Effect of iron supplementation on physical growth in children: systematic review of randomised controlled trials

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CRD summary
This review included randomised controlled trials evaluating the effect of iron supplementation on the physical growth of children. The authors concluded that iron supplementation does not have a positive effect on growth. These conclusions reflect the evidence presented, though the included studies were diverse and there was the potential for bias and error in the review process.

Authors' objectives
To evaluate the effect of iron supplementation on physical growth in children through a systematic review of randomised controlled trials (RCTs).

Searching
MEDLINE (1966 to March 2003), the Cochrane Controlled Trials Register, EMBASE, IBIDS and HealthSTAR were searched; the search terms were reported. The authors also screened the reference lists of identified articles, handsearched reviews, bibliographies of books and abstracts, and reviewed the proceedings of international conferences and meetings. In addition, donor agencies, ‘experts’ and authors of recent iron supplementation trials were contacted.

Study selection
Study designs of evaluations included in the review
RCTs and non-RCTs where iron was administered through the parenteral route (as it would be difficult to administer a similar placebo) were eligible for inclusion. The duration of supplementation had to be 2 months or more for inclusion.

Specific interventions included in the review
Trials that investigated iron supplementation through the oral or parenteral route, or as formula milk or cereals supplemented with iron, were eligible for inclusion. Studies of other micronutrients and drugs were only eligible for inclusion if the only difference between the study and control groups was iron supplementation. The included studies were of iron supplementation given orally (doses ranged from 15 mg/week to 80 mg/day and 1 to 3 mg/kg), ferrous sulphate supplementation (3 mg/kg per day) and fortified food (the doses of iron these would provide were not given). The duration of supplementation was 2 to 15 months in the included trials and observations lasted from 2 to 12 months.

Participants included in the review
There were no stated inclusion criteria for the participants. The participants in the included studies were children aged from less than 45 days up to 12 years old who were from Europe, Asia, South America, Africa and the USA.

Outcomes assessed in the review
Studies evaluating one of the anthropometric parameters as an outcome measure were eligible for inclusion. The included studies measured weight-for-age, weight-for-height, height-for-age, mid upper-arm circumference, head circumference, triceps skinfold thickness and subscapular skinfold thickness.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed according to published criteria. These addressed: allocation concealment, attrition (loss to follow-up) and blinding (double-blinding, single-blinding, no blinding or unclear). The authors did not state how the validity assessment was performed.

Data extraction
One reviewer extracted the data from the primary studies. The mean change and standard deviation (SD) were extracted or calculated for the iron supplemented group and control group for each outcome. If the SDs were not available and could not be calculated from study data, they were estimated assuming correlations of $p=0.5$ and $p=0$ (independent) between pre- and post-test variances.

**Methods of synthesis**

How were the studies combined?
The standardised weighted mean differences (SMDs) from pre- to post-test were pooled, mostly using a random-effects model in the presence of statistical heterogeneity. Publication bias was explored using a funnel plot, Egger's regression method and Begg's rank correlation test.

How were differences between studies investigated?
A meta-regression was used to explore the contribution of variables (including methodological quality, participant and intervention characteristics) to heterogeneity. These variables were determined a priori.

**Results of the review**
The review included 25 studies ($n=4,640$). All were RCTs.

The funnel plot, Egger's test and Begg's rank correlation test did not indicate publication bias.

The studies assessing weight-for-age, weight-for-height and height-for-age were statistically heterogeneous ($p<0.001$).

The difference in change in weight-for-age between supplemented and control groups was statistically significant when $p=0.5$ (SMD 0.13, 95% confidence interval, CI: 0.01, 0.25, $p=0.04$). However, this result was not statistically significant when the SDs were calculated with the independence assumption $p=0$, with the post-test scores, or with the analytical components where the actual SDs were available (SMD 0.13, 95% CI: -0.05, 0.32, $p=0.145$).

Sensitivity analyses indicated that the change in weight-for-age was greater in studies carried out in malarial hyperendemic regions. It was also found that the effect size was greater in children aged over 5 years old for change in weight-for-height. Iron supplementation was also found to negatively affect the linear growth of children in developed countries (SMD -0.27, 95% CI: -0.49, -0.05, $p=0.018$), while supplementation for more than 6 months was associated with statistically significantly slower linear growth (SMD -0.13, 95% CI: -0.24, -0.01, $p=0.039$).

There was no statistically significant difference in overall weight-for-height, height-for-age, head circumference, subscapular skinfold thickness, triceps skinfold thickness or mid upper arm circumference between iron supplemented groups and control groups.

Further analyses for each of these outcomes were reported in the paper.

**Authors' conclusions**
This review of largely heterogeneous data derived from randomised controlled efficacy trials did not document a positive effect of iron supplementation on the physical growth of children.

**CRD commentary**
The research question addressed was stated and the inclusion criteria were clear with regard to the intervention, outcomes and study design. However, the inclusion criteria did not specify participant characteristics, which might have resulted in subjective decisions regarding inclusion. The search included three relevant databases, handsearches and attempts to identify unpublished studies, which reduces the possibility of publication bias. However, the languages searched were not specified. The authors stated that they assessed validity but the results of this assessment were not presented for individual studies. One reviewer extracted the data, thereby increasing the likelihood of reviewer bias and error. The results of tests for heterogeneity indicated that the studies were statistically heterogeneous, so pooling these studies might not have been appropriate. There were also significant clinical differences between the studies combined, as they included a wide range of interventions, different settings, and children at many different stages of growth and development. However, this heterogeneity was investigated to some extent though the use of a priori subgroup analyses.
The authors’ conclusions are appropriate on the basis of the evidence presented, though the reader should interpret these conclusions in light of the potential biases highlighted.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated the need for well-designed intervention studies that evaluate the role of micronutrient interactions in determining the physical growth of children.

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