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Review Article

Impact of iron-fortified foods on Hb concentration in children (<10 years): a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective: To combine evidence from randomized controlled trials to assess the effect of Fe-fortified foods on mean Hb concentration in children (<10 years).
Design: We conducted a meta-analysis of randomized, controlled, Fe-fortified feeding trials that evaluated Hb concentration. The weighted mean difference was calculated for net changes in Hb by using random-effects models. Meta-regression and covariate analyses were performed to explore the influence of confounders on the net pooled effect.
Setting: Trials were identified through a systematic search of PubMed, the Cochrane Library and secondary references.
Subjects: Eighteen studies covering 5142 participants were identified. The duration of feeding of fortified foods ranged from 6 to 12 months in these studies.
Results: Eighteen studies were included and evaluated in the meta-analysis. The overall pooled estimate of Hb concentration showed a significant increase in the fortification group compared with the control group (weighted mean difference = 5·09 g/l; 95 % CI 3·23, 6·95 g/l; $I^2 = 90\,\%$, $\tau^2 = 18{\cdot}37$, $P < 0{\cdot}0001$). Meta-regression analysis indicated that duration of feeding was positively related to the effect size (regression coefficient = 0·368; 95 % CI 0·005, 0·731; $P < 0{\cdot}05$). The net pooled effect size after removing the confounders was 4·74 (95 % CI 3·08, 6·40) g/l.
Conclusions: We observed an association between intake of Fe-fortified foods and Hb concentration in children aged <10 years. Fe-fortified foods could be an effective strategy for reducing Fe-deficiency anaemia in children.

Keywords
Meta-analysis
Iron fortification
Meta-regression
Covariate meta-analysis

Deficiencies of micronutrients are a major public health problem in developing countries. Fe-deficiency anaemia is a worldwide public health problem; global prevalence is estimated at 24·8 % and the highest prevalence occurs in sub-Saharan Africa and south central Asia[1]. In the case of breast-fed children aged ≥6 months, complementary food is expected to meet the requirements for almost all micronutrients[2]. Although modest information exists on the nutritional status of schoolchildren, studies from several developing countries have demonstrated a high prevalence of micronutrient deficiencies in this age group[3–5]. Undernutrition in general and Fe deficiency in particular among schoolchildren can lead to anaemia and negatively affect growth[6], motor and cognitive development[7] and immune function[8]. All of these can adversely affect academic performance[9]. However, on account of suboptimal feeding practices in terms of quantity and quality, children often tend to receive Fe much below their daily requirement. Therefore an alternative method of providing Fe for this vulnerable segment of the population is required. Among the various strategies, Fe fortification of foods has been suggested as a cost-effective, long-term, population-based strategy with better compliance to improve Fe status and to prevent Fe deficiency worldwide[10,11]. Despite several studies during the last 25 years, Fe deficiency still continues as a significant public health problem[12] and its prevention is essential, especially in developing countries[13]. The prevalence of Fe deficiency in developed countries has declined substantially in the past 15–20 years due to the

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introduction of fortified foods[14] and other public health programmes such as nutritional advice, emphasis on breast-feeding, education and hygiene[15–18].

In India, limited studies have evaluated the effect of Fe-fortified iodized common salt on Hb levels. The results suggested progressive increase in net Hb concentration in the range of 10–30 g/l after 1 year in rural communities and 5 g/l in urban schoolchildren[19]. Thus, there is evidence that children might benefit more from Fe fortification like their counterparts in developed countries.

An array of Fe fortificants suitable for different food vehicles is available. However, the extent of the effect of Fe-fortified foods depends on several factors, like the amount of endogenous Fe in the diet, the amount of Fe fortification, the bioavailability of the Fe fortificant, the food matrix, the frequency of consumption of the fortified food and its duration of feeding, and the Fe status of the individual, as well as the overall nutritional status of the target population[12,20]. The efficacy of Fe fortification strategies is generally evaluated by longitudinal, targeted or population-based, randomized controlled trials (RCT) carried out in a fixed time frame. Fe fortification is considered efficacious when it significantly improves the biomarkers of Fe status and reduces the prevalence of Fe-deficiency anaemia in a population by almost 10 %[21,22]. However, conducting an efficacy trial is costly, invasive and logistically demanding.

In recent years robust study design and meta-analysis have advanced significantly and are readily available[23]. In the present study, we aimed to systematically review the current literature and to perform a meta-analysis to estimate the effect of Fe-fortified foods on Hb concentration in children. Since we expected heterogeneity among studies, we also explored whether factors such as age, duration of the study and levels of fortification could predict the effects on Hb concentration in children.

Methods

Literature search

The steps in this process were conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines for meta-analysis[24]. We searched both PubMed and the Cochrane Library databases from 1990 up to December 2010, and also reviews and the reference lists of the articles, using the keyword ‘food fortification’ paired with ‘iron’ or ‘hemoglobin’ or ‘dual fortification’ or ‘triple fortification’ or ‘multiple micronutrient fortification’ and ‘fortification trial’.

Selection criteria

The search was regardless of language and publication status. These studies included multiple intervention groups with other micronutrients that were administered simultaneously; the outcome measure was the effect of Fe fortification on Hb concentration only. The studies were limited to publications where RCT evaluated Fe fortification among children aged <10 years for its effect on Hb concentration.

Data extraction and quality assessment

The title and abstracts of the studies identified in the web search were read and irrelevant studies were excluded. Full texts of the remaining studies were retrieved. To avoid publication bias, only peer-reviewed published studies were included. The extraction of data consisted of obtaining sample size, age, duration of intervention, levels of fortification and mean change and standard deviation of Hb concentration in the intervention and control groups. The search, data extraction and quality assessment were completed independently by two content experts according to the inclusion criteria and confirmed by using recommended criteria for RCT[25,26]. Concealment of allocation was classified as ‘adequate’, ‘unclear’, ‘inadequate’ or ‘not used’, based on randomization, blinding and reporting of withdrawals. Blinding was classified as ‘double blinding’, ‘single blinding’, ‘no blinding’ or ‘unclear’. In designs employing two or more different intervention groups (different levels of fortification or administration regimens) and a single control group, the sample size of the control group was equally allotted to the number of intervention groups while retaining the same mean value for the change and its standard deviation. In reporting such designs, each intervention subgroup was analysed separately. Thus, some studies contributed more than one intervention component with a single control group for the statistical analysis and resulted in a greater number of trials than the number of studies included.

Statistical analysis

Our primary outcome was the mean change in Hb concentration on account of consumption of Fe-fortified foods. The effect size, which is the difference in means between the Fe-fortified and the control groups, is referred to as the weighted mean difference (WMD) and was calculated for the selected trials. Once an effect size was estimated for each trial, the overall effect of these results was assessed by the Q statistic, that measures the extent of inconsistency among studies. The Q test was computed under the assumption of homogeneity among the effect sizes and the statistic follows the χ^2 distribution with $k-1$ degrees of freedom, k being the number of studies. Another strategy for quantifying the heterogeneity in a meta-analysis consists of estimating the variance (τ^2) between studies. The parameter I^2 quantifies the extent of heterogeneity from a collection of effect sizes, which is interpreted as approximately the percentage of total variation in study estimates due to heterogeneity rather than sampling error. The overall WMD of these results was assessed for sampling error (homogeneous, $\tau^2 = 0$). A fixed-effects meta-analysis was applied to obtain the pooled effect size with 95 % confidence interval or else a random-effects meta-analysis was performed (heterogeneous, $\tau^2 > 0$)[27,28].

The heterogeneity of results was represented in the form of a forest plot. Typically, for each study, there is a blob in the middle of the 95 % confidence interval that represents the single best mean estimate of the Hb concentration found in that study. The pooled or combined result of the WMD in Hb is represented by a diamond, the width of which is the 95 % confidence interval for the pooled data. A vertical line is displayed to indicate no effect and to differentiate between the studies that favour the intervention group or the control group. The forest plot also describes the χ^2 (Q-test statistic), τ^2, df, I^2, Z and P value. An I^2 value of more than 50 % is considered to indicate significant heterogeneity between the trials[29]. Publication bias was assessed with the funnel plot and Egger regression test. This is equivalent to a weighted, linear, ordinary least squares regression model with standard error as a covariate[30].

If heterogeneity existed ($I^2 > 50$ %), a meta-regression approach was used to test the study heterogeneity by relating study characteristics. The confounders were identified and a covariate meta-analysis was performed to estimate the net pooled effect size, after removing the effect of covariates (confounders).

Statistical analyses were performed with Review Manager (RevMan) software version 5·1, IBM SPSS version 19·0 and Comprehensive Meta-Analysis (CMA) software trial version (www.meta-analysis.com).

Results

Search results

A total of 846 articles were identified, of which 779 were excluded because they were not RCT or their interventions were not relevant to the purpose of the current analysis. Sixty-seven potentially relevant articles were selected for full text evaluation, out of which eighteen relevant articles were submitted to meta-analysis after employing the inclusion and exclusion criteria (Fig. 1).

Study characteristics and data quality

Characteristics of the eighteen studies included in the analysis[31–48] are shown in Table 1. All of these were RCT, out of which six were double blind, two were cluster randomized trials and the remaining ten were randomized trials. Of the ten RCT, all had similar Hb concentrations in intervention and control groups at baseline. A total of 5142 children of average age 6 months to 9·5 years, with levels of Fe fortification such that daily Fe intake through fortified food ranged between 3·5 and 12·7 mg per child, with intervention duration ranging between 6 and 24 months, were studied. These studies have been carried out over the past 20 years. Included in the analysis were five studies each from Brazil and India; two each from Vietnam and South Africa; and one each from Indonesia, Kenya, Korea and the USA.

All eighteen studies evaluated the effect of various levels of fortification on Hb concentration. Four studies of multiple interventions with multiple micronutrients were

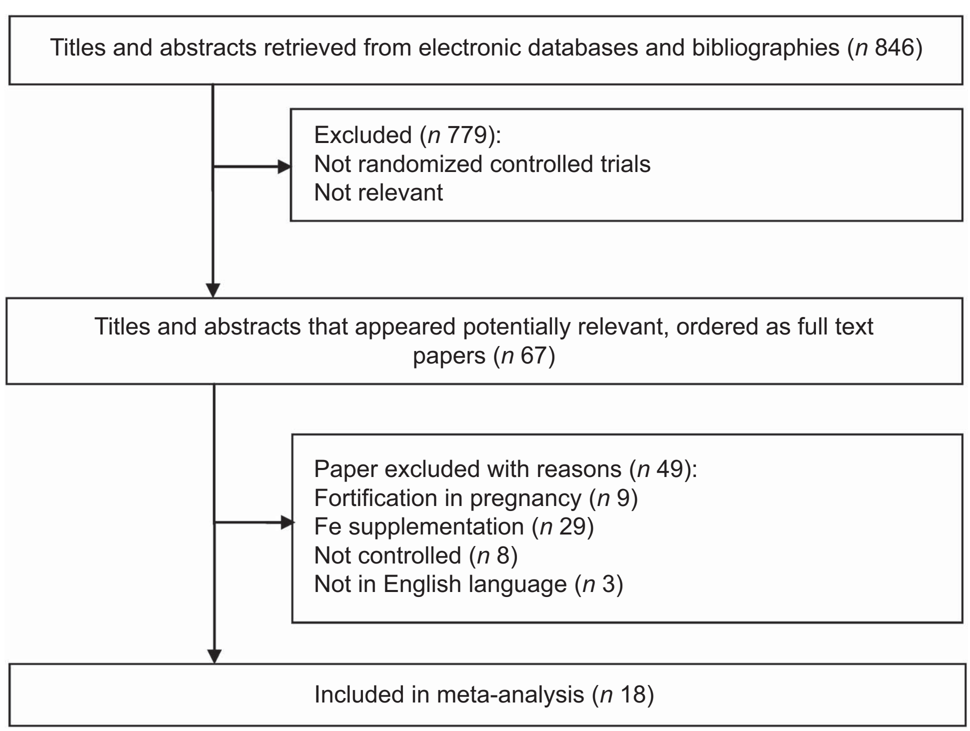

Fig. 1 Flow diagram for inclusion in the present meta-analysis of randomized controlled trials assessing the effect of iron-fortified foods on mean Hb concentration in children (<10 years)

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Table 1 Summary of trials assessing the effect of iron-fortified foods on mean Hb concentration in children (<10 years)

Reference	Year	Study duration (months)	Average age (years)	Level of fortification (mg/child per d)	Food vehicle	Fe compound	Country	Initial sample size	Study design
Bradley *et al.*[31]	1993	6	0·6	12·7 and 7·4	Milk	Ferrous sulfate	USA	347	B/A, DB
de Oliveira *et al.*[32]	1996	6	3·5	10	Water	Ferrous sulfate	Brazil	88	RCT, B/A
Giorgini *et al.*[33]	2001	6	3·5	4	Sweet roll	Iron bis-glycinate	Brazil	92	B/A
Sari *et al.*[34]	2001	3	5	4·5	Candies	Elemental ferrous	Indonesia	117	DB, PC
van Stuijvenberg *et al.*[35]	2001	12	8·5	5	Biscuits	Ferrous fumarate	South Africa	108	B/A
de Almeida *et al.*[36]	2003	4	3·5	4	Orange juice	Ferrous sulfate·7H_2O	Brazil	50	B/A
Beinner *et al.*[37]	2005	4	2·7	12	Water	Ferrous sulfate·7H_2O	Brazil	160	B/A
Moretti *et al.*[38]	2006	3·5	9·5	5	Rice	Ferric pyrophosphate	India	184	RCT, DB
van Stuijvenberg *et al.*[39]	2006	7·5	8·5	3·7	Sliced bread	Ferrous bis-glycinate	South Africa	160	RCT
Zimmermann *et al.*[40]	2006	4	7	10	Rice	Micronized ferric pyrophosphate	India	134	DB, RCT
Andang'o *et al.*[41]	2007	5	4·5	5·9	Maize	NaFeEDTA	Kenya	516	RCT
Le Huong *et al.*[42]	2007	6	7	10·7	Noodles	NaFeEDTA	Vietnam	425	RCT
Moreira-Araújo *et al.*[43]	2007	9	3·5	10	Snacks	Ferrous fumarate	Brazil	380	B/A
Varma *et al.*[44]	2007	6	4·3	14	Khichidi	Ferrous fumarate	India	516	CRT, DB
Rim *et al.*[45]	2008	6	0·8	10	Rice	Ferrous sulfate	Korea	234	RCT
Nga *et al.*[46]	2009	4	7	6	Biscuits	Ferrous fumarate	Vietnam	510	DB, RCT
Osei *et al.*[47]	2010	8	8	10	Micronutrient premix	NaFeEDTA	India	499	CRT, PC
Sazawal *et al.*[48]	2010	24	2	9·6	Milk	Ferrous sulfate	India	633	RCT
Mean		6·5	4·7	8·3					
SD		4·2	3·0	3·4					

B/A, before-and-after study; DB, double blind; RCT, randomized controlled trial; PC, placebo controlled; CRT, cluster randomized trial.

included and only those groups that received Fe were considered[31,38,44,46]. Of these four included studies, each one had more than one trial. The trials were either based on different levels of intervention of food fortification conducted on two occasions (before and after) or they were compared with placebo. In each trial the number of participants, mean and standard deviation of Hb concentration were estimated for conducting meta-analysis.

Effects of Fe fortification on Hb concentration

The meta-analysis results indicated that the mean change in Hb concentration was significantly higher in the Fe-fortified group than in the control group (n 5142; WMD = 5·09 g/l, 95 % CI 3·23, 6·95 g/l; $P<0·00001$), as depicted on the forest plot (Fig. 2). There was significant heterogeneity for the mean Hb concentration reported among the included trials. All statistical tests of heterogeneity – such as the Q statistic ($\chi^2 = 226·03$, df = 23), which was more than df; τ^2 greater than zero ($\tau^2 = 18·37$); and I^2 greater than 50 % ($I^2 = 90$ %) – were higher than the expected value, indicating heterogeneity among the studies. Meta-regression analysis was performed to detect the source of heterogeneity and indicated that the duration of the intake of fortified food was positively related to the effect size (regression coefficient = 0·368, 95 % CI 0·005, 0·731; $P<0·05$). The significant differences in the extent of improvement in Hb levels as reported in the forest plot (Fig. 2) are perhaps due to different time periods of the feeding regimens of Fe-fortified foods to the children. Increased duration of receiving fortified foods might have resulted in higher levels of Hb.

Covariate meta-analysis was performed to eliminate the effect of the confounder, duration of the study. Upon removal of the confounders the net effect of fortification on Hb concentration in children was found to be 4·74 (95 % CI 3·08, 6·40) g/l, as compared with the calculated pooled effect size of 5·09 (95 % CI 3·23, 6·95) g/l.

Publication bias

The funnel plot (Fig. 3) was symmetrical, indicating the probable absence of publication bias which was confirmed using Egger's weighted regression method (Egger test, $P = 0·6276$).

Discussion

The Fe fortification intervention varied across trials; hence, results should be interpreted accordingly. The present meta-analysis of eighteen studies consisting of twenty-four trials found that Fe fortification was significantly associated with increased Hb concentration in intervention children compared with the controls. However, there was heterogeneity in the results across the trials.

The present study adopted sequential statistical methods to verify that implementation of fortified foods with

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Study or subgroup	Intervention Mean	Intervention SD	Intervention n	Control Mean	Control SD	Control n	Weight (%)	Mean difference IV, random (95 % CI)
Osei (2010)	123·2	14·8	220	122·5	15.3	235	4·4	0·70 (–2·07, 3·47)
de Almeida (2003)	116·0	10·9	50	104·8	16.6	50	3·4	11·20 (5·70, 16·70)
Bradley (1993)_1	122	11	34	118	12	41	3·5	4·00 (–1·21, 9·21)
Bradley (1993)_2	119	10	20	115	8	21	3·4	4·00 (–1·56, 9·56)
Bradley (1993)_3	122	11	28	120	10	41	3·6	2·00 (–3·10, 7·10)
Bradley (1993)_4	117	11	21	113	7	26	3·4	4·00 (–1·42, 9·42)
Moretti (2006)_1	123	10	92	112	12	92	4·3	11·00 (7·81, 14·19)
Moretti (2006)_2	119	9	92	116	11	92	4·4	3·00 (0·10, 5·90)
de Oliveira (1996)	117	11	44	109	12	44	3·7	8·00 (3·19, 12·81)
Giorgini (2001)	126	13	89	115	11·1	89	4·1	11·00 (7·45, 14·55)
Rim (2008)	118·0	11·7	107	110·0	11·1	104	4·3	8·00 (4·92, 11·08)
Le Huong (2007)	125·4	14·5	72	123·4	15·0	73	3·7	2·00 (–2·80, 6·80)
Varma (2007)_1	116·9	10·3	244	109·9	10·3	269	4·7	7·00 (5·22, 8·78)
Varma (2007)_2	128	11	244	124	14	269	4·6	4·00 (1·83, 6·17)
Beinner (2005)	124	9	160	118	13	160	4·5	6·00 (3·55, 8·45)
van Stuijvenberg (2006)	127·1	7·5	53	127·5	7·4	51	4·4	–0·40 (–3·26, 2·46)
Sari (2001)	120·8	7·8	57	115·3	7·9	60	4·4	5·50 (2·65, 8·35)
Andang'o (2007)	112·2	9·9	127	115·7	9·7	128	4·5	–3·50 (–5·91, –1·09)
Moreira-Araújo (2007)	131	10	130	118	12	130	4·4	13·00 (10·31, 15·69)
Sazawal (2010)	109·0	11·4	233	95·4	15·4	232	4·5	13·60 (11·14, 16·06)
Nga (2009)_1	121·2	7·3	114	120·1	8·0	118	4·6	1·10 (–0·87, 3·07)
Nga (2009)_2	122·2	6·2	118	120·1	8·0	118	4·7	2·10 (0·27, 3·93)
van Stuijvenberg (2001)	129·1	8·1	108	125·5	8·1	108	4·6	3·60 (1·44, 5·76)
Zimmermann (2006)	121	9	66	119	12	68	4·1	2·00 (–1·58, 5·58)
Total (95 % CI)			2523			2619	100·0 %	5·09 (3·23, 6·95)

Heterogeneity: $\tau^2 = 18·37$; $\chi^2 = 226·03$, df = 23 ($P < 0·00001$); $I^2 = 90$ %
Test for overall effect: $Z = 5·38$ ($P < 0·00001$)

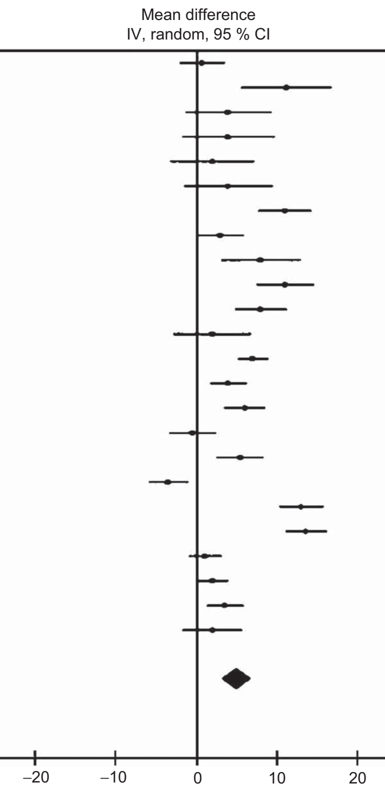

Fig. 2 Forest plot: effect of iron fortification on mean difference in Hb concentration in comparison with no intervention or placebo control in children (<10 years). Random-effects meta-analysis of weighted mean difference (WMD; and 95 % CI) on Hb concentration with iron-fortified food intervention compared with control group. The sizes of data markers indicate the weight of each study in the analysis. Horizontal lines represent 95 % CI. Blob indicates best estimate and diamond indicates the summary estimate of the WMD

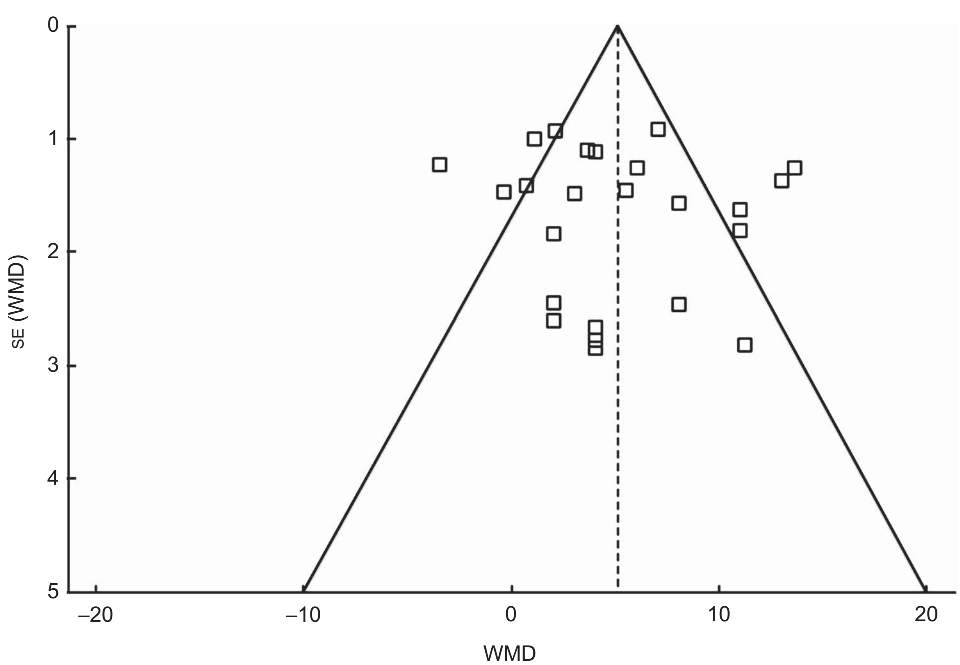

Fig. 3 Funnel plot of all individual studies in the meta-analysis. Studies that evaluated the effect of iron fortification on Hb concentration in children (<10 years) were plotted with their weighted mean difference (WMD) on the x-axis and the corresponding standard error of the WMD along the y-axis

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Fe improves Hb concentration in the child beneficiaries. The presence of heterogeneity is an important attribute of meta-analysis that can influence the results and was tested by the Q statistic, τ^2 and I^2, with the results represented in the form of a forest plot. The results of each trial included in the analysis showed the mean difference in Hb concentration (5·09 g/l) favours the intervention group, suggesting that the Fe fortification improves the mean Hb level of children. We found that the value of Q is more than the degrees of freedom, indicating heterogeneity and suggesting that the variation in the mean changes of Hb between intervention and control groups is due to systematic underlying differences[28,49]. One of the limitations of this statistic could be due to the inclusion of studies with $n < 30$[31] and this might have contributed to the heterogeneity. Similarly, the second measure of heterogeneity, τ^2, also indicated that the variance of WMD was more than zero, which confirms that there existed heterogeneity among the trials. A third measure of heterogeneity, the I^2 statistic, which is a derivative of Q, was 90 %, also suggesting heterogeneity among the selected trials[50,51].

Since there was heterogeneity among the trials, fixed-effects meta-analysis could not be performed and we applied the random-effects meta-analysis. The random-effects meta-analysis showed a significant impact of Fe fortification on Hb concentration among the child beneficiaries and provides evidence to suggest that food fortification with Fe is an ideal strategy to correct Fe-deficiency anaemia among children <10 years of age.

Further, to understand the true effect of food fortification with Fe on Hb concentration, meta-regression analysis was performed to explain the influence of confounders such as age, duration of intervention and levels of fortification[52]. We observed that the duration of the study is an effective confounder. The covariate meta-analysis showed that the net effect was 4·74 g/l after removing the effect of confounders. Yet another critical step in meta-analysis is the publication bias which can lead to inflated estimates of efficacy. We observed that there was heterogeneity among trials as some of the trials did not fit into the funnel. However, Egger's regression test suggested that there was no publication bias ($P = 0 \cdot 6276$).

One concern is related to the unresolved issue regarding an interaction between Fe and infection. As per the review by Oppenheinmer[53], most adverse effects of Fe supplementation have been reported following the use of parenteral Fe in geographical areas where malaria is endemic. Subsequently, the results of a trial conducted in Pemba, Zanzibar showed an increase in risk of hospitalization and mortality after Fe supplementation among Fe-replete children in a malaria-endemic setting[54]. A very similar trial in malaria-free areas in Nepal found no such adverse effect[55]. However, no adverse effects were reported in the studies covered in present paper where Fe-fortified foods were involved.

There is emerging evidence to suggest that reports of RCT from certain countries mostly have statistically positive results on micronutrients[56]. This may be due to the fact that in those countries, anaemia is largely due to Fe deficiency (single nutrient) rather than the multi-factorial aetiology reported from developing countries. However, the present study suggests the possibility of a positive effect of Fe fortification on Hb in children. This phenomenon needs to be investigated further. There is a need to conduct more trials in developing countries so as to investigate whether Fe fortification improves Hb concentration and also to assess other confounders, such as intakes of protein, energy and folic acid, which could contribute in improving Hb levels.

Conclusion

This present study suggests that consumption of Fe-fortified foods significantly increases the Hb concentration in children aged <10 years. Further research efforts should concentrate on higher quality and more rigorous randomized trials with longer follow-up to resolve the uncertainty regarding the safety and clinical effectiveness.

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