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

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CRD summary
This review found the addition of multiple micronutrients to iron supplementation may only marginally improve haemoglobin response in children, compared with iron supplementation alone. However, addition of "other micronutrients" may have a negative effect. Several methodological shortcomings of this review indicate that these conclusions may not be reliable.

Authors' objectives
To investigate the effect of combining at least two micronutrients with iron supplementation on haemoglobin response compared with placebo or with iron supplementation in children.

Searching
The following databases were searched for English language studies: MEDLINE (1996 to February 2006), EMBASE (1982 to January 2006), Cochrane Central Register of Controlled Trials (CENTRAL), IBIDS (International Bibliographic Information System on Dietary Supplements) and HealthSTAR (dates not reported). Search terms were reported. Reference lists of identified articles, reviews, books were checked. Abstracts and proceedings of international conferences or meetings were also searched. Donor agencies, experts in the field and authors of recent relevant trials were also contacted for ongoing trials.

Study selection
Randomised controlled trials (RCTs) that involved iron supplementation combined with two or more other micronutrients compared with placebo or iron alone in children were eligible for inclusion. Eligible trials were required to have haemoglobin response as one of the outcomes measured. If both intervention and control groups received the concomitant medications (simultaneously administered), the trial could also be included.

The included trials that compared iron plus micronutrients with placebo were from Asia, South America and Africa; approximately half were conducted in infants and pre-school children (zero to five years) and half in older children (older than five years). In almost half of the trials, a medicinal supplement was used; the rest used fortified foods.

The included trials that compared iron plus micronutrients with iron alone were conducted in Asia, South and Latin America, Africa and North America. The majority of trials were conducted in infants and pre-school children (zero to five years); only two trials involved older children. In almost half of the trials, iron and micronutrient supplementation was given in the form of oral medicine; in the remainder used fortified foods.

The additional micronutrients given and doses varied.

The authors did not report the number of reviewers that performed study selection.

Assessment of study quality
The methodological quality of trials was assessed using published criteria for: allocation concealment (adequate, unclear, inadequate or not used); attrition (percentage of participants lost to follow-up less than3%, 3 to 9.9%, 10 to 19.9% and 20% or more); and blinding (double blinding, single blinding, no blinding and unclear).

The authors did not report how many reviewers assessed validity.

Data extraction
Change in haemoglobin and standard deviation (SD) were extracted or computed by one reviewer. Pre-specified forms were used for extraction. Where standard deviations were computed, they were tested for robustness. Authors were
contacted for further information if necessary.

**Methods of synthesis**

Pooled weighted mean differences (WMDs) were calculated using fixed-effect and random-effects models (random-effects results were mainly reported). Where two or more interventions were present (different dosage or administration) and a single control group was present, the sample size of the control group was cleaved (how this was done depended on whether the split was even or uneven) in order to avoid double counting.

As standard deviation could not be extracted for all trials, the effect of extracting standard deviation for change of haemoglobin directly was compared with computation of standard deviation using the following assumptions: correlation of 0.5 between the pre-test and post-test variances; and pre-test and post-test samples considered independent.

Stratified analyses (specified a priori) were also conducted for: trial quality; route of iron and micronutrient administration (oral medicinal supplement or food fortification); duration of supplementation; baseline haemoglobin of supplemented group; nature and number of micronutrients given; nutritional status of population; and development status and malarial endemicity of the trial area. The contribution of these variables to heterogeneity was also assessed using meta-regression analyses. Heterogeneity was assessed using the Q statistic and the $I^2$ test.

Publication bias was examined using a funnel plot and Begg's and Egger's tests.

**Results of the review**

Thirty RCTs were included in the review (contributing 50 analytic components). Randomisation was adequate in nine RCTs, allocation concealment was adequate in nine RCTs, loss to follow-up was less than 3% in 18 RCTs, and 10 RCTs were double blinded.

**Iron and micronutrient supplementation versus placebo** (25 RCTs; 35 analytic components; n=4,981 children): Iron and micronutrient supplementation was associated with greater increases in haemoglobin change compared with placebo (WMD 0.65g/dL, 95% CI 0.50 to 0.80), but this was associated with significant heterogeneity ($I^2$=89%). Results were similar for subgroup analyses of different methods of obtaining standard deviation. Sensitivity and stratified analyses suggested that a higher haemoglobin response was seen in the following trials: attrition rates over 10%; non double-blinded; malarial non-endemic regions; with medical supplementation; with increasing dose, duration and frequency; and in children with lower weight-for-age, weight-for-height and height-for-age Z scores. Participants receiving micronutrients other than zinc, vitamin A, riboflavin, B12, folic acid and ascorbic acid had a significantly lower haemoglobin response. Follow-up was two months or less in three RCTs, and more than this in the other RCTs.

**Iron and micronutrient supplementation versus iron supplementation alone** (13 RCTs; 15 analytic components; n=1,483 children): Iron and micronutrient supplementation was associated with greater increases in haemoglobin change compared with iron alone (WMD 0.14g/dL, 95% CI 0.00 to 0.28), but this was associated with significant heterogeneity ($I^2$=76%). The results were similar when standard deviations were calculated by assuming $p=0.5$ and by independence assumption, but not significant when using post-test scores. The effect size was higher with trials with available (or imputed) haemoglobin change standard deviation scores. The stratified and sensitivity analyses did not identify any significant predictors. Follow-up was two months or less in two RCTs, and more than this in 11 RCTs.

Funnel plots did not suggest the presence of publication bias.

**Authors' conclusions**

The addition of multiple micronutrients to iron supplementation may only marginally improve haemoglobin response compared with iron supplementation alone. However, addition of "other micronutrients" may have a negative effect.

**CRD commentary**

The research question was supported by inclusion criteria for participants, intervention, outcome and study design. Published and unpublished studies were sought and publication bias was assessed (and not found). Restriction to English language studies may have increased the risk of language bias. The number of reviewers that performed the review
process was not reported, so it was not known whether steps were taken to reduce error and bias.

Validity was assessed using appropriate criteria, but not discussed in the analysis. The meta-analyses were associated with significant heterogeneity, which may have affected the reliability of the results. The authors acknowledged that multiple subgroup and meta-regression analyses increased the possibility of false positive results.

Several methodological shortcomings of this review indicate that the authors' conclusions may not be reliable.

Implications of the review for practice and research

Practice: The authors stated that routine addition of unselected multiple micronutrients to iron appears unjustified for nutritional anaemia control programmes.

Research: The authors did not state any implications for research.

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