Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions

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CRD summary
This review concluded that interventions containing iron only, vitamin A only, and combinations of iron and zinc, iron and vitamin A, or zinc and vitamin A, did not improve growth or weight gain in children under five years old. Due to limitations in the review methods and reporting these findings should be treated with caution.

Authors' objectives
To evaluate the effects of micronutrients on the growth of children under five years old.

Searching
PubMed (from inception), EMBASE, and the Cochrane Library were searched to April 2008. Search terms were reported and the reference lists of review articles were also searched. Only studies reported in English were included.

Study selection
Randomised, placebo-controlled trials of micronutrients (vitamin A, iron, zinc, or multiple micronutrients) in children aged five years or younger were eligible. The treatment groups had to only differ in the administration of the micronutrients. Trials of children with chronic diseases likely to affect growth, such as sickle cell disease or cystic fibrosis, those with a follow-up of less than eight weeks, and those that did not report sufficient data for the calculation of effect sizes, were excluded. The outcomes of interest were the change in height (z-score or cm per year), change in weight (z-score or kg per year), and change in weight-for-height (z-score).

The included trials assessed vitamin A, iron, zinc, or combinations of two or multiple (three or more) micronutrients. Doses varied widely, as did the trial settings, with most of them being conducted in developing countries, including Asia, Africa, and Latin America. The duration of treatment ranged from eight to 104 weeks.

The authors did not state how the trials were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The mean change in height, weight, or weight-for-height was extracted. If these were not reported, they were calculated as the difference in the means before and after the intervention. The changes in z-score were used for trials that did not report the actual mean changes. The smallest number of participants was used for trials with different sample sizes at baseline and follow-up. When the standard deviations were not reported they were calculated from the 95% confidence intervals or standard errors or they were estimated by assuming a similar correlation to that observed in other trials. The changes in outcome were converted into effect sizes, using Cohen's d, which is the difference in means between treatment and control divided by the pooled standard deviation.

The authors did not report how many reviewers performed the data extraction.

Methods of synthesis
Effect sizes were pooled using a random-effects model, which was weighted by the inverse variance. They were calculated with and without outliers. Statistical heterogeneity was assessed with a $X^2$ test and a $p<0.05$ was statistically significant. Subgroup analyses assessed the impact of the pre-defined factors of baseline age, duration of intervention, baseline nutritional status, and haemoglobin. For multiple micronutrient interventions, the analyses were also subgrouped by mode of administration and micronutrient combinations.
Sensitivity analyses were performed, using different standard deviations, to investigate the impact on the results of the estimates used for trials that did not report standard deviations. Publication bias was assessed using a funnel plot, the Egger regression test and the Begg-Mazumdar correlation test.

Results of the review
Eighty-seven RCTs were included: 17 for vitamin A (n=69,320); 27 for iron (n=6,671); 43 for zinc (n=11,615), 12 for two micronutrients (n=5,148) and 20 for multiple micronutrients (n=3,873). Some trials provided more than one set of results.

Vitamin A: There was no significant difference in height gain (ES 0.08, 95% CI -0.18 to 0.34; 11 RCTs). There no evidence that vitamin A increased weight gain overall, but there was significant heterogeneity (p<0.01) resulting from a greater weight loss in underweight children (ES -0.34 compared with 0.00 for those above a z-score of -2 or more). There was also no effect on weight-for-height gain.

Iron: There was no evidence that iron had any effect on height gain (ES -0.01, 95% CI -0.17 to 0.15), weight gain or weight-for-height gain, with pooled effect sizes being less than 0.1 and not statistically significant. A subgroup analysis of the 18 trials that only reported change in weight found that iron resulted in a significant reduction in weight (ES -0.11, 95% CI -0.20 to -0.02).

Zinc: There was no significant difference in height gain (ES 0.07, 95% CI -0.03 to 0.17; 40 RCTs). There was no evidence that zinc affected weight gain, but zinc showed a small positive effect on weight-for-height gain (ES 0.06, 95% CI 0.006 to 0.11; 22 RCTs) and there was no heterogeneity (p=0.29).

Two micronutrients: Seven trials provided results for iron and zinc, three for vitamin A and zinc, and three for iron and folic acid, but none showed any statistically significant benefits for the micronutrients.

Multiple micronutrients: Most of the 20 trials of combinations of three or more micronutrients contained vitamin A, iron, and zinc and these showed a statistically significant increase in height for the micronutrient group compared with placebo (ES 0.09, 95% CI 0.008 to 0.17), but no benefit for weight or weight-for-height gain.

There was some evidence of publication bias for the trials of zinc, with asymmetry in the funnel plot and statistical probability values of 0.01 and 0.02.

Authors’ conclusions
Interventions containing iron only, vitamin A only, and combinations of iron and zinc, iron and vitamin A, or zinc and vitamin A, did not improve gain in height, weight, nor weight-for-height in children under five years. Zinc had a small positive effect on weight-for-height gain and multiple micronutrient interventions had a similar effect on height gain.

CRD commentary
This review had a clear question and provided sufficient detail for the inclusion criteria. The search was fairly limited. Little attempt was made to locate unpublished trials and only trials reported in English were included, so some trials might have been missed. Publication bias was assessed and it was a potential problem only for trials assessing zinc. The number of reviewers who performed aspects of the review was not reported, so the possibility of errors in trial selection and data extraction cannot be ruled out. There was no formal assessment of trial quality. The methods of meta-analysis were appropriate and suitable subgroup and sensitivity analyses were performed.

The authors’ conclusion about the lack of an effect of micronutrients appears to be appropriate, but there was potential for publication bias, no validity assessment, and poor reporting of the review methods, and so these findings should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that micronutrients could do little to prevent stunting and more comprehensive approaches to improving the diets of small children were needed to promote child health and nutrition.
Research: The authors did not state any implications for research.

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