Effect of iron-fortified foods on hematologic and biological outcomes: systematic review of randomized controlled trials

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ABSTRACT

Background: The utility of iron fortification of food to improve iron deficiency, anemia, and biological outcomes is not proven unequivocally.

Objectives: The objectives were to evaluate 1) the effect of iron fortification on hemoglobin and serum ferritin and the prevalence of iron deficiency and anemia, 2) the possible predictors of a positive hemoglobin response, 3) the effect of iron fortification on zinc and iron status, and 4) the effect of iron-fortified foods on mental and motor development, anthropometric measures, and infections.

Design: Randomized and pseudorandomized controlled trials that included food fortification or biofortification with iron were included.

Results: Data from 60 trials showed that iron fortification of foods resulted in a significant increase in hemoglobin (0.42 g/dL; 95% CI: 0.28, 0.56; \( P < 0.001 \)) and serum ferritin (1.36 μg/L; 95% CI: 1.23, 1.52; \( P < 0.001 \)), a reduced risk of anemia (RR: 0.59; 95% CI: 0.48, 0.71; \( P < 0.001 \)) and iron deficiency (RR: 0.48; 95% CI: 0.38, 0.62; \( P < 0.001 \)), improvement in other indicators of iron nutriture, and no effect on serum zinc concentrations, infections, physical growth, and mental and motor development. Significant heterogeneity was observed for most of the evaluated outcomes. Sensitivity analyses and meta-regression for hemoglobin suggested a higher response with lower trial quality (suboptimal allocation concealment and blinding), use of condiments, and sodium iron edetate and a lower response when adults were included.


INTRODUCTION

Iron deficiency anemia is a widespread problem with health and economic consequences, such as poor cognitive development in children, lower worker productivity, and increased maternal mortality (1, 2). Anemia affects nearly one-third of the world’s population, primarily infants and young children from developing countries (3–5).

Dietary strategies to counter anemia include iron supplementation, food fortification, or dietary modification. Food fortification is often propagated as the most realistic way to increase iron intake on a widespread and sustainable basis and is currently implemented in the United States, Britain, and most of Latin America, among other locations. Currently, biofortification of crops is also being intensively evaluated as a more sustainable and complementary alternative to food fortification.

Hemoglobin and ferritin are currently considered the most efficient indicators of population response to iron interventions (6). Relevant randomized controlled trials provide conflicting evidence regarding the utility of iron-fortified foods in improving the iron status and reducing anemia in populations (7–9). A recent systematic review of randomized controlled trials in children documented that iron-fortified foods resulted in a substantially lower average hemoglobin response in comparison with oral medicinal iron supplementation (0.25 compared with 0.74 g/dL) (7). The success of iron-fortified food interventions depends on several factors, including the consumption pattern of the fortified food, effect of the fortificants on the taste and appearance of the food vehicle, shelf life of the fortified food, bioavailability of the iron fortificants, and the baseline iron status of the population (10, 11), which need greater evaluation for the success of this strategy.

A new dimension has been added with the emergence of zinc as an important micronutrient for child health (12). Iron and zinc deficiencies frequently coexist in populations that consume diets with insufficient animal-source foods (13). Iron and zinc have been thought to compete for absorptive pathways at the enterocyte level (14). It is, therefore, important to determine how iron fortification of foods affects zinc deficiency, particularly in vegetarian populations subsisting on borderline zinc nutriture.

Policy makers, program implementers, and the target population need to carefully weigh the benefits and safety of food fortification and biofortification with iron before recommending them for populations. The current systematic review was therefore conducted to evaluate 1) the effect of iron-fortified foods and biofortified crops on hemoglobin and serum ferritin and the prevalence of iron deficiency and anemia and other

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biochemical indicators of iron status; 2) possible predictors of a positive response, particularly focusing on the food vehicle, iron fortification compound, iron content, baseline hemoglobin and ferritin concentrations, and duration of fortification; 3) the effect of iron-fortified foods and biofortified crops on zinc status; and 4) the effect of iron-fortified foods on other functional outcomes, namely mental and motor development, anthropometric measures, and infections.

SUBJECTS AND METHODS

Types of trials

The predefined criteria for inclusion were randomized placebo-controlled trials with variations in design, including random allocation of individuals or clusters; multi-arm trials; factorial trials; and crossover trials for the first period of measurement only. Quasirandomized controlled trials were also eligible for inclusion.

Types of participants

The participants were apparently healthy (nondiseased) individuals, families, or communities irrespective of age and sex considerations. Trials conducted exclusively in specifically diseased participants (eg, those with AIDS or tuberculosis or inhabitants of mental rehabilitation centers) were excluded.

Intervention

The intervention was additional dietary iron through the route of food fortification or biofortification. Food for the purpose of this systematic review was defined as a usually consumed dietary item in the population, either in a raw or cooked form. Use of iron as a separate additive to dietary items (eg, as sprinkles) was not considered food fortification.

Comparison

Participants provided similar food without iron fortification served as the comparison group. Trials with simultaneous fortification of additional micronutrients were included if the only difference between the intervention and comparison arms was iron fortification. Similarly, trials using simultaneous co-interventions, such as health education and/or drugs (eg, deworming or anti-malarials), were included if the only difference between the intervention and comparison arms was iron fortification.

Outcome measures

The primary outcomes evaluated included 1) hemoglobin (g/dL), 2) anemia (%), as defined in individual trials), 3) serum ferritin (µg/L), 4) iron deficiency (%), as defined in individual trials), and 5) serum or plasma zinc (µmol/L). Secondary outcomes evaluated included the following: 1) serum transferrin receptor, 2) transferrin saturation (%), 3) total-iron-binding capacity, 4) serum or plasma iron, 5) zinc protoporphyrin, 6) adverse effects (any, as defined in individual trials), 7) malaria (as defined in individual trials), 8) diarrhea (as defined in individual trials), 9) pneumonia or acute lower respiratory tract infections (as defined in individual trials), 10) upper respiratory tract infections (as defined in individual trials), 11) weight-for-age in children aged <5 y (z scores or crude weight), 12) height-for-age in children aged <5 y (z scores or crude height), 13) weight-for-height in children aged <5 y (z scores), 14) cognitive or mental development in children aged <18 y (specific tests reported in individual trials), and 15) motor development in children aged <18 y (specific tests reported in individual trials).

Method for identification of trials

We aimed to identify all relevant trials regardless of language or publication status. Computerized bibliographic databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com), Web of Knowledge (http://thomsonreuters.com/products_services/science/science_products/a-z/isi_web_of_knowledge/), Cochrane Controlled Trials Register (http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html), and International Bibliographic Information on Dietary Supplements (http://ods.od.nih.gov/health_information/ibids.aspx) were searched by using appropriate key words. Websites of the organizations such as the Food and Agriculture Organization (www.fao.org), International Nutritional Anemia Consultative Group (http://www.iiisi.org/ResearchFoundation/Pages/INACG-IVACG.aspx), International Food Policy Research Institute (www.ifpri.org), Micronutrient Initiative (www.micronutrient.org), and Micronutrient Forum (www.micronutrientforum.org) were searched, and key researchers working in the field were contacted to identify ongoing and unpublished trials. The reference lists of the identified articles were also reviewed to search for citations that were not listed in the computerized databases, which were supplemented by hand searches of reviews and proceedings over the past 3 y of Micronutrient Forum international conferences or meetings.

Data collection and analyses

The title and abstract of the trials identified were scanned in duplicate to exclude studies that were obviously irrelevant. The full text of the remaining trials was retrieved, and the relevant reports were identified and the data were extracted by 2 investigators independently. Differences in opinion (if any) were resolved by mutual discussion. The data included in the review were derived from the published manuscript or as provided by the authors for unpublished studies. The authors were contacted for clarifications, if required.

Assessment of quality and risk of bias

Trial quality and risk of bias were evaluated by considering 6 features (Cochrane recommendations): sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and “other” potential sources of bias (15).

Quantitative data synthesis

In factorial trials and in multi-arm designs yielding ≥2 iron-intervention groups (eg, different dose or duration or iron salts) and a single control group, the data in the intervention groups, including the variation in the intervention characteristic, were pooled and compared against the single comparison arm to prevent unit-of-analysis error (16). However, for sensitivity
and subgroup analyses [eg, multi-arm designs using iron salts with wide variation in bioavailability, such as ferrous sulfate or fumarate compared with sodium iron edetate (NaFeEDTA)], we split the “shared” comparison group into ≥2 groups with smaller sample sizes (analytic components) and included ≥2 (reasonably independent) comparisons. For dichotomous outcomes, both the number of events and the total number of participants were divided up. For continuous outcomes, only the total number of participants was divided up, and the means and SDs were left unchanged (16).

For variables usually known to have a skewed distribution (eg, serum ferritin and serum transferrin receptor), pooling was performed on natural logarithm–transformed values (17). To maximize the data input for pooled outcome measures, we primarily used the postintervention values (means and SDs) in preference to the changes from baseline, which were not reported in all trials (18). For the primary outcome variable hemoglobin, we also performed the pooled analyses for changed values without imputing variances (19) for trials not providing such data. For cluster-randomized trials, the stated cluster-adjusted values were used, irrespective of the method used.

Data entry and initial analysis were performed by using SPSS (version 17.0) software. Meta-analysis and meta-regression were performed with user-written programs on Stata (version 9.2) software. The presence of bias in the extracted data were evaluated quasistatistically by using the funnel plot (20). Formal statistical tests for funnel plot asymmetry, namely the Beggs’s and Egger’s methods, were also conducted with the user-written “metabias” command in Stata (21, 22). Pooled estimates of the evaluated outcome measures were primarily calculated by using the generic inverse variance method by using the user-written “metan” command in Stata (21, 23). This program also computes the formal tests of heterogeneity, namely the Cochran Q and I² statistics (24). Binary outcomes were pooled as RRs and 95% CIs. If the continuous outcome variable was reported in different units or measurements across trials, effort was made to convert them to one standard unit for pooled estimates; when this was not possible, the standardized mean difference was used instead of the weighted mean difference (WMD). Pooled estimates were made by using both fixed-effects and random-effects model assumptions. The random-effects model was preferred if there was evidence of significant heterogeneity (I² > 25% and/or P < 0.05 for Cochran Q).

Sensitivity and subgroup analyses (specified below) were conducted for the primary outcome hemoglobin to explore predictors of positive response. This was done by disaggregating results with the user-written “metan” command (“by option”) in Stata (21, 23). The contribution of these variables to heterogeneity was also explored by meta-regression by using the “metareg” command in Stata with the restricted maximum likelihood option (25). The specified variables for subgroup analyses and metaregression included the following: 1) risk of bias (low compared with others) (26), 2) age group (only children compared with adults included), 3) fortification vehicle, 4) fortification compound, 5) iron consumed as fortificant (mg), 6) fortification duration (mo), 7) compliance estimation (directly observed or replacement compared with others), 8) baseline hemoglobin (<12 compared with >12 g/dL), 9) baseline serum ferritin (geometric mean ≤20 compared with >20 µg/L), 10) geographic location (developed compared with developing countries and malarial endemic areas compared with malarial nonendemic areas), and 11) type of trial (cluster or individual randomized or quasi-randomized).

We report this systematic review as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines outlined at http://www.prisma-statement.org.

RESULTS

Trial flow

A total of 185 reports (8, 9, 27–209), were identified to be potentially eligible for inclusion in the systematic review. After thorough scrutiny, 116 of these were excluded for specific reasons (Figure 1) (85, 95–209). Thus, 60 trials reported in 69 publications (8, 9, 27–84, 86–94) were included.

Baseline characteristics

The baseline characteristics, fortification details, and risk of bias in the analyzed trials are summarized elsewhere (see Supplemental Tables 1–3 under “Supplemental data” in the online issue). These 60 trials contributed 85 analytic components for sensitivity and subgroup analyses and provided data on 11,750 iron-fortified subjects and 9077 control subjects. The distribution of analytic components according to continents was as follows: Asia, 41; Africa, 13; South America, 14; Europe, 9; Australia, 1; and North America, 7. Most of the studies were from low- to middle-income countries (71 of 85 analytic components) and nonmalarial endemic regions (77 of 85 analytic components). Almost two-thirds of the analytic components were conducted exclusively in children (60 of 85), whereas the remaining also included adults (25 of 85). Of the 85 analytic components, 48 used individual randomization, 23 were cluster randomized, and 14 were quasi-randomized. Thirty-seven of the 85 analytic components had a parallel arm study design, 42 had a multi-arm study design, and 6 studies used factorial design. The duration of fortification was <7 mo in 44 (51%), 7–12 mo in 30 (35%), and >12 mo in 11 (13%) studies.

Cereal-based fortification was commonly used (n = 36 studies; 42%) followed by salt (12; 14%), sauces (fish and soy) (9; 11%), and milk (9; 11%). The most common iron fortificant used was ferrous sulfate (24; 28%) followed by NaFeEDTA (17; 20%), electrolytic iron (11; 13%), ferric pyrophosphate (7; 8%), hydrogen-reduced iron (3; 3%), and heme (3; 3%) or ferric orthophosphate (3; 3%), ferrous fumarate (6; 7%), amino acid chelates (2; 2%), iron gluconate (1; 1%), or ammonium citrate (1; 1%). Only one biofortification trial, which was rice based, was identified. Three trials did not mention the salt used. Fortified food was consumed daily in 50 analytic components and intermittently in the rest. The computed additional iron intake per day from the fortified food in the 78 analytic components providing this information was ≤10 mg in 49 (63%) and >10 mg in 29 (37%). The mean baseline hemoglobin concentration was ≤120 g/L in 49 of 80 (57%), and the geometric mean baseline serum ferritin was ≤20 µg/L in 22 of 47 (47%).

Details of sequence generation were clearly mentioned in 15 (18%) analytic components, were unclear in 65 (76%) trials, and were not mentioned in 5 of the 85 (6%) components. Allocation was concealed in almost one-third of the analytic components
(28/85; 33%), not concealed in 8 (9%), and unclear in 49 of 85 (58%). Most of the included trials were double blind (57 of 85; 67%), 6 of 85 (7%) were not blinded, and details were unclear in the remaining 22 (26%). Selective outcome data reporting was done in 20 of 85 (24%) analytic components. Incomplete outcome data were reported in 1 trial, and other threats to validity were apparent in 1 trial. Because of the paucity of analytic components for contrast, the sensitivity analyses were not feasible for incomplete outcome data and other threats to validity.

Primary outcome variables

Hemoglobin

Data on hemoglobin were available from 54 trials providing 77 analytic components on 10,895 iron-fortified subjects and 8,266 control subjects. The funnel plot (Figure 2) was symmetrical, which suggests an absence of a publication bias in the included trials. This was confirmed by using the Egger (weighted regression) method ($P_{\text{bias}} = 0.46$) or the Begg (rank correlation) method (continuity corrected $P = 0.46$). The pooled WMD for postintervention hemoglobin by random-effects model was 0.42 g/dL (95% CI: 0.28, 0.56; $P < 0.001$; $I^2 = 94.9%$; $Q$ test for heterogeneity = 1048.57, $P < 0.001$) (Figure 3). Similar estimates were obtained with the fixed-effects model (0.37 g/dL; 95% CI: 0.34, 0.40; $P < 0.001$). For hemoglobin change (data from 18 trials), the pooled WMD by random-effects model was similar, namely 0.40 g/dL (95% CI: 0.21, 0.59; $P < 0.001$; $I^2 = 94.6%$; $Q$ test for heterogeneity = 314.59, $P < 0.001$) (Table 1). However, the pooled WMD for hemoglobin change with the fixed-effects model was lower (0.18 g/dL; 95% CI: 0.14, 0.21; $P < 0.001$). There was evidence of considerable and statistically significant heterogeneity with all of these estimates. To perform the sensitivity and subgroup analyses, we split the “shared” intervention group in some included trials into reasonably independent analytic components. The pooled WMD for postintervention hemoglobin in these 77 analytic components by both random- and fixed-effects model was similar to the pooled estimate obtained with trials as unit of analysis.

The stratified (sensitivity) analyses for the prespecified variables are detailed in Table 1. The overall test for heterogeneity
between subgroups was significant for all of these prespecified variables (generally \( P < 0.001 \)). Important exploratory leads in this context related to the possibility of higher hemoglobin response in developing countries, in malarial nonendemic countries, in suboptimal trial quality (sequence generation, allocation concealment, outcome reporting, and blinding), in directly observed intake, in quasirandomized trials, in the use of salt or sauce as fortification vehicles, in NaFeEDTA salt, in the duration of fortification <1 y, and in lower baseline hemoglobin concentrations. The response with sulfate, pyrophosphate, or fumarate salts was also substantial. A significant improvement in hemoglobin was shown in a post hoc analysis of the subgroup of trials conducted on cereals (\( n = 33 \)). The largest effect size in this subset was again with NaFeEDTA, and the response with sulfate, pyrophosphate, or fumarate salts appeared lower but was statistically significant. The sole biofortification trial that used rice did not document an improvement in hemoglobin (51).

The results of univariate and multivariate meta-regression analyses to explore heterogeneity are summarized in Table 2. In view of the potential limit to the number of explanatory factors used in the multivariate model, only significant predictors on univariate analysis and factors of practical importance (iron intake, fortification vehicle, and iron compound) were included in the model. For analytic purposes, condiments were defined as a grouping of salt, sugar, sauce, or spices (masala), and consumption of any cereal in any form was grouped as “cereals.” The significant predictors of heterogeneity on univariate analyses included a higher hemoglobin response with suboptimal trial quality (allocation concealment, blinding, and quasirandomization), use of condiments, and NaFeEDTA salt and a lower hemoglobin response when adults were included. On multivariate analyses, a higher hemoglobin response with suboptimal blinding retained its statistical significance.

**Anemia**

Data pertaining to anemia were available from 33 trials conducted on 7606 subjects in the fortification group and 5725 control subjects at the end of the intervention period. The trial definition of anemia, which invariably accounted for age and sex differences for defining hemoglobin cutoff concentrations, was used for pooling the RR by random-effects model. A significantly lower RR of remaining anemic was observed at the end of fortification, namely 0.59 (95% CI: 0.48, 0.71; \( P < 0.001 \); \( I^2 = 89.5\% \), \( Q \) test for heterogeneity = 304.94, \( P < 0.001 \)).

**Serum ferritin**

Data on serum ferritin were available from 33 trials conducted on 6796 subjects in the intervention group and 5354 control subjects at the end of the intervention period (Table 3). The pooled WMD for postintervention values was 1.36 \( \mu g/L \) (random-effects model; 95% CI: 1.23, 1.52; \( P < 0.001 \); \( I^2 = 95.6\% \), \( Q \) test for heterogeneity = 724.43, \( P < 0.001 \)).

**Iron deficiency**

Data pertaining to iron deficiency were available from 21 trials conducted on 3234 subjects in the intervention group and 2531 control subjects at the end of the intervention period. A significantly lower risk of being iron deficient was found (RR: 0.48, random-effects model; 95% CI: 0.38, 0.62; \( P < 0.001 \); \( I^2 = 84.6\% \), \( Q \) test for heterogeneity = 130.25, \( P < 0.001 \)).

**Serum or plasma zinc**

Serum or plasma zinc concentrations were estimated in only 2 trials. The zinc concentrations were similar in the 2 arms of both the trials at the end of the intervention (Table 3). The pooled estimates of WMD in the intervention and control groups for the serum zinc concentrations were 0.05 mg/dL (95% CI: −0.33, 0.42; \( P = 0.810 \); \( I^2 = 0.0\% \), \( Q \) test for heterogeneity = 0.07, \( P = 0.793 \)).

**Secondary outcome variables**

**Iron status**

The available data on biomarkers of iron status suggested an improvement in iron nutriture (Table 3). However, there was evidence of significant heterogeneity for all of these biomarkers, except for serum iron (6 trials).

**Infections**

For acute respiratory tract infection (both lower and upper), 4 trials were included incorporating information from 439 iron-fortified subjects and 359 control subjects. There was no evidence of an effect of iron fortification on upper and lower respiratory tract infections (RR: 0.81; 95% CI: 0.30, 2.22; \( P = 0.687 \); \( I^2 = 0.0\% \), \( Q \) test for heterogeneity = 0.11, \( P = 0.99 \)). Diarrhea was evaluated in 4 trials on 341 iron-fortified subjects and 280 control subjects. There was no evidence of an effect on the risk of developing diarrhea (RR: 0.83; 95% CI: 0.35, 1.93; \( P = 0.657 \); \( I^2 = 0.0\% \), \( Q \) test for heterogeneity = 0.85, \( P = 0.836 \)). Malaria was studied in one trial only. No significant effect of iron fortification on malaria was found (RR: 0.94; 95% CI: 0.75, 1.18; \( P = 0.602 \)).

**Anthropometric measures**

No evidence of a significant effect on weight, height, or weight-for-height were observed (see Supplemental Table 4 under “Supplemental data” in the online issue).
Mental and motor development

Three trials (263 iron-fortified subjects and 267 controls) evaluated the impact on mental development. The pooled estimates of the SMD of the postintervention levels was $-0.03$ (95% CI: $-0.23$, $0.17$; $P = 0.799$; $I^2 = 24.4$%, $Q$ test for heterogeneity $= 2.65$, $P = 0.266$), which indicated no evidence of an effect on mental development. Of the 3 trials, 2 studies used the Bayley Mental Development Index score to assess the mental development. No evidence of a significant difference in the pooled estimate of WMD was found ($0.36$; 95% CI: $-2.31$, $3.04$; $P = 0.791$; $I^2 = 17.7$%, $Q$ test for heterogeneity $= 1.21$, $P = 0.270$). Psychomotor development was studied in 2 trials with the Bayley Psychomotor Development Index score in 210 iron-fortified subjects and 212 control subjects. The pooled estimate of WMD was $1.09$ (95% CI: $1.33$, $3.51$; $P = 0.376$; $I^2 = 32.9$%, $Q$ test for heterogeneity $= 1.49$, $P = 0.22$), which indicated no significant effect of fortification.

**DISCUSSION**

Iron fortification of foods resulted in a significant increase in hemoglobin, serum ferritin, and other biomarkers of iron nutrition and a reduced risk of anemia and iron deficiency, but there was no evidence of an effect on zinc concentrations, infections, anthropometric measures, or mental and motor development. Significant heterogeneity was found for most of the evaluated outcomes. Sensitivity analysis and metaregression for hemoglobin suggested a higher response with lower trial quality (suboptimal allocation concealment and blinding), use of condiments, and NaFeEDTA salts and a lower effect when adults were included.

**Strengths and limitations**

The main conclusion regarding the rise in hemoglobin after iron fortification remained stable over a large spectrum of sensitivity analyses. Significant explanatory variables could be identified to explain heterogeneity, including study quality, fortification vehicle, and compound, and the age group of the subjects. No evidence of publication bias was found. Another influence on the analyses, namely the omission of one study at a time, did not show an overwhelming effect of any single trial (data not depicted). However, the following possible limitations merit consideration.
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<td>93.7 1109.81</td>
<td>&lt;0.001 0.39 (0.36, 0.42)</td>
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<td>0.217</td>
<td>0.0 3.98 0.552</td>
<td>0.09 (−0.05, 0.23)</td>
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<td>Allocation concealment</td>
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<tr>
<td>Yes</td>
<td>25</td>
<td>0.16 (0.08, 0.25)</td>
<td>&lt;0.001</td>
<td>52.6 50.67</td>
<td>0.01 0.15 (0.09, 0.20)</td>
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<td>96.11 &lt;0.001</td>
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<tr>
<td>Others</td>
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<td>0.53 (0.36, 0.71)</td>
<td>&lt;0.001</td>
<td>94.8 983.3</td>
<td>0.01 0.48 (0.44, 0.51)</td>
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<td>Sequence generation</td>
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<td>14</td>
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<td>63.4 35.51</td>
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<td>40.41 &lt;0.001</td>
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<tr>
<td>Others</td>
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<td>&lt;0.001</td>
<td>94.1 1054.16</td>
<td>&lt;0.001 0.43 (0.39, 0.46)</td>
<td>0.001</td>
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<tr>
<td>Blinding</td>
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<td>Yes</td>
<td>52</td>
<td>0.27 (0.18, 0.37)</td>
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<td>83.6 310.27</td>
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<tr>
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<tr>
<td>Selective outcome</td>
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<td>Others</td>
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<td>0.001</td>
<td>93.1 202.46</td>
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<td>&lt;0.001</td>
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<tr>
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<td>62</td>
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<td>&lt;0.001</td>
<td>93.4 920.21</td>
<td>&lt;0.001 0.36 (0.32, 0.39)</td>
<td>&lt;0.001</td>
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<tr>
<td>Compliance</td>
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<tr>
<td>Directly observed</td>
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<td>0.008</td>
<td>95.8 474.71</td>
<td>&lt;0.001 0.44 (0.37, 0.50)</td>
<td>&lt;0.001</td>
<td>4.22 0.04</td>
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<td>Others</td>
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<td>0.41 (0.28, 0.54)</td>
<td>&lt;0.001</td>
<td>91.6 651.15</td>
<td>&lt;0.001 0.36 (0.32, 0.39)</td>
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<td>Type of trial</td>
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<td></td>
<td></td>
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<tr>
<td>Individual randomized</td>
<td>42</td>
<td>0.28 (0.15, 0.40)</td>
<td>&lt;0.001</td>
<td>83.8 253.38</td>
<td>&lt;0.001 0.23 (0.19, 0.28)</td>
<td>&lt;0.001</td>
<td>113.69 &lt;0.001</td>
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<td>Cluster randomized</td>
<td>22</td>
<td>0.38 (0.20, 0.56)</td>
<td>&lt;0.001</td>
<td>90.6 222.39</td>
<td>&lt;0.001 0.37 (0.33, 0.42)</td>
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<tr>
<td>Quasirandomized</td>
<td>13</td>
<td>0.89 (0.38, 1.39)</td>
<td>0.001</td>
<td>97.8 540.62</td>
<td>&lt;0.001 0.71 (0.64, 0.79)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Stratification variable</th>
<th>No. of analytic components</th>
<th>Random-effects model (95% CI)</th>
<th>Fixed-effects model (95% CI)</th>
<th>Tests for heterogeneity</th>
<th>Fixed-effects model (95% CI)</th>
<th>Heterogeneity between subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>P value</td>
<td></td>
<td>I²</td>
<td>Q</td>
<td>P value</td>
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<td>Fortification vehicle</td>
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<td></td>
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<tr>
<td>Cereals</td>
<td>33</td>
<td>0.31 (0.14, 0.48)</td>
<td>0.001</td>
<td>92.0</td>
<td>398.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheat and rice</td>
<td>19</td>
<td>0.41 (0.13, 0.70)</td>
<td>0.004</td>
<td>94.8</td>
<td>345.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Salt</td>
<td>10</td>
<td>0.84 (0.55, 1.13)</td>
<td>&lt;0.001</td>
<td>86.5</td>
<td>66.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sauce</td>
<td>8</td>
<td>0.86 (0.36, 1.36)</td>
<td>0.001</td>
<td>97.5</td>
<td>282.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Milk</td>
<td>8</td>
<td>0.50 (0.22, 0.79)</td>
<td>0.001</td>
<td>79.6</td>
<td>34.39</td>
<td>&lt;0.001</td>
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<tr>
<td>Others</td>
<td>18</td>
<td>0.14 (-0.07, 0.35)</td>
<td>0.194</td>
<td>85.0</td>
<td>113.58</td>
<td>&lt;0.001</td>
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<td>Fortification salt</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaFeEDTA</td>
<td>14</td>
<td>0.70 (0.31, 1.09)</td>
<td>&lt;0.001</td>
<td>97.7</td>
<td>568.05</td>
<td>&lt;0.001</td>
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<tr>
<td>Electrolyte iron</td>
<td>11</td>
<td>0.15 (0.04, 0.27)</td>
<td>0.010</td>
<td>33.9</td>
<td>15.14</td>
<td>0.127</td>
</tr>
<tr>
<td>Sulfate or fumarate</td>
<td>27</td>
<td>0.51 (0.33, 0.69)</td>
<td>&lt;0.001</td>
<td>86.5</td>
<td>192.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrophosphate</td>
<td>7</td>
<td>0.51 (0.20, 0.82)</td>
<td>0.001</td>
<td>80.7</td>
<td>31.16</td>
<td>&lt;0.001</td>
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<tr>
<td>Others</td>
<td>15</td>
<td>0.11 (-0.18, 0.39)</td>
<td>0.471</td>
<td>93.3</td>
<td>208.24</td>
<td>&lt;0.001</td>
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<tr>
<td>Various iron salts in cereals only</td>
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</tr>
<tr>
<td>NaFeEDTA</td>
<td>3</td>
<td>1.13 (-0.21, 2.47)</td>
<td>0.098</td>
<td>98.5</td>
<td>133.75</td>
<td>&lt;0.001</td>
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<tr>
<td>Electrolyte iron</td>
<td>9</td>
<td>0.08 (-0.01, 0.18)</td>
<td>0.09</td>
<td>0.0</td>
<td>6.98</td>
<td>0.539</td>
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<tr>
<td>Sulfate or fumarate</td>
<td>9</td>
<td>0.55 (0.30, 0.79)</td>
<td>&lt;0.001</td>
<td>81.4</td>
<td>43.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrophosphate</td>
<td>3</td>
<td>0.41 (0.22, 0.61)</td>
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<td>0.0</td>
<td>1.42</td>
<td>0.490</td>
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<tr>
<td>Others</td>
<td>9</td>
<td>-0.05 (-0.37, 0.26)</td>
<td>0.746</td>
<td>92.7</td>
<td>109.68</td>
<td>&lt;0.001</td>
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<tr>
<td>Iron dose (mg/d)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>44</td>
<td>0.42 (0.28, 0.56)</td>
<td>0.001</td>
<td>93.0</td>
<td>610.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;10</td>
<td>26</td>
<td>0.39 (0.09, 0.69)</td>
<td>0.01</td>
<td>94.1</td>
<td>421.59</td>
<td>&lt;0.001</td>
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<tr>
<td>Fortification duration (mo)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>≤6</td>
<td>41</td>
<td>0.48 (0.29, 0.68)</td>
<td>&lt;0.001</td>
<td>92.7</td>
<td>548.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7–12</td>
<td>25</td>
<td>0.42 (0.18, 0.66)</td>
<td>0.001</td>
<td>93.5</td>
<td>368.57</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;12</td>
<td>11</td>
<td>0.19 (-0.04, 0.42)</td>
<td>0.099</td>
<td>93.3</td>
<td>149</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline hemoglobin, mean (g/dL)</td>
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<td></td>
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<tr>
<td>≤12</td>
<td>46</td>
<td>0.47 (0.28, 0.66)</td>
<td>&lt;0.001</td>
<td>94.4</td>
<td>799.16</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;12</td>
<td>28</td>
<td>0.31 (0.15, 0.48)</td>
<td>&lt;0.001</td>
<td>90.8</td>
<td>295.03</td>
<td>&lt;0.001</td>
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<tr>
<td>Baseline ferritin, geometric mean (μg/L)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>≤20</td>
<td>22</td>
<td>0.26 (0.07, 0.45)</td>
<td>0.008</td>
<td>91.6</td>
<td>248.53</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;20</td>
<td>23</td>
<td>0.59 (0.31, 0.86)</td>
<td>&lt;0.001</td>
<td>95.1</td>
<td>447.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 The pooled estimates (fixed- and random-effects models) and their statistics were derived by using the generic inverse variance method with the user-written "metan" command in Stata (version 9.2) software (21, 23). NA, not applicable; NaFeEDTA, sodium iron edetate.

2 No. of trials.
TABLE 2
Meta-regression analyses for the WMDs in hemoglobin (restricted maximum likelihood method)\(^1\)

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Univariable analysis</th>
<th>Control for additional variables</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>WMD (95% CI)</td>
<td>(P)</td>
</tr>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (yes compared with others)</td>
<td>0.35 (0.08, 0.62)</td>
<td>0.011</td>
</tr>
<tr>
<td>Sequence generation (yes compared with others)</td>
<td>0.28 (−0.05, 0.61)</td>
<td>0.097</td>
</tr>
<tr>
<td>Blinding (yes compared with others)</td>
<td>0.44 (0.18, 0.71)</td>
<td>0.001</td>
</tr>
<tr>
<td>Incomplete outcome reported (yes compared with others)</td>
<td>0.17 (−0.69, 1.03)</td>
<td>0.69</td>
</tr>
<tr>
<td>Directly observed compared with others</td>
<td>−0.03 (−0.33, 0.27)</td>
<td>0.86</td>
</tr>
<tr>
<td>Quasirandomized compared with others</td>
<td>0.19 (0.08, 0.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adults included compared with only children</td>
<td>−0.27 (−0.55, 0.01)</td>
<td>0.062</td>
</tr>
<tr>
<td>Only adults compared with only children ((n = 69))</td>
<td>−0.26 (−0.60, 0.07)</td>
<td>0.127</td>
</tr>
<tr>
<td>Developed compared with developing country</td>
<td>−0.18 (−0.53, 0.18)</td>
<td>0.326</td>
</tr>
<tr>
<td>Malarial endemic compared with others</td>
<td>−0.33 (−0.83, 0.18)</td>
<td>0.205</td>
</tr>
<tr>
<td>Unit increase in mean iron dose (mg/d)</td>
<td>−0.0004 (−0.02, 0.02)</td>
<td>0.958</td>
</tr>
<tr>
<td>Unit increase in duration of fortification (mo)</td>
<td>0.02 (−0.04, 0.01)</td>
<td>0.135</td>
</tr>
<tr>
<td>Others compared with cereals</td>
<td>0.19 (−0.07, 0.46)</td>
<td>0.151</td>
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<tr>
<td>Others compared with condiments</td>
<td>−0.40 (−0.68, −0.114)</td>
<td>0.006</td>
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<tr>
<td>Others compared with milk</td>
<td>−0.13 (−0.58, 0.31)</td>
<td>0.557</td>
</tr>
<tr>
<td>Others compared with NaFeEDTA</td>
<td>−0.34 (−0.67, −0.02)</td>
<td>0.040</td>
</tr>
<tr>
<td>Others compared with sulfate/fumarate</td>
<td>−0.15 (−0.42, 0.13)</td>
<td>0.298</td>
</tr>
<tr>
<td>Unit increase in mean baseline hemoglobin status (g/L)</td>
<td>0.05 (−0.07, 0.17)</td>
<td>0.399</td>
</tr>
<tr>
<td>Unit increase in log mean serum ferritin ((\mu g/L)) ((n = 20))</td>
<td>0.001 (−0.08, 0.08)</td>
<td>0.964</td>
</tr>
</tbody>
</table>

\(^1\) Meta-regression was performed by the “metareg” command in Stata (version 9.2) software with the restricted maximum likelihood option (25). NaFeEDTA, sodium iron edetate; NI, not included in multivariable analyses because of a limit to the number of variables that can be introduced; WMD, weighted mean difference.

First, several trials (23 of 85 analytic components) used a cluster randomization design but none adjusted the study estimates or mentioned it in the published text. In the absence of relevant information, a cluster design–corrected pooled estimate could not be computed. The estimated CIs should therefore be considered to be spuriously narrower. Although, considering the significance levels, it is highly unlikely that the main interpretation would be altered with this correction, the computed pooled effect size is probably a slight overestimate.

Second, there is a distinct possibility of false-positive results from multiple analyses in view of the relatively large number of prespecified variables for exploring heterogeneity. The identified predictors should therefore be considered exploratory in nature only.

Third, only a few trials had adjusted for the subclinical infection-induced rise in serum ferritin concentrations. However, all of the included trials were randomized and controlled, which should have minimized aberrations as a result of this factor.

Fourth, we had used the author definitions for anemia and iron deficiency. Whereas the age-specific hemoglobin cutoffs for defining anemia were largely consistent across the studies, there was variability in defining iron deficiency, which may have had some bearing on the impact estimates for this variable.

Finally, anemia is a disease with a multifactorial etiology. Most of the included trials did not attempt to identify the cause of anemia and the relative contribution of additional micronutrient deficiencies, worm infestation, malaria, and other coexistent infections. However, the included trials were randomized and

TABLE 3
Pooled estimates (weighted mean difference) of iron fortification on biochemical markers of iron status and serum zinc concentrations\(^1\)

<table>
<thead>
<tr>
<th>Biochemical marker</th>
<th>No. of trials</th>
<th>Random-effects model (95% CI)</th>
<th>(P) value</th>
<th>(I^2)</th>
<th>(Q)</th>
<th>(P) value</th>
<th>Fixed-effects model (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin ((\mu g/L))(^2)</td>
<td>33</td>
<td>1.36 (1.23, 1.52)</td>
<td>&lt;0.001</td>
<td>95.6</td>
<td>724.63</td>
<td>&lt;0.001</td>
<td>1.17 (1.15, 1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum zinc ((\mu mol/L))</td>
<td>2</td>
<td>0.05 (−0.33, 0.42)</td>
<td>0.810</td>
<td>0.0</td>
<td>0.07</td>
<td>0.793</td>
<td>0.05 (−0.33, 0.42)</td>
<td>0.810</td>
</tr>
<tr>
<td>Serum transferrin receptor (mg/L)(^2)</td>
<td>15</td>
<td>0.88 (0.80, 1.03)</td>
<td>0.008</td>
<td>98.4</td>
<td>870.89</td>
<td>&lt;0.001</td>
<td>0.81 (0.81, 0.82)</td>
<td>&lt;0.001</td>
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<tr>
<td>Transferrin saturation (%)</td>
<td>8</td>
<td>2.47 (0.76, 4.19)</td>
<td>0.005</td>
<td>85.0</td>
<td>46.54</td>
<td>&lt;0.001</td>
<td>2.24 (2.03, 2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total-iron-binding capacity ((\mu g/dL))</td>
<td>5</td>
<td>−12.92 (−34.31, 8.46)</td>
<td>0.236</td>
<td>81.4</td>
<td>21.5</td>
<td>&lt;0.001</td>
<td>−11.71 (−19.88, −3.53)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum iron ((\mu g/dL))</td>
<td>6</td>
<td>0.130 (0.04, 0.22)</td>
<td>0.004</td>
<td>41.6</td>
<td>8.57</td>
<td>0.128</td>
<td>0.134 (0.08, 0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zinc protoporphyrin ((\mu g/dL))</td>
<td>4</td>
<td>−12.22 (−23.71, −0.74)</td>
<td>0.037</td>
<td>94.3</td>
<td>52.56</td>
<td>&lt;0.001</td>
<td>−5.02 (−7.34, −2.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) The pooled estimates (fixed- and random-effects models) and their statistics were derived by using the generic inverse variance method with the user-written “metan” command in Stata (version 9.2) software (21, 23).

\(^2\) Geometric estimate (antilog of natural log-transformed values).
controlled, which should have controlled for most of these factors.

Implications

This systematic review provides unambiguous evidence that iron-fortified foods can improve iron nutriture and hemoglobin concentrations. When all of the evaluated age groups were considered, the pooled postintervention reductions in anemia and iron deficiency were 41% and 52%, respectively. A systematic review in children (7) indicated that pharmacologic iron supplementation results in a greater hemoglobin response (0.53 g/dL higher; 95% CI: 0.02, 1.04), and the average (“ballpark”) expected reductions in anemia (hemoglobin <110 g/L) prevalence range from 38% to 62%. These ballpark expectations appear higher but are not substantially greater than estimates from food fortification. However, it would be prudent to caution that these ballpark assessments from different systematic reviews are not based on “head-to-head” comparisons. Furthermore, apart from the efficacy for anemia reduction, pragmatic public health choices require careful evidence-based comparative analyses of additional aspects, including biological benefits (development, growth, and physical performance), adverse effects, organoleptic qualities, economic considerations, and logistics, which are infrequently reported. Future iron-fortification trials should record these outcomes and economic aspects and preferably compare them with pharmacologic supplementation to guide policy.

Exploratory analyses for heterogeneity suggested that the hematologic response varies with the choice of fortification vehicle and the iron compound used. The hemoglobin response was significantly higher with condiments, particularly salt and sauce. Use of NaFeEDTA predicted a greater hemoglobin response. A promotive effect of soy sauce on iron absorption has been documented in humans, which is either a result of the lack of soy protein content or the presence of fermentation products other than organic acids (210). Similarly, fish sauce has highly bioavailable heme iron. Also the iron-fortified condiments may have been infrequently consumed with a diet high in iron-absorption inhibitors, such as cereals. The relatively high bioavailability of NaFeEDTA in humans is well documented, and it also acts as an enhancer of iron absorption, such as ascorbic acid (211–214).

Earlier reports comment on the scarcity of controlled evidence regarding the utility of iron fortification of major staple foods, such as cereals or cereal flours, in improving anemia and iron deficiency (211, 212). Phytic acid, which is widely present in cereals, inhibits absorption of even the most bioavailable compounds (211–213). However, in this meta-analysis, cereal fortification proved efficacious. This could be attributed to 3 factors: 1) the use of more bioavailable iron compounds such as NaFeEDTA, ferrous sulfate, or fumarate; 2) the use of strategies to improve the bioavailability of iron, such as low-extraction flours (50); and 3) a larger number of trials in developing countries with a higher prevalence of iron deficiency and anemia, which are likely to respond more to iron fortification.

These findings suggest that iron fortification of foods is effective and can be a viable public health option to combat iron deficiency. Even fortification of cereals, hitherto considered ineffective, can constitute potential vehicles by increasing the fortified iron content, using more bioavailable compounds (eg, NaFeEDTA), and using innovative strategies to enhance bioavailability (eg, encapsulation of iron salts in lipid coatings or micronization).

A higher hemoglobin response with greater compliance and poorer methodologic quality (suboptimal allocation concealment and blinding) is not surprising. A lower hemoglobin effect in trials including adults ($P = 0.06$) may represent a dose effect phenomenon as a result of decreased iron consumption per unit weight. Contrary to expectations, the duration of fortification did not emerge as a significant predictor of hematologic response in this and an earlier review (7). Evidence from pregnant women in Bangladesh indicates that, over a period of 12 wk, 50% of the iron in a daily regimen (60 mg elemental Fe/d) is sufficient for a maximum hemoglobin effect (215). The current analysis suggests that a 6-mo intervention may be sufficient to determine the likelihood of a hematologic response with fortification.

A useful contribution of this review is to provide better quantification of the expected hematologic response for designing and evaluating the efficacy of future iron fortification and biofortification trials. In view of heterogeneity related to the fortification vehicle, it would be prudent to refer to effect sizes of the corresponding food item. On the basis of the limited data from 2 trials, no evidence of zinc depletion was found—a result consistent with radioisotope labeling trials (216–219). Nevertheless, future iron fortification trials should also include zinc nutriture as an outcome measure to address this issue definitively.

The lack of benefit on infections and growth is consistent with previous systematic reviews (220, 221). However, there is unequivocal evidence of a beneficial effect of iron supplementation, albeit modest, on mental development in older children. The absence of a similar demonstrable effect with fortification could be attributed either to a dose effect (lower dose of iron being used in fortification in comparison with medicinal supplementation) or most likely to a scarcity of data (only 3 trials). Given the importance of this biological consequence for human resource development, it is imperative to urgently generate relevant high-quality data.

Conclusions

Synthesized evidence indicates that iron-fortified foods result in a significant improvement in hemoglobin, serum ferritin, and iron nutriture and a reduced risk of remaining anemic and iron deficient at the end of intervention. No evidence of zinc depletion was observed from the extremely limited data for this outcome. Important exploratory predictors of heterogeneity were a higher response associated with suboptimal trial quality, the use of condiments, and the use of NaFeEDTA salt and a lower response when adults were included. Future work on fortification should focus on increasing the iron content and using more bioavailable compounds (eg, NaFeEDTA) or innovative strategies to enhance bioavailability in the foodstuffs and demonstrating the effect of (or lack thereof) of fortification on biological outcomes, particularly mental development in children.

The authors’ responsibilities were as follows—HSS and TG: designed the study, conducted the search, extracted the data, performed the statistical analyses, and drafted the manuscript; and EB: contributed to the study design and drafting of the manuscript. HSS and TG were guarantors. None of the authors had any conflict of interest with regard to this manuscript. The funders had no role in the design, implementation, or analysis and interpretation of the data.
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