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Effect of combining multiple micronutrients with iron supplementation on Hb response in children: systematic review of randomized controlled trials

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Abstract

Objectives: To study the effect of combining multiple (two or more) micronutrients with Fe supplementation on Hb response, when compared with placebo and with Fe supplementation, in children.
Data sources: Electronic databases, personal files, hand search of reviews, bibliographies of books, and abstracts and proceedings of international conferences.
Review methods: Randomized controlled trials evaluating change in Hb levels with interventions that included Fe and multiple-micronutrient supplementation in comparison to placebo alone or Fe alone were analysed in two systematic reviews.
Results: Twenty-five trials were included in the review comparing Fe and micronutrient supplementation with placebo. The pooled estimate (random effects model) for change in Hb with Fe and micronutrient supplementation (weighted mean difference) was 0·65 g/dl (95 % CI 0·50, 0·80, $P < 0·001$). Lower baseline Hb, lower height-for-age Z score, non-intake of 'other micronutrients' and malarial non-hyperendemic region were significant predictors of greater Hb response and heterogeneity. Thirteen trials were included in the review comparing Fe and micronutrient supplementation with Fe alone. The pooled estimate for change in Hb with Fe and micronutrient supplementation (weighted mean difference) was 0·14 g/dl (95 % CI 0·00, 0·28, $P = 0·04$). None of the variables were found to be significant predictors of Hb response.
Conclusions: Synthesized evidence indicates that addition of multiple micronutrients to Fe supplementation may only marginally improve Hb response compared with Fe supplementation alone. However, addition of 'other micronutrients' may have a negative effect. Routine addition of unselected multiple micronutrients to Fe therefore appears unjustified for nutritional anaemia control programmes.

Keywords
Anaemia
Haemoglobin
Iron supplementation
Multiple-micronutrient supplementation
Meta-analysis

Anaemia is a major public health problem, particularly in the developing countries[1]. The problem is of more serious concern and magnitude in infants and children. Recent estimates from India documented an anaemia prevalence of approximately 80 % in children aged between 6 and 36 months[2]. Among the various causes of anaemia, nutritional deficiencies are believed to be of foremost importance[3], the most common being Fe deficiency. The association between Fe deficiency and anaemia has long been considered so strong that one is often used as a surrogate for the other.

Combating Fe deficiency through either supplementation or fortification is, therefore, considered the most important component of the current global initiatives for reducing rates of anaemia in children. However, the benefits of Fe supplementation demonstrated through clinical trials have not translated into a substantial reduction in the prevalence of anaemia on a public health scale. The earlier assumption that Fe supplementation might control anaemia to a major extent is, therefore, now being increasingly questioned[4,5]. In a recent meta-analysis evaluating the effects of Fe supplementation on anaemia in developing countries, the authors concluded that 'there is a suggestion in the data, not well documented except in a couple of studies, that something other than Fe may be operating to limit hemoglobin response and anaemia control'[5]. A recent systematic review evaluating the effect of Fe supplementation alone on Hb response in children estimated that on an average,

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in non-malarial endemic areas, between 38 % and 62 % of anaemia (Hb < 11 g/dl) is Fe responsive; the corresponding range for malarial hyperendemic regions was 6–32 %[6].

A probable reason for this is that apart from Fe, several other micronutrient deficiencies can cause anaemia[7–9]. For example, it is now established that vitamin A deficiency is associated with anaemia. Riboflavin, folate, ascorbic acid, Zn and vitamin B_{12} deficiencies are known to impair Hb synthesis. In addition to nutrient deficiencies, infections and parasites also contribute to anaemia; these include malaria, HIV infection and helminth infections[10–12].

Thus public health intervention to control anaemia should attempt to address all other causes, in addition to the obvious problem of Fe deficiency. One possibility would be to supplement other micronutrients in addition to Fe. Such an approach on a public health scale may also have the benefit of addressing the problems of various micronutrient deficiencies with a unified programmatic approach. Although such an approach of simultaneous supplementation with multiple micronutrients may seem attractive, there is a strong possibility that there may not be any additional haematinic benefit to Fe supplementation alone because of the possible negative interactions they may have on each other *in vivo*. In order to address this complex issue, two systematic reviews of randomized controlled trials (RCT) in children were conducted to: (i) study the effect of combining multiple (two or more) micronutrients with Fe supplementation on Hb response when compared with placebo; and (ii) study the effect of combining multiple (two or more) micronutrients with Fe supplementation on Hb response when compared with Fe supplementation alone.

Methods

Searching

A Medline search (from 1966 until 6 February 2006) was conducted by using the search word 'iron' with limits pertaining to 'English language' and 'human' for both clinical trials and RCT; and by using the search words 'iron fortif*' and 'iron supplement*' with similar limits. A similar search of the COCHRANE controlled trials register using the search words 'iron fortif*' or 'iron supplement*' was also conducted. A search of the EMBASE database from 1982 to 29 January 2006 using the search words 'iron supplement*' or 'iron fortif*' limited to 'human' and 'English' was also made. Similar searches were also made using the IBIDS database and the Healthstar database. The title and abstract of the studies identified in the computerized search were scanned to exclude studies that were obviously irrelevant. The full text of the remaining studies was retrieved and relevant articles were identified. The reference lists of the identified articles were also reviewed to search for citations not listed in the computerized databases. These were supplemented by hand searches of reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings. Finally donor agencies, 'experts' and authors of recent Fe and micronutrient supplementation trials were contacted for their knowledge of any additional or ongoing trials. To avoid publication bias, effort was made to include both published and unpublished trials.

Selection

The predefined criteria for inclusion of trials in the systematic review were: (i) randomized placebo-controlled efficacy trials involving Fe supplementation in combination with two or more other micronutrients; and (ii) Hb as one of the evaluated outcome measures.

Studies in which other drugs were also simultaneously administered were included if the only difference between the study and the control groups was supplementation with two or more micronutrients, for the second objective, and Fe plus two or more micronutrients for the first objective.

Validity assessment

We assessed the quality of trials using recommended criteria[13,14]. Concealment of allocation was classed as adequate, unclear, inadequate, or not used. To assess attrition we classified studies by percentage of participants lost to follow-up (<3 %, 3–9·9 %, 10–19·9 % and ≥20 %). Blinding was classified as double blinding, single blinding, no blinding, and unclear.

Data abstraction

Data abstraction was done using preformed questionnaires. The data included in the review were derived from the published manuscript or were those provided by the authors (in cases of unpublished studies). Wherever possible, the authors were contacted for further clarifications, if required. T.G. abstracted all of the data.

Study characteristics

The studies were grouped and analysed for change in Hb before and after the supplementation period. To study the efficacy of multiple-micronutrient supplementation with Fe, one systematic review was done including those RCT which compared their haematinic effect with a placebo. To study the additive haematinic effect provided by the multiple micronutrients, a separate systematic review was done including those studies whose two treatment arms were Fe alone *v.* Fe and multiple micronutrients.

The contribution to heterogeneity of the variables in the pre-specified stratified analyses was also explored by meta-regression analysis using the METAREG command in STATA software with the restricted maximum likelihood option[15].

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Quantitative data synthesis

For computing the pooled estimates we were primarily interested in the extraction of sample size, mean change in Hb from the beginning to the end of intervention, and the SD of this change in the intervention and the control groups. Wherever available, the stated (or communicated/clarified) values were utilized for the computations.

In designs employing two or more different intervention groups (different dosage or administration regimens) and a single control group, to avoid multiple counting of the control group, the sample size of the control group was equally cleaved into the number of intervention groups while retaining the same value for the change and its SD (A Oxman, personal communication, 2003; J Deeks, personal communication, 2003). For an uneven split, a higher size in the cleaved control group was given to the intervention group with lower sample size or higher SD. In publications reporting such designs, each intervention subgroup was analysed separately for the purpose of meta-analysis. Thus, some trials contributed more than one 'analytic component' for the purpose of statistical analyses. This resulted in a greater number of 'analytic components' than the included trials.

The following principles were employed for derivations, if actual variables of interest were not stated: (i) in a group, the lower of the two stated sample sizes at the beginning or the end of a trial was assumed to be the sample size for the change; (ii) wherever feasible, SD were imputed (back-calculated) from the stated SE, *t* or *P* values; (iii) wherever unstated, the mean age of subjects was computed as the average of the stated range; and (iv) wherever unstated, the mean change in Hb was computed as the difference of mean post- and pre-intervention levels.

The SD for the change in Hb could be extracted or imputed (from SE, *t* or *P* values) in several but not all studies. In the remaining trials, these SD were computed using the following assumptions: (i) correlation of 0·5 between the pre-test and post-test variances[16]; and (ii) pre-test and post-test samples considered to be independent (no correlation). Considering the number of assumptions and imputations involved, for a confident interpretation, three types of pooled estimates were calculated. In two of these, the change SD for unstated or non-imputable values were computed with the assumptions of correlation (*p*) equal to 0·5 or of independence, while for the third the post-intervention levels and their respective SD were utilized. If the statistical significance was synchronous for all the three types of computations, the interpretation was obviously robust. However, for any discrepancy in significance computations by these three methods, the interpretation was considered to be statistically significant only if at least two of the three estimates had a probability value below 0·05.

The presence of publication bias in the extracted data was evaluated quasi-statistically using the funnel plot[17]. Statistical tests for funnel plot asymmetry, namely Begg's and Egger's methods, were conducted using the METABIAS command in the STATA software[15]. The pooled estimates of the weighted mean difference of the evaluated change in Hb between the control and treatment group were calculated by both fixed effects and random effects model assumptions using the METAN command in STATA software[15]. This program (STATA version 9·2; StataCorp LP, College Station, TX, USA) also computes the formal test of heterogeneity, the statistic *Q*. We report primarily random effects estimates because of frequent statistical heterogeneity in the pooled results.

Stratified analyses (specified in advance) were conducted for: (i) methodological quality; (ii) route of Fe and micronutrient administration (oral medicinal supplement or food fortification); (iii) duration of supplementation; (iv) baseline Hb of the supplemented group; (v) nature and total number of micronutrients given; (vi) nutritional status of the study population; and (vii) development status and malarial endemicity of the study area. The contribution of these variables to heterogeneity was also explored by meta-regression analysis[15]. A variable was considered to be an important explanatory factor if statistical significance was consistently documented in the stratified and in the meta-regression analyses. A greater credence was attached to the meta-regression results, particularly those controlling for all variables.

Results

A total of thirty-six studies were identified as potentially eligible for inclusion in the systematic review. After thorough scrutiny, six of these trials were excluded for specific reasons (Fig. 1)[18–23]. Thus thirty trials (Table 1) were included in the systematic review, of which twenty-nine[24–52] were published in various indexed journals whereas one was unpublished (HA Abdelwahid, MS Khattab, MAA Mostaffa, HF El-sayed and AE Saad, The effect of treatment with Vit. A alone or in combination with iron in iron deficient anemic children in Ismailia city, unpublished results). Table 1 depicts the characteristics of the analysed trials. To evaluate the additional haematinic effect of multiple micronutrients, separate analyses were done for studies that compared the effect of Fe and micronutrient supplementation with placebo; and those studies that compared the effect of Fe and micronutrient supplementation with Fe supplementation.

Iron and multiple micronutrient supplementation v. *placebo*

Study characteristics

A total of twenty-five studies (contributing thirty-five analytic components) were included in this systematic review. All of the studies were from developing countries (eleven trials were from Asia, three were from South America and eleven were from Africa). The studies were

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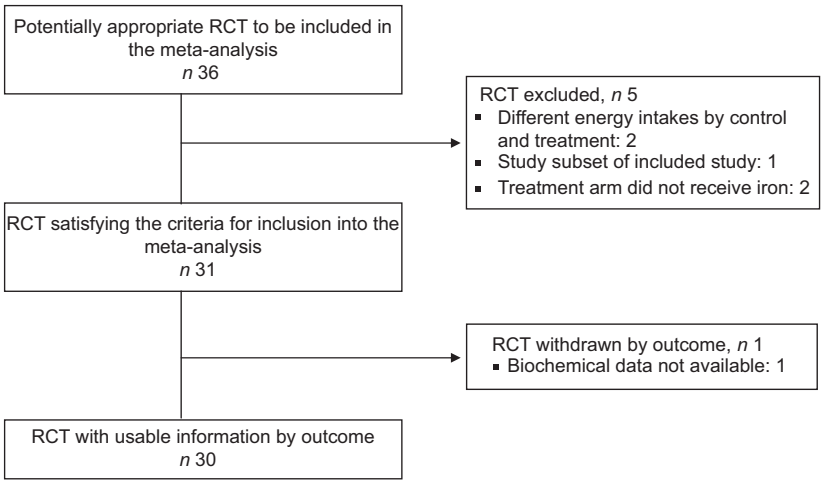

Fig. 1 Selection process for randomized controlled trials (RCT) included in the present meta-analysis

equally distributed with respect to the age group of the study population; thirteen were conducted in infants and pre-school children (0–5 years) and twelve trials included older children (>5 years of age). In three studies, evaluation was done for 2 months or less, while twenty-two investigators followed up the subjects for longer. In almost half of the studies (13/25) a medicinal supplement was used, the rest (12/25) used fortified foods. In the thirty-five analytic components, Fe and micronutrient supplementation was done daily in fifteen and intermittently in the rest.

Quantitative data synthesis

The funnel plot (Fig. 2) was symmetrical, indicating the probable absence of publication bias which was confirmed using Egger's (weighted regression) method (P for bias = 0·16) and Begg's (rank correlation) method (continuity corrected $P = 0·94$).

Data were available on 4981 subjects, 2675 of whom received Fe with other micronutrients and 2316 a placebo. The pooled weighted mean difference (WMD) of the Hb change (pre- to post-test difference) following Fe and micronutrient supplementation was 0·65 g/dl (95 % CI 0·50, 0·80, $P < 0·001$; test for heterogeneity $Q = 306·47$, $I^2 = 89·6\,\%$, $P < 0·001$) (Fig. 3). The results were similar when the SD were calculated by assuming $p = 0·5$ (depicted in previous sentence), by independence assumption (WMD = 0·65 g/dl, 95 % CI 0·5, 0·8, $P < 0·001$; test for heterogeneity $Q = 291·92$, $I^2 = 89·0\,\%$, $P < 0·001$) and with post-test scores (Table 2). The effect size also was similar when the analysis was restricted to studies with available (or imputed) Hb change SD scores (WMD = 0·65 g/dl, 95 % CI 0·47, 0·82, $P < 0·001$; test for heterogeneity $Q = 274·03$, $I^2 = 92·0\,\%$, $P < 0·001$).

Sensitivity and stratified analyses suggested that a higher Hb response was seen in studies with an attrition rate over 10 %, non double-blinded studies, in malarial non-endemic regions, with medicinal supplementation, with increasing dose, frequency and duration of supplementation, and in children with lower weight-for-age, weight-for-height and height-for-age Z scores. Also, subjects receiving 'other micronutrients' (micronutrients other than Zn, vitamin A, riboflavin, B_{12}, folic acid and ascorbic acid) had a significantly lower Hb response (Table 2).

Combined scrutiny of stratified and meta-regression analyses indicated that lower baseline Hb, lower height-for-age Z score and no intake of 'other micronutrients' (micronutrients other than Zn, vitamin A, riboflavin, B_{12}, folic acid and ascorbic acid) were significant predictors of a positive effect of Fe and multiple-micronutrient supplementation, whereas residence in a malarial non-endemic area was close to statistical significance ($P = 0·06$) on meta-regression with univariable analysis for a positive haematinic effect of the supplement (Table 3).

Iron and multiple-micronutrient supplementation v. *iron supplementation*

Study characteristics

A total of thirteen studies (contributing fifteen analytic components) were included in this systematic review. All studies, except one, were from developing countries (three in Asia, three in South and Latin America, one in North America and six in Africa). Most (11/13) of the trials were conducted in infants and pre-school children (0–5 years) and only two trials included older children (>5 years of age). In two studies, evaluation was done over 2 months or less, while eleven investigators followed the subjects for more than 2 months. In almost half of the studies the subjects received Fe and multiple-micronutrient supplementation in the form of oral medicine (7/13); in six studies fortified foods were ingested. In the fifteen analytic components, Fe and micronutrient

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Table 1 Characteristics of randomized controlled trials (RCT) included in the present meta-analysis

Study	Location	Age group	Methods: randomization, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Supplementation
Bradfield *et al.* (1968)[24]	Peru, South America	7–13 years	Not mentioned, B, B, A	All malaria-free prepubertal school children of a local school	Test suppl: Fe, Vit B_1, B_2, B_{12}, FA, niacin Control suppl: placebo or Fe Oral Dose: 5 mg/d Frequency of suppl: daily Duration of suppl: 2·5 months
Bates *et al.* (1987)[25]	Gambia, Africa	5–14 years	Stratified randomization, B, A, B	Resident of Keneba village	Test suppl: Fe, Vit B_1, B_2, C Control: matching placebo Oral Frequency of suppl: 2/week Duration of suppl: 3 months
Stekel *et al.* (1988)[26]	Chile, South America	0–12 months	By date of birth, D, C, A	Inclusion criteria: infant beneficiary of national health system Exclusion criteria: residents of child care centre; residents of other area	Test suppl: Fe, Vit A, C, D Control: unfortified milk Fortification Frequency of suppl: daily Duration of suppl: 9 months
Liu *et al.* (1993)[27]	China, Asia	6–13 months	Block randomization, B, B, D	Inclusion criteria: BW $>$ 2·5 kg Exclusion criteria: Hb $<$ 10 g/dl	Test suppl: Fe, Ca, Zn, Vit A, D, B_1, B_2, B_{12}, FA, niacin Control: unfortified rusk Fortification Dose: 5 mg/d Frequency of suppl: daily Duration of suppl: 3 months
Bates *et al.* (1994)[28]	Gambia, Africa	8–14 years	Stratified randomization, A, A, A	Residents of Keneba and Kanton Kundar villages of eligible age	Test suppl: Fe, Vit A, D, E, C, B_1, B_2, B_6, B_{12}, biotin, nicotinamide, pantothenate, PGA Control: lactose tablet Oral Dose: 60 mg/d Frequency of suppl: 1/week Duration of suppl: 1·5 months
Husaini *et al.* (1996)[29]	Indonesia, Asia	1 year	Block randomization, B, B, A	Infants who attended day care centres, WHZ $= -1$ to -2, LAZ < -1	Test suppl: Fe, Zn, Cu, Ca, P, Mn, Mg, Vit A, C, D, E, B_1, B_2, B_6, B_{12}, FA, biotin, pantothenate, nicotinamide Control: placebo Oral Dose: 24 mg/d Frequency of suppl: daily Duration of suppl: 12 months
Dalton *et al.* (1997)[30]	USA, North America	2·5–5 months	Simple randomization, B, A, D	Inclusion criteria: resident of area, drinking $>$ 600 ml milk/d, BW $>$ 2 kg, ht and wt above 5th centile for age, no history of rickets, parathyroid dysfunction, no medicine/vitamins Exclusion criteria: haematuria/ hypercalciuria, failure to follow-up, poor compliance	Test suppl: standard formula, Ca, P Control: standard formula Fortification Frequency of suppl: daily Duration of suppl: 9 months

Table 1 *Continued*

Study	Location	Age group	Methods: randomization, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Supplementation
Angeles-Agdeppa *et al.* (1997)[31]	Indonesia, Asia	14–18 years	Simple randomization, B, A, D	Hb < 12 g/dl, menstruating regularly	Test suppl: Fe, Vit A, C, FA Control: placebo Oral Dose: 60 mg/d or 120 mg/d Frequency of suppl: 5/week or 1/week Duration of suppl: 3 months
Thu *et al.* (1999)[32]	Vietnam, Asia	6–24 months	Simple randomization, B, A, A	Inclusion criteria: resident of Chi Lang Bac commune Exclusion criteria: infection at enrolment, BW < 2·5 kg	Test suppl: Fe, Zn, Vit A, C Oral Dose: 8 mg/d or 20 mg/d Frequency of suppl: 5/week or 1/week Duration of suppl: 3 months
Ekvall *et al.* (2000)[33]	Tanzania, Africa	5 months–3 years	Computer-generated random numbers, B, A, B	Inclusion criteria: resident of Fukiyaso village of eligible age Exclusion criteria: congenital malformations, Hb < 5 g/dl, migration plans	Test suppl: Fe, Vit A, D, C, E, B1, B2, B6, niacin Control: promethazine placebo Oral Dose: 10 mg/d Frequency of suppl: 3/week Duration of suppl: 5 months
Sharma *et al.* (2000)[34]	India, Asia	11–18 years	Not mentioned, B, D, A	Residents of the study area	Test suppl: Fe, Vit C, FA Control: placebo Oral Dose: 100 mg/d Frequency of suppl: 1/week Duration of suppl: 6 months
Jinabhai *et al.* (2001)[35]	South Africa, Africa	8–10 years	Simple randomization, B, A, B	Grade 3 students of selected schools	Test suppl: Fe, Vit A, B, Ca, Zn Control: unfortified biscuit Fortification Dose: 5 mg/d Frequency of suppl: 5/week Duration of suppl: 4 months
Abdelwahid *et al.* (2001)†	Egypt, Africa	6–12 years	Simple randomization, B, D, A	Fe-deficient anaemic children with low Vit A levels	Test suppl: Fe, multivitamins (not mentioned) Control: nothing or Fe Oral Dose: not mentioned Frequency of suppl: 7/week Duration of suppl: 2 months
Dossa *et al.* (2001)[36]	Benin, Africa	18–30 months	Random numbers table, B, D, A	Inclusion criteria: Hb < 11 g/dl, HAZ < −2 Exclusion criteria: HAZ < −5, did not like/eat rice	Test suppl: Fe, Zn, Cu, I, Mn, Cr, Se, Mb, Ca, Mg, Vit A, B_1, B_2, B_6, B_{12}, C, D, E, FA, niacin, pantothenate Control: placebo or Fe Oral Dose: 66 mg/d Frequency of suppl: 7 week Duration of suppl: 3 weeks

Table 1 *Continued*

Study	Location	Age group	Methods: randomization, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Supplementation
Sari *et al.* (2001)[37]	Indonesia, Asia	4–6 years	Simple randomization, A, A, C	Apparently healthy children, Hb > 8 g/dl	Test suppl: Fe, I, Vit A, C, E, B_1, B_2, B_6, B_{12}, FA, niacin Control: identical candy Fortification Dose: 10 mg/d Frequency of suppl: 3 week Duration of suppl: 3 months
Ahmad *et al.* (2001)[38]	Bangladesh, Asia	14–19 years	Simple randomization, A, A, D	Inclusion criteria: Hb = 8–12 g/dl Exclusion criteria: chronic or infectious disease	Test suppl: Fe, Vit A, FA Control: placebo Oral Dose: 120 mg/d Frequency of suppl: 1/week Duration of suppl: 3 weeks
van Stuijvenberg *et al.* (2001)[39]	South Africa, Africa	6–11 years	Systematic randomization, B, B, B	Students of Ndunakazi public school	Test suppl: Fe, I, Vit A, C Control: unfortified biscuit and drink Fortification Dose: 5 mg/d Frequency of suppl: 5 week Duration of suppl: 12 months
Young (2001)[40]	Malawi, Africa	15–60 months	Not mentioned, D, D, D	Children attending the mobile health clinic	Test suppl: Fe, Vit A, C, D_3, B_1, B_2, B_3 Control: Fe Oral Dose: 60 mg/d Frequency of suppl: 1/week Duration of suppl: 3 months
Tomashek *et al.* (2001)[41]	Tanzania, Africa	6–59 months	Stratified randomization, C, B, C	Inclusion criteria: Hb = 5–8 g/dl Exclusion criteria: heart failure, severe malaria, splenomegaly, sickle cell disease	Test suppl: Fe, FA, Vit A, C, SP Control: Fe, FA and SP Oral Dose: 60 mg/d Frequency of suppl: 3/week Duration of suppl: 3 months
Oelofse *et al.* (2003)[42]	South Africa, Africa	6 months	Not mentioned, B, D, D	BW > 2·5 kg, no congenital anomaly	Test suppl: Fe, Vit A, C, D, B_1, B_2, B_6, B_{12}, Ca, Zn Control: Fe, Vit A Fortification Dose: 8 mg/d Frequency of suppl: 7/week Duration of suppl: 6 months
Ash *et al.* (2003)[43]	Tanzania, Africa	6–11 years	Not mentioned, B, A, B	Inclusion criteria: students of selected schools Exclusion criteria: Hb < 7 g/dl, xerophthalmia, serious chronic disease	Test suppl: Fe, I, Zn, Vit A, C, E, B_2, B_6, B_{12}, FA Control: identical beverage Fortification Dose: 5·4 mg/d Frequency of suppl: 5/week Duration of suppl: 6 months
Lopriore *et al.* (2004)[44]	Algeria, Africa	3–6 years	Not mentioned, A, A, D	Inclusion criteria: resident of Saharawi refugee camp, HAZ < −2 Exclusion criteria: severe or chronic illness, severe clinical malnutrition, congenital abnormality	Test suppl: Fe, Zn, Cu, Ca, P, K, Mg, Vit A, D, E, C, B_1, B_2, B_6, B_{12}, folate, niacin, pantothenate Control: unfortified spread Fortification Dose: 21 mg/d Frequency of suppl: 7/week Duration of suppl: 6 months

Table 1 *Continued*

Study	Location	Age group	Methods: randomization, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Supplementation
Black *et al.* (2004)[45]	Bangladesh, Asia	6 months	Not mentioned, B, A, A	Inclusion criteria: informed consent given, MUAC > 110 mm, Hb > 9 g/dl Exclusion criteria: received infant formula, obvious neurological disorders, physical disability or chronic illness	Test suppl: Fe, Zn, I, Cu, Mn, Se, Vit C, D, E, B_1, B_2, B_6, B_{12}, FA, niacin, pantothenate Control: Zn or riboflavin or Fe or Fe, Zn Oral Dose: 20 mg/d Frequency of suppl: 1/week Duration of suppl: 6 months
Alarcon *et al.* (2004)[46]	Peru, South America	6–35 months	Block randomization, B, A, A	Inclusion criteria: Hb = 7·0–9·9 g/dl Exclusion criteria: severe anaemia, chronic disease, dietary restriction, previous treatment with micronutrients, measles in past 2 months, WHZ/HAZ < −3	Test suppl: Fe, Zn, Vit A Control: Fe Oral Dose: 30 mg/d Frequency of suppl: 6/week Duration of suppl: 4·5 months
Faber *et al.* (2005)[47]	South Africa, Africa	6–12 months	Block randomization, C, B, C	Inclusion criteria: all eligible infants Exclusion criteria: BW < 2·5 kg, Hb < 8·0 g/dl, baseline sample not obtained, consent refused	Test suppl: Fe, Vit A, B_2, B_6, B_{12}, C, E, Zn, Cu, Se Control: unfortified cereal Fortification Dose: 11 mg/d Frequency of suppl: 7 week Duration of suppl: 6 months
Le Hop & Berger (2005)[48]	Vietnam, Asia	6–12 months	Simple randomization, A, A, D	Inclusion criteria: residents of the study area who gave informed consent Exclusion criteria: WHZ < −3, fever, BW < 2·5 kg, Hb<8 mg/dl, premature birth	Test suppl: Fe, Zn, Cu, I, Vit A, C, D, E, B_1, B_2, B_6, B_{12}, FA, niacin Control: placebo or Fe Fortification Dose: 10 mg/d Frequency of suppl: 7 or 1/week Duration of suppl: 6 months
Smuts *et al.* (2005)[49]	South Africa, Africa	6–12 months	Simple randomization, A, A, D	Inclusion criteria: residents of the study area who gave informed consent Exclusion criteria: WHZ < −3, fever, BW < 2·5 kg, Hb < 8 g/dl, premature birth	Test suppl: Fe, Zn, Cu, I, Vit A, C, D, E, B_1, B_2, B_6, B_{12}, FA, niacin Control: placebo or Fe Fortification Dose: 10 mg/d Frequency of suppl: 7 or 1 week Duration of suppl: 6 months
López de Romaña *et al.* (2005)[50]	Peru, South America	6–12 months	Simple randomization, A, A, C	Inclusion criteria: residents of the study area who gave informed consent Exclusion criteria: WHZ < −3, fever, BW < 2·5 kg, Hb < 8 g/dl, premature birth	Test suppl: Fe, Zn, Cu, I, Vit A, C, D, E, B_1, B_2, B_6, B_{12}, FA, niacin Control: placebo or Fe Fortification Dose: 10 mg/d Frequency of suppl: 7 or 1/week Duration of suppl: 6 months
Untoro *et al.* (2005)[51]	Indonesia, Asia	6–12 months	Simple randomization, A, A, B	Inclusion criteria: residents of the study area who gave informed consent Exclusion criteria: WHZ < −3, fever, BW < 2·5 kg, Hb < 8 g/dl, premature birth	Test suppl: Fe, Zn, Cu, I, Vit A, C, D, E, B_1, B_2, B_6, B_{12}, FA, niacin Control: placebo or Fe Fortification Dose: 10 mg/d Frequency of suppl: 7 or 1/week Duration of suppl: 6 months

Table 1 *Continued*

Study	Location	Age group	Methods: randomization, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Supplementation
Tielsch *et al.* (2006)[52]	Nepal, Asia	1–35 months	Block randomization, A, A, D	Inclusion criteria: all children living in the study area Exclusion criteria: refusal to give consent	Test suppl: Fe, FA, Zn Control: placebo Oral Dose: 12·5 mg/d Frequency of suppl: 7/week Duration of suppl: 12 months

BW, birth weight, WHZ, weight-for-height *Z* score; LAZ, length-for-age *Z* score; ht, height; wt, weight; Vit, vitamin(s); HAZ, height-for-age *Z* score; MUAC, mid upper-arm circumference; suppl, supplement/supplementation; PGA, pteroyl glutamic acid; FA, folic acid; SP, sulfadoxine-pyrimethamine.
*Allocation concealment: A, adequate; B, unclear; C, inadequate; D, not used. Follow up: A, <3 % of participants excluded; B, 3 % to 9·9 % of participants excluded; C, 10 % to 19·9 % of participants excluded; D, 20 % or more of participants excluded. Blinding: A, double blinding; B, single blinding; C, no blinding; D, unclear.
†Unpublished study (HA Abdelwahid, MS Khattab, MAA Mostaffa, HF El-sayed and AE Saad, The effect of treatment with Vit. A alone or in combination with iron in iron deficient anemic children in Ismailia city, unpublished results).

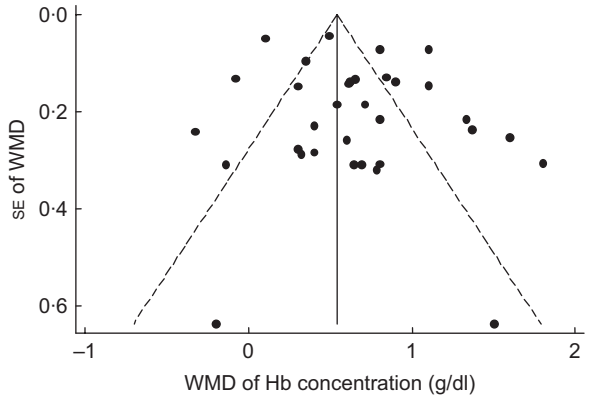

Fig. 2 Funnel plot with pseudo 95 % confidence limits of weighted mean difference (WMD) in Hb concentration for iron and multiple micronutrients *v.* placebo, with unknown SD derived with assumption $p = 0{\cdot}5$

supplementation was done daily in eleven and intermittently in the rest.

Quantitative data synthesis

The funnel plot (Fig. 4) was symmetrical, indicating the probable absence of publication bias, which was confirmed using Egger's (weighted regression) method (P for bias = 0·62) and Begg's (rank correlation) method (continuity corrected $P = 0{\cdot}92$).

This systematic review provides pooled data on 1483 subjects, 707 received Fe and multiple micronutrients while 776 received Fe alone (Table 4). The pooled WMD of the Hb change (pre- to post-test difference) following Fe with micronutrient supplementation compared with Fe alone was 0·14 g/dl (95 % CI 0·00, 0·28, $P = 0{\cdot}044$; test for heterogeneity $Q = 58{\cdot}41$, $I^2 = 76{\cdot}0\,\%$, $P < 0{\cdot}001$) (Fig. 5). The results were almost the same when the SD were calculated by assuming $p = 0{\cdot}5$ (depicted in previous sentence) and by independence assumption but not significant when using post-test scores. The effect size was higher when the analysis was restricted to those studies with available (or imputed) Hb change SD scores (WMD = 0·22 g/dl, 95 % CI 0·05, 0·39, $P = 0{\cdot}014$; test for heterogeneity $Q = 46{\cdot}42$, $I^2 = 87{\cdot}1\,\%$, $P < 0{\cdot}001$) (Table 4).

On combined scrutiny of stratified and meta-regression analyses, none of the variables was found to be a significant predictor (Tables 4 and 5).

Discussion

The results from the present largely heterogeneous data set derived from randomized controlled efficacy trials reveal that combined Fe and micronutrient supplementation in comparison to placebo alone resulted in a significant increase in Hb in children (WMD = 0·65 g/dl, 95 % CI 0·50, 0·80, $P < 0{\cdot}001$). The rise was greater in initially anaemic subjects and children with lower height-for-age *Z* scores;

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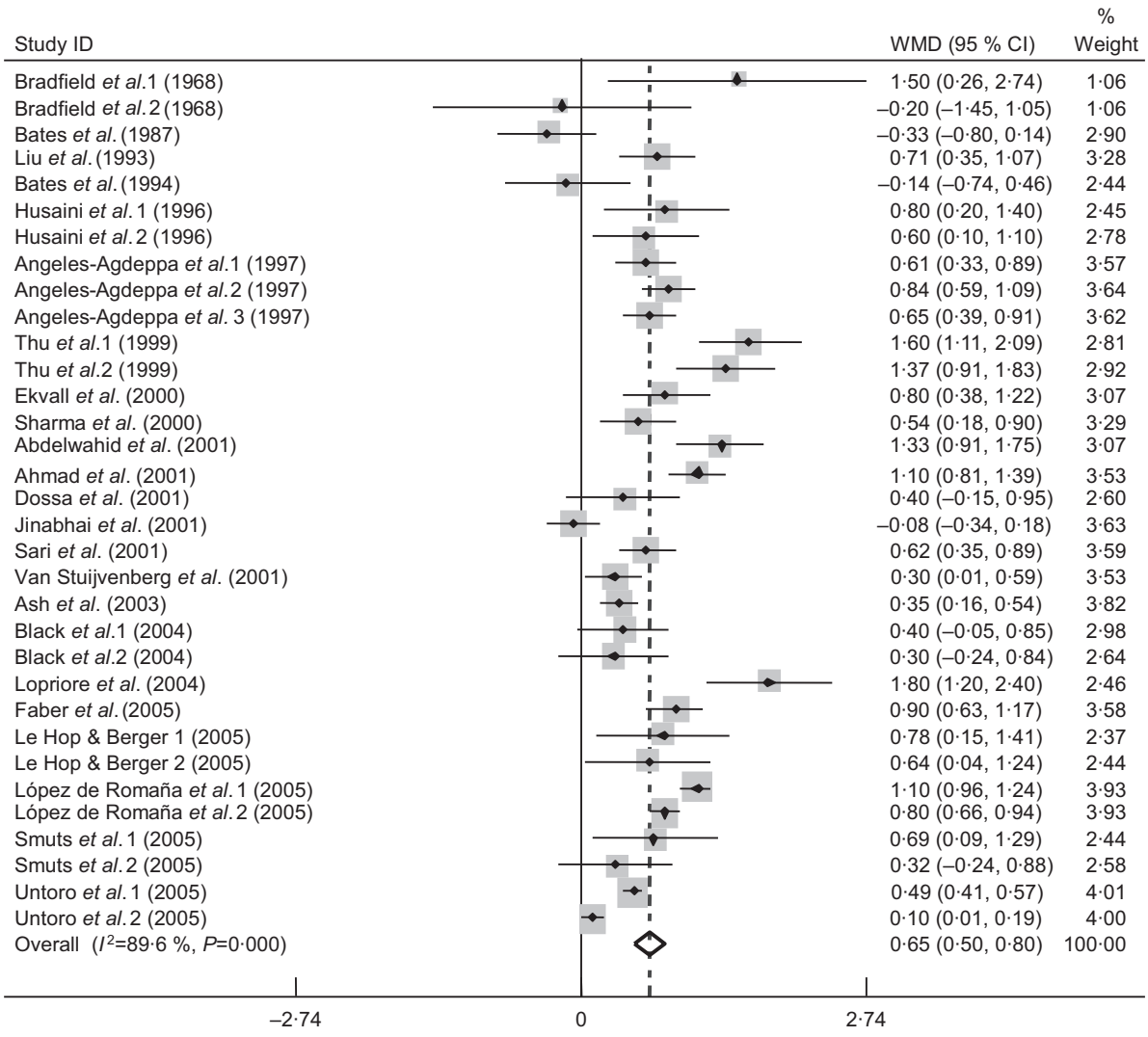

Fig. 3 Forest plot for iron and multiple micronutrient *v.* placebo with unknown SD derived with assumption $p = 0{\cdot}5$. Weighted mean difference (WMD) in Hb concentration, 95 % confidence interval and weights from random effects analysis are given; see Table 1 for details of the studies

and was lower in malarial hyperendemic areas and with addition of micronutrients other than vitamin A, riboflavin, Zn, vitamin B_{12}, folic acid and ascorbic acid. These parameters were also significant predictors for heterogeneity on meta-regression analysis. On pooled analyses of studies comparing combined Fe and micronutrients *v.* Fe supplementation alone, the addition of multiple micronutrients to Fe resulted in a small but significant increase in Hb (WMD = 0·14 g/dl, 95 % CI 0·00, 0·28, $P = 0{\cdot}04$). On stratified and meta-regression analyses, none of the variables emerged as a significant predictor.

It is prudent to examine the strengths and limitations of these analyses before drawing operational inferences. The main conclusion in relation to the rise in Hb concentration remained stable over the large spectrum of sensitivity analyses performed. Influence analyses, i.e. the effect of omitting one study at a time (data not depicted), did not reveal an overwhelming effect of any single trial.

However, the following limitations merit consideration. First, anaemia is a disease with multifactorial aetiology. Most of the included trials did not identify the cause of anaemia or the relative contribution from Fe and micronutrient deficiencies. This is important because lower Hb levels have often been attributed to other potential confounding factors such as poverty, undernutrition, maternal hypoferraemia, haemoglobinopathies, worm infestation, malaria and other coexistent infections. Second, we could not confidently differentiate between the therapeutic and preventive effects of Fe and multiple-micronutrient supplementation. This was because very few studies provided relevant data or they were not conducted with the objective and sample sizes to evaluate a preventive role. Third, in the absence of actually stated data on the variability of the change in outcome scores, several imputations had to be done on the basis of pre-specified assumptions. The sensitivity analyses suggest

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Table 2 Sensitivity and subgroup analyses of pooled estimates of Hb weighted mean difference (WMD) for studies comparing iron and micronutrient supplementation *v.* placebo

Stratification variable	No.*	Random effects model			Tests for heterogeneity			*P* for heterogeneity in subgroups
		WMD	95 % CI	*P*	I^2 (%)	*Q*	*P*	
Overall								
Change SD available	23	0·65	0·47, 0·82	<0·001	92·0	274·03	<0·001	
SD by $p = 0·5$	33	0·65	0·50, 0·80	<0·001	89·6	306·47	<0·001	
SD by independence	33	0·65	0·50, 0·80	<0·001	89·0	291·92	<0·001	
Post-test scores & SD	35	0·54	0·40, 0·69	<0·001	79·3	164·29	<0·001	Not applicable
Allocation concealment								
Others	21	0·63	0·44, 0·82	<0·001	94·5	199·08	<0·001	0·411
Adequate	12	0·69	0·43, 0·94	<0·001	81·3	106·71	<0·001	
Attrition								
<10 %	19	0·50	0·32, 0·69	<0·001	86·7	135·80	<0·001	
>10 %	14	0·83	0·69, 0·96	<0·001	66·1	38·30	<0·001	<0·001
Blinding								
Double-blind	23	0·64	0·46, 0·81	<0·001	92·1	277·54	<0·001	
Others	10	0·69	0·46, 0·93	<0·001	62·3	23·87	0·005	0·024
Malaria hyperendemicity								
Yes	11	0·44	0·16, 0·73	0·002	90·9	230·76	<0·001	
No	22	0·76	0·58, 0·94	<0·001	84·7	65·19	<0·001	0·001
Supplementation route								
Fortification	15	0·61	0·40, 0·81	<0·001	93·4	213·03	<0·001	
Oral	18	0·69	0·48, 0·91	<0·001	77·0	73·89	<0·001	<0·001
Fe dose (mg)								
<30	24	0·67	0·50, 0·85	<0·001	90·9	252·50	<0·001	
≥30	7	0·64	0·42, 0·87	<0·001	67·7	18·58	0·005	0·003
Frequency (per week)								
<5	15	0·55	0·32, 0·78	<0·001	90·3	143·68	<0·001	
≥5	18	0·74	0·53, 0·95	<0·001	88·4	146·60	<0·001	<0·001
Supplement duration (months)								
<6	16	0·68	0·43, 0·93	<0·001	85·7	104·78	<0·001	
≥6	17	0·62	0·43, 0·82	<0·001	91·7	193·04	<0·001	0·003
Mean age (months)								
<24	18	0·71	0·51, 0·91	<0·001	91·6	203·41	<0·001	
≥24	15	0·58	0·34, 0·82	<0·001	86·4	103·05	<0·001	0·911
Mean baseline Hb (g/dl)								
<11	15	0·71	0·47, 0·95	<0·001	92·9	198·24	<0·001	
≥11	18	0·61	0·41, 0·81	<0·001	84·1	106·99	<0·001	0·266
Weight-for-age *Z* score								
<−0·9	10	0·76	0·49, 1·03	<0·001	91·7	108·32	<0·001	
≥−0·9	5	0·85	0·64, 1·06	<0·001	72·1	14·31	0·006	<0·001
Weight-for-height *Z* score								
<0	9	0·81	0·52, 1·10	<0·001	92·6	108·22	<0·001	
≥0	7	0·73	0·51, 0·95	<0·001	75·0	23·97	<0·001	<0·001
Height-for-age *Z* score								
<−0·9	9	0·88	0·60, 1·16	<0·001	78·2	36·66	<0·001	
≥−0·9	7	0·61	0·27, 0·94	<0·001	96·0	148·79	<0·001	<0·001
Additional Zn								
No	13	0·54	0·34, 0·74	<0·001	73·8	45·75	<0·001	
Yes	19	0·70	0·49, 0·90	<0·001	92·6	244·26	<0·001	0·094
Additional vitamin A								
No	6	0·30	−0·09, 0·68	0·127	61·6	13·02	0·023	
Yes	26	0·68	0·52, 0·85	<0·001	90·9	274·89	<0·001	0·027
Additional riboflavin								
No	10	0·71	0·42, 1·00	<0·001	87·8	73·90	<0·001	
Yes	22	0·59	0·41, 0·77	<0·001	90·2	214·60	<0·001	0·037
Additional vitamin B_{12}								
No	11	0·66	0·37, 0·95	<0·001	88·8	88·97	<0·001	
Yes	21	0·61	0·43, 0·80	<0·001	90·0	201·00	<0·001	0·091
Additional folic acid								
No	8	0·55	0·11, 1·00	0·015	91·3	80·73	<0·001	
Yes	24	0·66	0·49, 0·82	<0·001	89·1	211·38	<0·001	0·394
Additional ascorbic acid								
No	6	0·63	0·11, 1·15	0·018	88·4	43·13	<0·001	
Yes	26	0·63	0·47, 0·79	<0·001	90·0	249·67	<0·001	0·871
Additional vitamin B_{12} and/or folic acid								
No	6	0·60	0·04, 1·15	0·036	92·4	66·17	<0·001	
Yes	26	0·64	0·49, 0·80	<0·001	88·8	222·98	<0·001	0·055
Additional Zn, vitamin A, riboflavin, vitamin B_{12}, folic acid, ascorbic acid (No.)								
<6	19	0·61	0·41, 0·81	<0·001	82·9	105·32	<0·001	
≥6	13	0·66	0·42, 0·89	<0·001	93·4	182·28	<0·001	0·022
Additional other micronutrients								
No	7	0·92	0·67, 1·16	<0·001	75·7	24·70	<0·001	
Yes	26	0·57	0·40, 0·74	<0·001	90·1	251·98	<0·001	<0·001

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Table 2 *Continued*

Stratification variable	No.*	Random effects model WMD	95 % CI	*P*	Tests for heterogeneity I^2 (%)	*Q*	*P*	*P* for heterogeneity in subgroups
Additional Zn, B_{12}, folic acid, ascorbic acid (No.)								
<4	18	0·62	0·41, 0·84	<0·001	83·7	104·01	<0·001	
≥4	14	0·64	0·41, 0·86	<0·001	92·9	182·82	<0·001	0·014
Total number of micronutrients								
<10	13	0·66	0·38, 0·94	<0·001	87·0	92·56	<0·001	
≥10	19	0·61	0·42, 0·80	<0·001	90·9	197·33	<0·001	0·086

Except for the all category, calculations performed by SD calculated with the assumption $p = 0·5$.
Not done for country development status, as all studies were from developing countries.
*Number of analytic components.

Table 3 Meta-regression analyses for Hb weighted mean difference (WMD) (restricted maximum likelihood method) for studies comparing iron and micronutrient *v.* placebo supplementation

Study characteristic	Univariable analysis WMD	95 % CI	I^2	*P*	Controlling for all variables WMD	95 % CI	*P*
Study quality							
Allocation concealment							
(not adequate *v.* adequate)	−0·06	−0·41, 0·30	0·90	0·737	0·17	−0·24, 0·59	0·393
Attrition							
(>10 % *v.* <10 %)	0·32	−0·01, 0·64	0·82	0·055	0·45	0·13, 0·77	0·007
Blinding							
(not double-blind *v.* double-blind)	0·06	−0·33, 0·44	0·90	0·766	0·07	−0·30, 0·44	0·704
Malaria hyperendemic *v.* not	−0·32	0·66, 0·03	0·90	0·069	−0·15	−0·47, 0·17	0·346
Oral supplement *v.* fortificant	0·08	−0·26, 0·43	0·89	0·626	−0·13	−0·52, 0·26	0·499
Unit increase in frequency of supplementation per week	0·04	−0·02, 0·11	0·89	0·161	–		–
Unit increase in mean Fe supplement dose (mg/d) (*n* 31)	0·00	−0·00, 0·01	0·89	0·836	–		–
Unit increase in duration of supplementation (months)	−0·01	−0·08, 0·05	0·90	0·680	0·03	−0·03, 0·09	0·276
Unit increase in mean baseline Hb status (g/dl)	−0·18	−0·32, −0·04	0·89	0·016	−0·26	−0·39, −0·12	0·001
Unit increase in weight-for-age *Z* score (*n* 15)	−0·25	−0·62, 0·12	0·92	0·167	–		–
Unit increase weight-for-height *Z* score (*n* 16)	−0·07	−0·41, 0·27	0·91	0·673	–		–
Unit increase in height-for-age *Z* score (*n* 16)	−0·37	−0·76, 0·01	0·93	0·056	–		–
Additional Zn *v.* none (*n* 32)	0·32	−0·17, 0·51	0·90	0·324	–		–
Additional vitamin A *v.* none (*n* 32)	0·38	−0·08, 0·85	0·90	0·102	–		–
Additional riboflavin *v.* none (*n* 32)	−0·11	−0·48, 0·25	0·90	0·525	–		–
Additional vitamin B_{12} *v.* none (*n* 32)	−0·05	−0·40, 0·31	0·90	0·787	–		–
Additional folic acid *v.* none (*n* 32)	0·11	−0·28, 0·50	0·90	0·574	–		–
Additional ascorbic acid *v.* none (*n* 32)	0·05	−0·46, 0·47	0·90	0·796	–		–
Additional other micronutrients *v.* none	−0·37	−0·75, 0·02	0·89	0·060	−0·49	−0·94, −0·03	0·036
Additional B_{12} and/or folate *v.* none (*n* 32)	0·07	−0·36, 0·50	0·88	0·750	−0·25	−0·65, 0·15	0·203

Unless specified separately, the number of analytic components is 33.
In the multivariate model, the number of analytic components is 32 and the proportion of residual variation due to heterogeneity (I^2) is 0·75. Some variables could not be included in the model because of insufficient observations and limit to the number of modelled variables.

these imputations were robust because the interpretation and quantification with various assumptions were invariably synchronous. Finally, multiple subgroup and meta-regression analyses increased the possibility of false positive results and, because of the relatively small number of trials, it is also possible while analysing individual micronutrients that similar data sets may sometimes be getting compared. The identified significant predictors of response should, therefore, be considered as exploratory in nature, rather than definitive.

A few interesting observations have emerged from the present systematic review, which have programmatic implications and can provide direction for future research.

In a previously conducted meta-analysis[6], the pooled estimate (random effects model) from fifty-six trials for the change in Hb concentration following Fe supplementation *v.* placebo (WMD) was 0·74 g/dl (95 % CI 0·61,

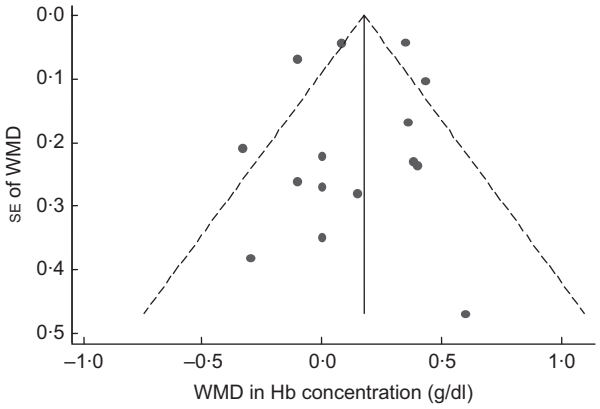

Fig. 4 Funnel plot with pseudo 95 % confidence limits of weighted mean difference (WMD) in Hb concentration for iron and multiple-micronutrient supplementation *v.* iron supplementation with unknown SD derived with assumption $p = 0·5$

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Table 4 Sensitivity and subgroup analyses of pooled estimates of Hb weighted mean difference (WMD) for studies comparing iron and micronutrient supplementation *v.* iron

Stratification variable	No.*	Random effects model			Tests for heterogeneity			*P* for heterogeneity in subgroups
		WMD	95 % CI	*P*	I^2 (%)	*Q*	*P*	
Overall								
Change SD available	7	0·22	0·05, 0·39	0·014	87·1	46·42	<0·001	
SD by $p = 0·5$	15	0·14	0·00, 0·28	0·044	76·0	58·41	<0·001	
SD by independence	15	0·17	0·02, 0·31	0·026	73·5	52·83	<0·001	
Post-test scores & SD	15	0·11	−0·04, 0·25	0·151	37·0	22·23	0·074	Not applicable
Allocation concealment								
Others	4	0·15	−0·07, 0·38	0·186	92·4	39·44	<0·001	
Adequate	11	0·14	−0·05, 0·32	0·159	46·1	18·56	0·046	0·524
Attrition								
<10 %	8	0·22	0·05, 0·39	0·014	53·7	15·11	0·035	
>10 %	7	0·05	−0·21, 0·31	0·706	85·6	41·75	<0·001	0·214
Blinding								
Double-blind	8	0·15	−0·03, 0·33	0·096	86·9	53·48	<0·001	
Others	7	0·15	−0·04, 0·34	0·127	0·0	4·85	0·564	0·771
Malaria hyperendemicity								
Yes	10	0·16	−0·01, 0·33	0·058	83·6	54·93	<0·001	
No	5	0·10	−0·13, 0·33	0·403	0·0	2·98	0·561	0·480
Supplementation route								
Fortification	6	0·06	−0·15, 0·27	0·551	89·3	46·59	<0·001	
Oral	9	0·27	0·13, 0·41	<0·001	8·5	8·75	0·364	0·080
Fe dose (mg)								
<30	9	0·14	−0·04, 0·32	0·131	81·8	44·06	<0·001	
≥30	4	0·22	−0·04, 0·47	0·095	39·8	4·99	0·173	0·135
Frequency (per week)								
<5	4		−0·13, 0·36	0·346	0·0	2·43	0·489	
≥5	11	0·15	−0·01, 0·31	0·070	82·1	55·72	<0·001	0·605
Supplement duration (months)								
<6	7	0·30	0·15, 0·45	<0·001	4·0	6·25	0·395	
≥6	8	0·08	−0·11, 0·27	0·390	85·6	48·62	<0·001	0·060
Mean age (months)								
<24	10	0·12	−0·04, 0·29	0·145	83·8	55·49	<0·001	
≥24	5	0·21	−0·00, 0·43	0·053	0·0	2·81	0·591	0·741
Mean baseline Hb (g/dl)								
<11	12	0·15	0·01, 0·30	0·042	78·4	50·85	<0·001	
≥11	3	0·15	−0·43, 0·73	0·620	70·5	6·79	0·034	0·382
Weight-for-age *Z* score								
<−0·9	4	0·20	−0·02, 0·42	0·069	86·6	22·42	<0·001	
≥−0·9	4	0·14	−0·23, 0·52	0·452	85·9	21·26	<0·001	0·021
Weight-for-height *Z* score								
<0	3	0·19	−0·05, 0·42	0·130	90·5	21·00	<0·001	
≥0	6	0·15	−0·14, 0·44	0·306	78·8	23·58	<0·001	0·026
Height-for-age *Z* score								
<−0·9	5	0·33	0·21, 0·46	<0·001	24·5	5·30	0·258	
≥−0·9	4	0·03	−0·14, 0·20	0·762	62·6	8·03	0·045	<0·001
Additional Zn								
No	6	0·07	−0·19, 0·33	0·601	29·6	7·10	0·213	
Yes	8	0·15	−0·03, 0·32	0·107	85·6	48·66	<0·001	0·229
Additional vitamin A								
No	5	0·05	−0·29, 0·38	0·782	44·1	7·16	0·128	
Yes	9	0·15	−0·02, 0·32	0·075	83·4	48·19	<0·001	0·172
Additional riboflavin								
No	3	0·06	−0·43, 0·55	0·812	83·5	12·09	<0·001	
Yes	11	0·13	−0·03, 0·29	0·119	77·5	44·46	<0·001	0·416
Additional vitamin B_{12}								
No	4	0·08	−0·30, 0·46	0·665	75·4	12·18	0·007	
Yes	10	0·13	−0·04, 0·30	0·141	79·8	44·45	<0·001	0·450
Additional folic acid								
No	4	0·08	−0·30, 0·46	0·665	75·4	12·18	0·007	
Yes	10	0·13	−0·04, 0·30	0·141	79·8	44·45	<0·001	0·450
Additional ascorbic acid								
No	4	0·15	−0·32, 0·62	0·542	74·6	11·80	0·008	
Yes	10	0·11	−0·05, 0·28	0·175	79·5	43·94	<0·001	0·227
Additional vitamin B_{12} and/or folic acid								
No	4	0·08	−0·30, 0·46	0·665	75·4	12·18	0·007	
Yes	10	0·13	−0·04, 0·30	0·141	79·8	44·45	<0·001	0·450
Additional Zn, vitamin A, riboflavin, vitamin B_{12}, folic acid, ascorbic acid (No.)								
<6	8	0·13	−0·11, 0·38	0·273	54·4	15·34	0·032	
≥6	6	0·11	−0·09, 0·31	0·287	87·9	41·35	<0·001	0·474

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Table 4 *Continued*

Stratification variable	No.*	Random effects model WMD	95 % CI	*P*	Tests for heterogeneity I^2 (%)	*Q*	*P*	*P* for heterogeneity in subgroups
Additional other micronutrients								
No	2	0·26	−0·15, 0·67	0·218	68·0	3·12	0·077	
Yes	13	0·12	−0·04, 0·27	0·132	76·7	51·46	<0·001	0·050
Additional Zn, B_{12}, folic acid, ascorbic acid (No.)								
<4	7	0·17	−0·10, 0·43	0·213	56·2	13·70	0·033	
≥4	7	0·09	−0·10, 0·28	0·348	85·8	42·39	<0·001	0·290
Total number of micronutrients								
<10	6	0·12	−0·18, 0·43	0·437	62·2	13·24	0·021	
≥10	8	0·12	−0·06, 0·30	0·194	83·9	43·37	<0·001	0·440

Except for the all category, calculations performed by SD calculated with the assumption $p = 0·5$.
Not done for country development status as, except one, all studies were from developing countries.
*Number of analytic components.

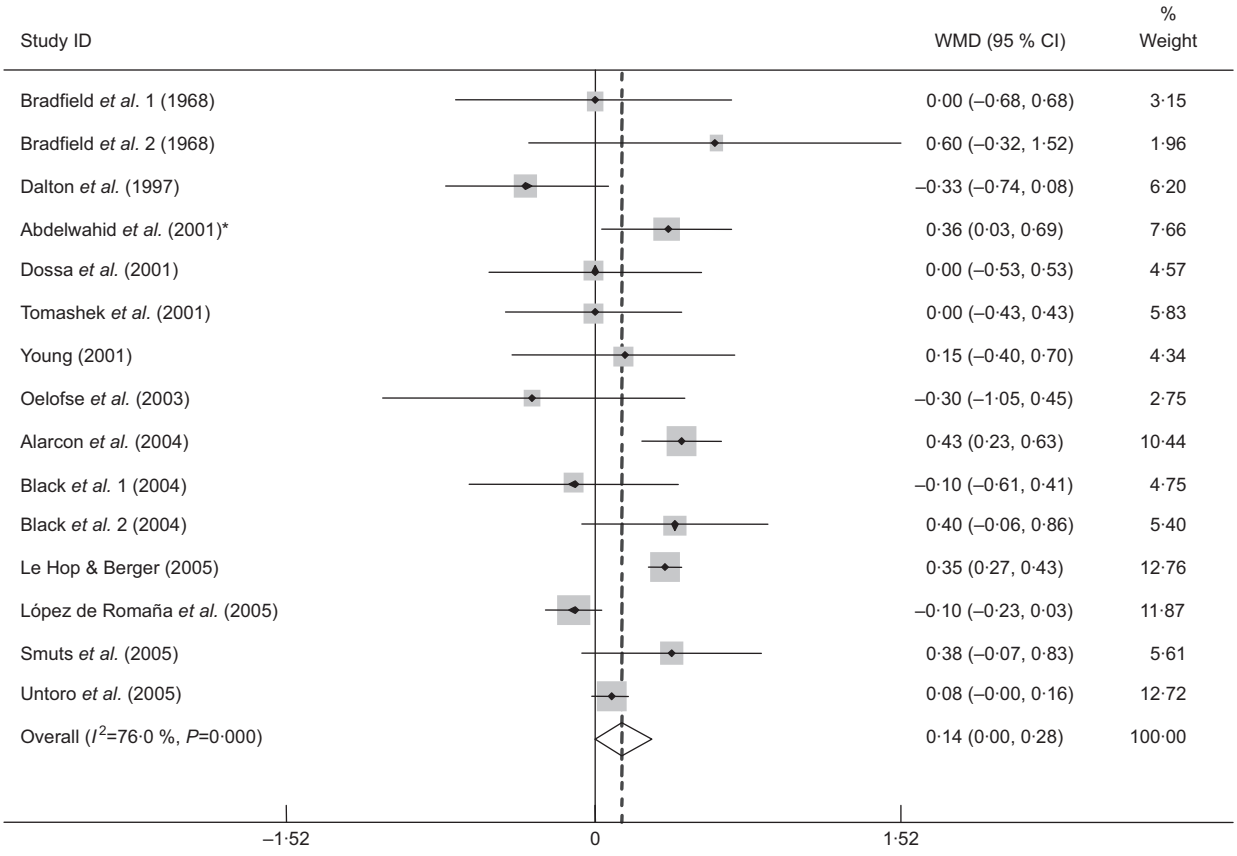

Fig. 5 Forest plot for iron and multiple-micronutrient supplementation *v.* iron supplementation with unknown SD derived with assumption $p = 0·5$. Weighted mean difference (WMD) in Hb concentration, 95 % confidence interval and weights from random effects analysis are given; see Table 1 for details of the studies. *Unpublished study (HA Abdelwahid, MS Khattab, MAA Mostaffa, HF El-sayed and AE Saad, The effect of treatment with Vit. A alone or in combination with iron in iron deficient anemic children in Ismailia city, unpublished results)

0·87, $P < 0·001$; $P < 0·001$ for heterogeneity). Lower baseline Hb level, oral medicinal Fe supplementation and non-hyperendemic malarial region were significant predictors of greater Hb response and heterogeneity. Projections suggested that between 38 % and 62 % of baseline anaemia (Hb < 11 g/dl) was responsive to Fe supplementation alone among children under 6 years old; the corresponding range for malarial hyperendemic regions was 5–31 %. The pooled estimate (random effects model) from the current thirty-six cohorts for change in Hb with Fe and multiple micronutrients *v.* placebo was 0·65 g/dl (95 % CI 0·50, 0·80, $P < 0·001$). Lower baseline Hb level and non-hyperendemic malarial region were significant predictors of greater Hb response, whereas 'other micronutrients' were a significant predictor of lower Hb increment on meta-regression analysis. From these two

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Table 5 Meta-regression analyses for Hb weighted mean difference (WMD) (restricted maximum likelihood method) for studies comparing iron and micronutrient *v.* iron supplementation

	Univariable analysis				Controlling for all variables		
Study characteristic	WMD	95 % CI	I^2	*P*	WMD	95 % CI	*P*
Study quality							
Allocation concealment (not adequate *v.* adequate)	−0·02	−0·34, 0·31	0·78	0·918	−0·59	−2·75, 1·57	0·490
Attrition (>10 % *v.* <10 %)	−0·15	−0·46, 0·15	0·77	0·295	0·16	−0·93, 1·25	0·701
Blinding (not double-blind *v.* double-blind)	−0·03	−0·37, 0·31	0·78	0·863	−0·04	−2·13, 2·06	0·964
Malaria hyperendemic *v.* not	−0·08	−0·44, 0·29	0·78	0·662	0·06	−0·85, 0·96	0·865
Oral supplement *v.* fortificant	0·16	−0·15, 0·46	0·77	0·286	0·75	−1·51, 3·02	0·408
Unit increase in frequency of supplementation per week	−0·00	−0·07, 0·07	0·78	0·939	–		–
Unit increase in mean Fe supplement dose (mg/d) (*n* 13)	−0·00	−0·01, 0·01	0·79	0·826	–		–
Unit increase in duration of supplementation (months)	−0·04	−0·12, 0·04	0·77	0·267	−0·00	−0·56, 0·55	0·991
Unit increase in mean baseline Hb status (g/dl)	−0·03	−0·17, 0·12	0·71	0·677	0·18	−0·39, 0·74	0·430
Unit increase in weight-for-age *Z* score (*n* 8)	−0·05	−0·50, 0·39	0·87	0·778	–		–
Unit increase weight-for-height *Z* score (*n* 9)	0·04	−0·40, 0·48	0·85	0·830	–		–
Unit increase in height-for-age *Z* score (*n* 9)	0·01	−0·30, 0·32	0·86	0·947	–		–
Additional Zn *v.* none (*n* 14)	0·07	−0·29, 0·43	0·79	0·666	–		–
Additional vitamin A *v.* none (*n* 14)	0·11	−0·27, 0·50	0·78	0·531	–		–
Additional riboflavin *v.* none (*n* 14)	0·03	−0·37, 0·42	0·79	0·875	–		–
Additional vitamin B_{12} *v.* none (*n* 14)	0·02	−0·35, 0·39	0·79	0·913	–		–
Additional folic acid *v.* none (*n* 14)	0·02	−0·35, 0·39	0·79	0·913	–		–
Additional ascorbic acid *v.* none (*n* 14)	−0·05	−0·44, 0·34	0·79	0·781	–		–
Additional other micronutrients *v.* none	−0·16	−0·57, 0·25	0·76	0·412	−0·45	−2·16, 1·25	0·502
Additional B_{12} and/or folate *v.* none (*n* 14)	0·02	−0·35, 0·39	0·79	0·913	0·07	−1·07, 1·21	0·867

Unless specified separately, the number of analytic components is 15.
In the multivariate model, the number of analytic components is 14 and the proportion of residual variation due to heterogeneity (I^2) is 0·87. Some variables could not be included in the model because of insufficient observations and limit to the number of modelled variables.

analyses it may be postulated that, compared with placebo, the effect size of the change in Hb concentration is not likely to alter much with the addition of multiple micronutrients to Fe supplementation. This postulation is strengthened by the second analysis, which showed that the difference in Hb levels in groups receiving Fe or Fe and multiple micronutrients was statistically significant but small (0·14 g/dl, 95 % CI 0·00, 0·28, $P = 0·04$). These analyses suggest that addition of multiple micronutrients to Fe supplementation may only marginally improve the Hb response in comparison to Fe supplementation alone.

The basic assumption behind giving many micronutrients as a supplement is that nutrients either act synergistically or in isolation. However, the interaction of many of these micronutrients is still poorly understood and under investigation[53,54]. The possibility of negative and unpredictable interactions with co-administration of several micronutrients is, therefore, real. One noteworthy finding is the possibility of a decremental Hb response with the addition of 'other micronutrients' in the first analysis. This supports the fact that micronutrients are often added to supplements without understanding of the possible complex interactions that may lead to a poorer Hb response than Fe supplementation alone and strengthens the case for a careful and judicious selection of micronutrients to be added for such purpose in health programmes.

Frequently scientists and public health professionals state that deficiencies of various micronutrients like Fe, vitamin A, Zn and I occur simultaneously in the developing countries. Multiple-micronutrient supplementation is therefore considered a cost-effective panacea for this problem[55]. However, the contribution of ecological factors to multiple deficiencies has been ignored. For instance, seasonality limits the availability of year-round access to micronutrient-rich foods in developing countries[56]. Similarly, poverty is an important factor that limits the access to and choice of food, leading to various deficiencies and chronic malnutrition[57]. A lower rise in Hb with Fe and multiple micronutrients in children with lower height-for-age Z scores, an indicator of chronic undernutrition, can be considered as a stimulus to generate more information on the role of food insecurity and chronic deprivation in the high prevalence of anaemia.

Parasitic infections or infestations also contribute to anaemia and are unlikely to respond to micronutrient supplementation. Malaria is an important cause of anaemia[58]. The lower Hb response to Fe and micronutrient supplementation in malaria hyperendemic areas (−0·15 g/dl on multivariable meta-regression analysis) confirms that these micronutrients alone cannot address the problem of anaemia in such settings. Evidence thus supports the current recommendations, which stress integrated strategies to control Fe deficiency and malaria where these conditions coexist[59]. Similarly, worm infestations lead to blood loss, reduced appetite and poor absorption of nutrients. Therefore, deworming along with haematinic

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supplementation has been suggested as an effective means to control anaemia[60,61].

In conclusion, synthesized evidence alone indicates that a judicious addition of multiple micronutrients to Fe supplementation alone is not likely to impair the Hb response to Fe supplementation in children and may even have marginal benefits. However, there is a suggestion that the addition of micronutrients other than Zn, vitamin A, riboflavin, B_{12}, folic acid and ascorbic acid may have a negative effect on Hb response. Routine addition of unselected multiple micronutrients to Fe therefore appears unjustified for nutritional anaemia control programmes.

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