined over 6 mo, with significantly lower scores in the IDA group at study entry and 3 mo IDA group: hemoglobin increased by 34 g/L at 3 mo and 35 g/L at 6 mo; anemia corrected for all by 6 mo Nonanemic iron-supplemented group: iron status improved
Lozoff et al, Guatemala (12)	6–24 mo	Total: 64 Iron group: 31 Placebo group: 33	Ferrous ascorbate (5 mg · kg^{-1} · d^{-1}) or placebo 1-wk duration	Residents of Guatemala City; hemoglobin <105 or >120 g/L; no birth complications, acute or chronic illness, neonatal distress, congenital anomalies, developmental retardation, generalized malnutrition, or iron therapy during the previous mo; mature infants	Anemic group: hemoglobin 95 ± 9 g/L; serum iron 34.5 ± 9.3 μg/dL; TS 7.9 ± 3.1%; serum ferritin 4.0 ± 5.0 μg/L; free erythrocyte protoporphyrin 166.6 ± 100.1 μg/dL packed RBCs Nonanemic group: hemoglobin 126 ± 5 g/L; serum iron 60.7 ± 22.3 μg/dL; TS 16.9 ± 6.4%; serum ferritin 14.4 ± 19.3 μg/L; free erythrocyte protoporphyrin 67.9 ± 28.5 μg/dL packed RBCs	Bayley MDI; Bayley PDI	Deficits at baseline in psychomotor development and mental development indexes were not reversed in 6–8 d of treatment

Study and location	Age group	Sample size by supplement	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Soewondo et al, Indonesia (13)	<5 y	Total: 127 Iron group: 51 Placebo group: 76	Iron (50 mg/d) or placebo 2-mo duration	Female head of household works as tea picker; husband present in household; one preschool-age child present; family lives on a farm	IDA group: hemoglobin >110 g/L plus 2 of the following: ferritin <12 μg/L, TS <16%, free erythrocyte protoporphyrin >1.77 μmmol/L RBCs Iron-depleted group: hemoglobin ≥110 g/L plus 2 of the following: ferritin <12 μg/L, TS <16%, free erythrocyte protoporphyrin >1.77 μmmol/L RBCs Iron-replete group: hemoglobin ≥110 g/L plus 2 of the following: ferritin ≥12 μg/L, TS ≥16%, free erythrocyte protoporphyrin ≤1.77 μmmol/L RBCs	Discrimination learning; three oddity learning tasks; PPVT	IDA associated with visual attention and concept acquisition, corrected by iron treatment No effect in iron-replete children
Stoltzfus et al, Zanzibar (16)	6–59 mo old	Total: 614 Households stratified by age strata and randomly assigned to receive iron or placebo; children then stratified by iron allocation and randomly assigned to receive mebendazole Iron group: 307 Placebo group: 307 Mebandazole group: 306 Placebo group: 308	Ferrous sulfate (10 mg/d) Mebandazole (500 mg) 12-mo duration	Resident of Kengeja village on Pemba; age eligibility for language development scale was 12–48 mo and that for motor development scale was 12–36 mo	97% were anemic (hemoglobin < 110 g/L); 18% were severely anemic (hemoglobin <70 g/L)	Language; motor score	Language development improved 0.8 points (range: 0.2–1.4) on 20-point scale Motor development improved in children with hemoglobin <90 g/L Interaction with baseline hemoglobin (P = 0.015)
Walter et al, Chile (14)	12 mo old	Total: 196 Iron group: 102 Placebo group: 94	Iron (45 mg/d) 10-d duration	Residents of well-defined geographical area	Anemic group: hemoglobin 100 ± 9 g/L; MCV 62 ± 5 gL; iron and iron-binding capacity 6.8 ± 2.9%; serum ferritin 5.4 μg/L; free erythrocyte protoporphyrin 195 ± 103.1 μg/dL packed RBCs Non-anemic iron-deficient group: hemoglobin 121 ± 7 g/L; MCV 70 ± 4 gL; iron	Bayley MDI; Bayley PDI	No treatment effect was observed for mental and psychomotor development after 10 d or 3 mo No differences by baseline status After 3 mo of iron treatment, anemia was corrected

Study and location	Age group	Sample size by supplement	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
					and iron-binding capacity 12.2 ± 0.7%; serum ferritin 11.9 μg/L; free erythrocyte protoporphyrin 108 ± 33 μg/dL packed RBCs Control group: hemoglobin 127 ± 8 g/L; MCV 76 ± 3 gL; iron and iron-binding capacity 16.7 ± 6.3%; serum ferritin 19.8 μg/L; free erythrocyte protoporphyrin 78 ± 13 μg/dL packed RBCs		

[1] MUAC, midupper arm circumference; BSID, Bayley Scales of Infant Development; HOME, Home Observation Measurement of Environment; PDI, Psychomotor Development Index; IDA, iron-deficiency anemia; MDI, Bayley Mental Development Index; TS, transferrin saturation; RBC, red blood cell; PPVT, Peabody Picture Vocabulary Test; MCV, mean corpuscular volume.

TABLE 3

Growth and iron supplementation[1]

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Angeles et al, Indonesia (19)	2–5 y old	Total: 76 Iron: 39 Placebo: 37	Ferrous sulfate (30 mg/d) 2-mo duration	WAZ between −2 and −3 SDs Hemoglobin > 80 to <110 g/L Ferritin <120 μg/L	Iron group: hemoglobin 102 ± 9 g/L Placebo group: hemoglobin 103 ± 8 g/L WAZ −2.53 HAZ −2.33 WHZ −1.48	Weight, height, dietary intake, hemoglobin, serum ferritin; fever (temperature > 37°C); diarrhea (<4 watery stools/d); RTI	Increases in height and HAZ in treatment group were larger than those in control group ($P < 0.01$); hemoglobin, serum ferritin, and MCV improved significantly Frequency of fever, respiratory infections, and diarrhea was significantly less in treatment group Study was adjusted for food intake effect on growth; decreased morbidity in supplementation group is suggested to have mediated the growth increase
Dewey et al, Sweden and Honduras (26) Domellof et al, Sweden and Honduras (23)	4–9 mo old	Total: 131	Ferrous sulfate (1 mg · kg^{-1} · d^{-1}) from 4 to 6 mo of age Placebo from 4 to 6 mo of age and then ferrous sulfate (1 mg · kg^{-1} · d^{-1}) from 7 to 9 mo of age Placebo from 4 to 9 mo of age	Gestational age ≥37 wk; birth weight >2500 g; no chronic illness; maternal age ≥16 y; infant exclusively breastfed at 4 mo (received <90 mL infant formula/d since birth); mother intended to continue breastfeeding until infant age 9 mo	Hemoglobin 90 g/L	Blood samples at 4, 6, and 9 mo (hemoglobin, ferritin, erythrocyte zinc protoporphyrin, MCV, plasma transferrin receptor); C-reactive protein; birth weight; weight, length, and head circumference by month; nutrient intake in complementary foods; morbidity by maternal records on calendar (stool frequency, consistency, cough, fever, nasal congestion or discharge, diarrhea, vomiting, or skin rash); morbidity by pediatrician diagnosis	Reduced gains in length in children 4–6 mo old and hemoglobin ≥110 g/L in iron group Weight gain lower in the infants receiving iron for 6–9 mo than in those receiving placebo within lower ferritin subgroup No significant effect on morbidity, but diarrhea was less common at 4 mo in infants in both Honduras and Sweden who had baseline hemoglobin <110 g/L; infants with hemoglobin ≥110 g/L at baseline had more diarrhea From age 4 to 6 mo, hemoglobin and ferritin improved; from age 6 to 9 mo, iron status indicators improved but not hemoglobin; IDA was significantly reduced at 9 mo

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Dijkhuizen et al, Indonesia (20)	4 mo old	Total: 478	Iron (10 mg/d) Iron (10 mg/d) + zinc (10 mg/d) 6-mo duration	Age; resident of any of 6 adjacent villages in West Java; exclusion based on chronic or severe illness, severe clinical malnutrition, or congenital anomalies	Hemoglobin and plasma ferritin not reported at baseline Iron-supplemented group baseline status: WAZ −0.06 HAZ −0.89 WHZ 0.77	—	No effect on growth; hemoglobin and plasma ferritin concentrations significantly higher in iron-treated group
Dossa et al, Benin (21)	3–5 y old	Total: 140	Iron (60 mg/d) Iron (60 mg/d) + albendazole 3-mo duration	Age 3–5 y; resident of semi- rural area of southern Benin; exclusion: no acute disease	Hemoglobin 10.1 g/L; 76% were anemic (hemoglobin <110 g/L) WAZ −1.59 HAZ −2.03 WHZ −0.53	Anthropometric measures; hemoglobin; eggs/g feces	No effect on growth in study groups or stratified groups by nutritional and hemoglobin status
Idjradinata et al, Indonesia (27)	12–18 mo old	Total: 47	Ferrous sulfate (3 mg · $kg^{-1} \cdot d^{-1}$) 4-mo duration	Birth weight >2500 g; singleton pregnancy; no major congenital anomalies or perinatal complications; no jaundice treated with phototherapy; no hospital admission or supplementation with micronutrients during the 6 mo before enrollment; no chronic illness or folic acid deficiency; hemoglobin >80 g/L; no signs of abnormal hemoglobin or thalassemia; weight, length, and head circumference 2 SDs of reference standards	Iron-replete (hemoglobin > 120 g/L; TS >10%; serum ferritin >12 μg/L)	Weight, length, and arm circumference (bi-weekly); morbidity (pediatrician diagnosis); illness incidence (gastrointestinal, upper or lower respiratory tract infection) for 2 wk	Reduced rate of weight gain in iron group (x ± SE: 0.106 ± 0.011 versus 0.070 ± 0.011 kg/2 wk, $P = 0.02$) No significant differences in length and arm circumference No significant difference in respiratory or gastrointestinal infections (Other confounding factors not corrected for)
Lind et al, Indonesia (18)	6-mo old	Total: 666 Iron group: 166 Iron + zinc group: 164 Zinc group: 167 Placebo group: 169	Iron (10 mg/d) Zinc (10 mg/d) Iron (10 mg) + zinc (10 mg) 6-mo duration	Resident in Purworejo, Central Java; singleton infants < 6 mo old; exclusions: metabolic or neurologic disorders; handicaps affecting development, feeding, or activity; severe or protracted illness; hemoglobin <90 g/L	Hemoglobin 114 g/L (hemoglobin <110 g/L observed in 41%; hemoglobin <110 and ferritin <12 μg/L observed in 8%) WAZ −0.42 HAZ −0.57 WHZ −0.02	Anthropometric indexes; developmental indexes (BSID); morbidity	No effect of iron alone on growth but iron + zinc significantly improved knee-heel length as compared with placebo; iron significantly improved BSID psychomotor development index as compared with placebo; no effect on morbidity
Majumdar et al, India (25)	6–24 mo old	Total: 150 Iron-replete group: Iron: 50	Iron-replete group: iron (2 mg · $kg^{-1} \cdot d^{-1}$) Iron-deficient group: iron (6 mg · $kg^{-1} \cdot d^{-1}$)	Birth weight >2500 g; singleton pregnancy; weight, length, and head circumference within 2	Hemoglobin 139 g/L Iron-replete group: hemoglobin >110 g/L,	Anthropometric indexes (weight, length, head circumference)	In iron-deficient children, significantly greater mean monthly weight gain ($P <$

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
		Placebo: 50 Iron-deficient group: 50	4-mo duration	SDs of NCHS reference; diet of adequate protein, calories, and micronutrients; exclusions: major congenital anomaly or prenatal complications, hospital admission or iron supplementation during the months before enrollment, chronic illness, anemia beyond iron deficiency, or recent blood transfusion	serum ferritin >12 μg/L, TS > 10% Iron-deficient group: hemoglobin 50–110 g/L, serum ferritin <12 μg/L, TS <10%		0.001) and linear growth (P < 0.001) In iron-replete children, significantly less weight gain (P < 0.001) and linear growth (P < 0.001)
Palupi et al, Indonesia (22)	2–5 y old	Total: 194 Iron: 96 Placebo: 98	Ferrous sulfate (15 mg/wk) 2-mo duration	Registered at village health center	Hemoglobin 113 g/L WAZ −1.84 HAZ − 1.92 WHZ −0.85	Worm infestation (as indicated by stool microscopy)	No effect on changes in height or weight (SD was large for increase in hemoglobin concentration in both iron and placebo groups; no hookworm prevalence and no additional effect of anthelminth treatment)
Rahman et al, Bangladesh (28)	0.5–6 y old	Total: 317	Ferrous gluconate (15 mg/d) + vitamins A, D, and C 1-y duration	Resident in poor periurban community of Dhaka; exclusions: congenital abnormality, metabolic disorder, or any clinical sign of anemia	WAZ −2.4 HAZ −2.3 WHZ −1.3 No hemoglobin reported		No differences in weight or height increments between intervention and control groups No differences when stratified by age or nutritional categories
Rosado et al, Mexico (24)	1.5–3 y old	Total: 219 Iron: 109 Placebo: 110	Ferrous sulfate (20 mg/d) Ferrous sulfate + zinc methionine 12-mo duration	Resident in 1 of 5 rural communities	Hemoglobin 108 g/L WAZ −1.6 HAZ −1.6 WHZ −0.7 Serum ferritin group: Placebo: 20.1 ± 44.6 Iron: 21.2 ± 38.1 Zinc: 18.9 ± 15.8 Zinc + iron: 14.7 ± 15.6	RTI (runny nose, common cold, sore throat, cough); diarrhea (maternal reporting); fever (maternal reporting)	No effect on growth velocity or body composition Zinc and zinc + iron significantly decreased diarrhea (P < 0.01) and disease episodes (P < 0.03) (No effect with iron alone)

[1] WAZ, weight-for-age *z* score; HAZ, height-for-age *z* score; MCV, mean corpuscular volume; WHZ, weight-for-height *z* score; RTI, respiratory tract infection; IDA, iron deficiency anemia; TS, transferrin saturation; BSID, Bayley Scales of Infant Development; NCHS, National Center for Health Statistics.

TABLE 4

Morbidity and iron supplementation[1]

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Angeles et al, Indonesia (19)	2–5 y old	Total: 76 Iron: 39 Placebo: 37	Ferrous sulfate (30 mg/d) 2-mo duration	WAZ between −2 and −3 SD Hemoglobin >80 to <110 g/L Ferritin < 120 μg/L	Iron group: hemoglobin 102 ± 9 g/L Placebo group: hemoglobin 103 ± 8 g/L WAZ −2.53 HAZ −2.33 WHZ −1.48	Weight, height, dietary intake; hemoglobin; serum ferritin; fever (temperature >37°C); diarrhea (>4 watery stools/d); respiratory tract infection	Frequency of fever, respiratory infections, and diarrhea significantly less in treatment group Increases in height and HAZ in treatment group were larger than in control group ($P < 0.01$) Hemoglobin, serum ferritin, and MCV significantly improved (Study adjusted for effect of food intake on growth; study suggested that the lower morbidity in the supplementation group mediated a growth increase)
Berger et al, Togo (31)	6–36 mo old	Total: 197 Iron: 100 Placebo: 97	Iron betainate (2–3 mg · kg^{-1} · d^{-1}) 3-mo duration 9-mo follow-up	Resident in selected village; aged 6–36 mo; hemoglobin ≤80 g/L	Iron group: hemoglobin 98.9 ± 11.6 g/L, TS 18.3 ± 10.1%, serum ferritin 109.2 ± 110.6 μg/L, free erythrocyte protoporphyrin 105 ± 63 μg/dL packed RBCs Placebo group: hemoglobin 100.4 ± 10.6 g/L, TS 17.0 ± 7.78%, serum ferritin 109.7 ± 138.6 μg/L, free erythrocyte protoporphyrin 101 ± 62 μg/dL packed RBCs	Upper RTI; lower RTI; malaria: parasite density measured smear; diarrhea; cutaneous infecti on; fever; worms	No effect on incidence of infections or malaria After adjustment for baseline status, hemoglobin TS, and ferritin at 3 mo were significantly improved; at 9 mo, only ferritin remained significantly higher in treatment group (Treatment and placebo groups were also given malaria prophylaxis and deworming)
Chippaux et al, Togo (33)	6–36 mo old	Total: 190 Iron: 95 Placebo: 95	Iron betainate (2.5 mg · kg^{-1} · d^{-1}) 3-mo duration 9-mo follow-up	Hemoglobin ≥80 g/L	NA	Malaria (smear positive); antibody titers	No effect on infant susceptibility to malaria or immune response High parasitanemia frequency in all groups during rainy season No variation in antibody tiers

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Dewey et al, Honduras and Seweden (26) Domellof et al, Honduras and Sweden (23)	4–9 mo old	Total: 131	Ferrous sulfate (1 mg · $kg^{-1} \cdot d^{-1}$) Iron (4–9 mo) Placebo (4–6 mo) + iron (6–9 mo) Placebo (4–9 mo)	Gestational age ≥37 wk; birth weight >2500 g; no chronic illness; maternal age ≥16 y; infant exclusively breastfed at 4 mo (received <90 mL infant formula/d since birth); mother intended to continue breastfeeding until 9 mo of age	Hemoglobin >90 g/L	Blood samples at 4, 6, and 9 mo (hemoglobin, ferritin, erythrocyte zinc protoporphyrin, mean corpuscular volume, plasma transferrin receptor); C-reactive protein; birth weight; weight, length, and head circumference by month; nutrient intake in complementary foods; morbidity by maternal record on a calendar (stool frequency; stool consistency; cough, fever, nasal congestion or discharge; diarrhea, vomiting, or skin rash) Morbidity by pediatrician diagnosis	No significant effect on morbidity in the data from Honduras but in the combined data from Honduras and Sweden, diarrhea was less common at 4 mo in supplemented infants with baseline hemoglobin <110 g/L; infants with hemoglobin ≥110 g/L at baseline had more diarrhea Reduced gains in length in children 4–6 mo old and with hemoglobin ≥110 g/L in the iron group Weight gain lower in the group receiving iron for 6–9 mo than in the placebo group within the lower ferritin subgroup
Idjradinata et al, Indonesia (27)	12–18 mo old	Total: 47 Iron: 24 Placebo: 23	Ferrous sulfate (3 mg · $kg^{-1} \cdot d^{-1}$) 4-mo duration	Birth weight >2500 g; singleton pregnancy; no major congenital anomalies or perinatal complications; no jaundice treated with phototherapy; no hospital admission or supplementation with micronutrients during the 6 mo before enrollment; no chronic illness or folic acid deficiency; hemoglobin >80 g/L; no signs of abnormal hemoglobin or thalassemia; weight, length, and head circumference 2 SDs of reference standards	Iron-replete hemoglobin group: >120 g/L; TS >10%; serum ferritin >12 μg/L	Weight, length and arm circumference (biweekly); morbidity (pediatrician diagnosis); illness incidence (gastrointestinal or upper or lower respiratory tract infection for 2 wk	No significant difference in respiratory or gastrointestinal infections Reduced rate of weight gain in iron group ($\bar{x}$ ± SE: 0.106 ± 0.010 versus 0.070 ± 0.011; kg/2 wk, $P = 0.02$) No significant differences in length and arm circumference (Other confounding factors were not corrected for)
Lind et al, Indonesia (18)	6 mo old	Total: 666 Iron: 166 Iron + zinc: 164 Zinc: 167 Placebo: 169	Iron (10 mg/d) Zinc (10 mg/d) Iron (10 mg) + zinc (10 mg) 6-mo duration	Resident in Purworejo, Central Java; singleton infants; < 6 mo old; exclusions: metabolic or neurologic disorders; handicaps affecting development, feeding, or	Hemoglobin 114 g/L (hemoglobin < 110 g/L observed in 41%; hemoglobin < 110 and ferritin < 12 μg/L observed in 8%) WAZ −0.42	Anthropometric indexes; development indexes (BSID); morbidity	No effect on morbidity No effect of iron alone on growth but iron + zinc significantly improved knee-heel length as compared with placebo

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
				activity; severe or protracted illness; hemoglobin < 90 g/L	HAZ −0.57 WHZ −0.02		Iron significantly improved BSID psychomotor development index compared with placebo
Mebrahtu et al, Tanzania (32)	6–59 mo old	Total: 614 Households stratified by age and randomly assigned to receive iron or placebo, and then children stratified by iron allocation and randomly assigned to mebendazole Iron: 307 Placebo: 307 Mebandazole: 306 Placebo: 308	Ferrous sulfate (10 mg/d) Mebandazole (500 mg) 12-mo duration	Resident of Kengeja village on Pemba	94.4% were anemic (hemoglobin <110 g/L) 17% were severely anemic (hemoglobin <70 g/L) 80% were infected with *Plasmamodium falciparum* 48.1% had HAZ <−2	Blood films were assessed monthly for prevalence and density of infection	No significant effects on malariometric measures or after adjustment for age and season
Menendez et al, Tanzania (27)	2 mo old	Total: 832	Ferrous glycine sulfate (2 mg · kg^{-1} · d^{-1}) Deltaprim malaria prophylaxis 4-mo duration 10-mo follow-up	Birth weight >1500 g; PCV > 25% at 8 wk; exclusions: congenital malformation, congenital or neonatal infection	P + P group: PCV 33.3 ± 5.6 I + P group: PCV 33.4 ± 5.0 D + P group: PCV 33.4 ± 6.4 P + I group: PCV 33.0 ± 5.3	Malaria (axillary temperature >35.5°C with asexual *P. falciparum* parasitemia of any density)	No effect on frequency of malaria; 12.8% protective efficac y (−12.8– 32.5%)
Mitra et al, Bangladesh (34)	2–48 mo old	Total: 349 Iron: 172 Placebo: 177	Ferrous gluconate (15 mg/d) Vitamins 3-mo duration	Exclusions: critically ill, congenital malformations, metabolic disorders		Diarrhea (≥3 liquid stools/d and maternal report for breastfed infants): dysentery (blood, mucus, or both in stools) Acute respiratory infection >50 breaths/min in child <1 y old, ≥40 breaths/min in child 1–5 y old	No effect on number of episodes, mean duration of each episode, total days of illness due to diarrhea, dysentery, and acute respiratory infection 49% of children <12 mo old had an increase in the number of episodes of dysentery in supplementation group
Palupi et al, Indonesia (122)	2–5 y old	Total: 194 Iron: 96 Placebo: 98	Ferrous sulfate (15 mg/wk) 2-mo duration	Registered at village health center	Hemoglobin <112 ± 10 g/L	Worm infestation (as indicated by stool microscopy)	No effect on hookworm prevalence

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Rosado et al, Mexico (24)	1.5–3 y old	Total: 219 Iron: 109 Placebo: 110	Ferrous sulfate (20 mg/d) Ferrous sulfate + zinc methionine 12-mo duration and follow-up	Resident in 1 of 5 rural communities; age as stated	Hemoglobin 108 g/L WAZ −1.6 HAZ −1.6 WHZ −0.7 Serum ferritin group: Placebo: 20.1 ± 44.6 Iron: 21.2 ± 38.1 Zinc: 18.9 ± 15.8 Zinc + iron: 14.7 ± 15.6	RTI (runny nose, common cold, sore throat, cough); diarrhea (maternal reporting); fever (maternal reporting)	No effect on morbidity with iron treatment alone No effect on growth velocity or body composition
Sazawal et al, Tanzania (36)	1–35 mo old	Total: 24 076 Iron + folic acid: 7950 Iron + folic acid + zinc: 8120 Placebo: 8006 Substudy: 2413	Ferrous sulfate (12.5 mg) Folic acid (50 μg) Zinc (10 mg) Tablet daily for children > 12 mo old; half-tablet for children <12 mo old 12-mo duration	Age; resident on island of Pemba; no severe malnutrition; substudy exclusion: hemoglobin <70 g/L		Serious adverse events; all-cause mortality; cause-specific mortality; hospitalizations; malaria (parasite count and fever), meningitis, diarrhea, dysentery, pneumonia	12% greater risk of mortality or severe illness leading to hospitalization with iron and folic acid (2–23%; $P = 0.02$) 16% greater risk of adverse events due to malaria (2–32%; $P = 0.03$) No effect with cumulative dose Substudy findings: in iron-deficient anemic children, iron and folic acid treatment significantly reduced the risk of adverse events (RR: 0.51; 95% CI: 0.31, 0.83; $P = 0.006$) In iron-replete children, the trend was toward greater risk of adverse events: with anemia (RR: 2.00; 95% CI: 0.46, 8.75; $P = 0.36$); without anemia (RR: 1.51; 95% CI: 0.54, 3.98; $P = 0.41$) [Children with malaria (parasite count >5000 and axillary temperature >37.5 °C) were given a dose of sufadoxine/pyrimethamine]
Smith et al, Gambia (37)	6 mo–5 y old	Total: 213 Iron: 106 Placebo: 107	Ferrous sulfate in orange juice (3–6 mg · kg^{-1} · d^{-1}) 3-mo duration	Hemoglobin and MCV <3% of reference population Exclusion: infants with hemoglobin <50 g/L	Hemoglobin and MCV <3rd percentile of reference population	Malaria (axillary temperature >37.5°C with *P. falciparum* positivity)	Significantly increased fever-associated severe malaria in iron-treated group than in placebo group

Study and location	Age group	Sample size	Dosage and duration	Eligibility and exclusion criteria	Baseline status	Outcome measures	Results
		n					
Tielsch et al, Nepal (30)	1–35 mo old	Total: 25 490	Placebo, iron and folic acid, zinc, iron and folic acid + zinc: Ferrous sulfate (12.5 mg) Folic acid (50 μg) Zinc (10 mg) Tablet daily for children aged ≥12 mo; half-tablet for children aged <12 mo 12-mo duration	1–35 mo living in study area		All cause mortality; secondary: cause-specific mortality; incidence or severity of diarrhea; dysentery; ARI, clinic utilization	No effect on mortality: iron and folic acid (HR 1.03, 95% CI: 0.78, 1.37) or iron and folic acid + zinc (HR 1.00, 95% CI: 0.74, 1.34) No significant differences in attack rates for diarrhea, dysentery, or respiratory infections Greater risk of "other infections" and deaths in iron and folic acid group
van den Hombergh et al, Tanzania (35)	< 30 mo old	Total: 100 Iron: 50 Placebo: 50	Ferrous sulfate (200 mg/d) Folic acid 3-mo duration and follow-up	Hemoglobin ≤50 g/L; positive smear for malaria parasites; exclusions: cerebral malaria, nonfalciparum malaria, sickle cell anemia, other significant illness	Hemoglobin 41 ± 8 g/L	Malaria (smear positive); pneumonia; other infections	No effect on rate of parasitemia or parasite density Increase in morbidity from other causes in iron group (P = 0.004) Significant difference in pneumonia incidence; higher in iron group (P = 0.004)

[1] WAZ, weight-for age *z* score; HAZ, height-for-age *z* score; WHZ, weight-for-height *z* score; MCV, mean corpuscular volume; TS, transferrin saturation; RTI, respiratory tract infection; RBC, red blood cell; NA, not applicable; BSID, Bayley Scales of Infant Development; P + P, placebo + placebo; I + P, iron + placebo; D + P, Deltaprim malaria syrup + placebo; D +I, Deltaprim malaria syrup + iron; PCV, packed cell volume; ARI, acute respiratory infection: bpm, beats/min; RR, risk ratio; HR, hazard ratio.

TABLE 5

Effects determined by baseline hemoglobin, iron status, or both

Study Design					
Screening or restriction			Stratification or adjustment		
Outcomes	**Effect**	**No effect**	**Outcomes**	**Differential effect**	**No differential effect**
Development	Idjradinata et al (11)	Lozoff et al (12)	Development	Stoltzfus et al (16)	Black et al (17)
	Lozoff et al (15)	Walter et al (14)			Lind et al (18)
	Soewondo et al (13)		Growth	Dewey et al (26)	Dossa et al (21)
Growth	Majumdar et al (25)	Angeles et al (19)			Lind et al (18)
Morbidity	Smith et al (37)	Angeles et al (19)			Palupi et al (22)
	van den Hombergh et al (35)	Chippaux et al (33)			Rahman et al (28)
		Mebrahtu et al (32)	Morbidity	Sazawal et al (36)	Lind et al (18)
		Menendez et al (27)			Palupi et al (22)