Zinc supplementation in children is not associated with decreases in hemoglobin concentrations
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CRD summary
This review assessed the impact of zinc supplementation on haemoglobin concentrations in apparently healthy children. The authors concluded that zinc supplementation at doses used in trials was safe and there may be benefits in children with severe anaemia or zinc deficiency. This conclusion was only partly based on the review evidence and the overall reliability of the conclusions is unclear.

Authors' objectives
To evaluate the effect of zinc supplementation on haemoglobin concentrations in apparently healthy children.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to March 2009 without language restrictions. Search terms were reported. Web of Science, ClinicalTrials.gov and ClinicalTrialResults.org were searched together with references from included studies.

Study selection
Randomised controlled trials (RCTs) that assessed the association between zinc supplementation and change in haemoglobin concentrations in apparently healthy children (aged 0 to 15 years) were eligible for inclusion in the review. Additionally, it appeared that a separate review of trials in malnourished children or those with underlying illnesses was conducted; it was not clear whether this used systematic review methods.

Included trials were conducted in countries in Latin America, Asia and Africa. The baseline ages of children enrolled in the trials ranged from four months to 15 years. The most trials used supplements of zinc sulphate; the remainder employed zinc gluconate, zinc acetate, zinc methionine or zinc oxide (where reported); most used a zinc dose of 10 or 20mg/day. Most trials were placebo controlled. Although the inclusion criteria stated that healthy children should be enrolled, seven trials had mean baseline haemoglobin concentrations below 110g/L.

Two reviewers independently selected the studies for inclusion in the review with disagreements resolved through consensus.

Assessment of study quality
Validity was assessed using the Jadad scale, awarding up to 5 points for the criteria of randomisation, blinding, and treatment of withdrawals and drop-outs.

The authors did not state how many reviewers performed the assessment.

Data extraction
Data were extracted to permit the calculation of effect sizes for between-group differences in changes in haemoglobin concentrations from baseline, with 95% confidence interval (CI).

The authors did not state how many reviewers carried out the data extraction.

Methods of synthesis
The trials were combined using a random-effects meta-analysis to calculate the weighted mean difference (WMD) with 95% confidence intervals (CI). Heterogeneity was assessed using the $I^2$ and $X^2$ statistics.

Sensitivity analyses without trials identified as outliers and of trials with the highest Jadad score were conducted.
Sensitivity analyses were also used to explore the impact of using post-intervention values for trials which did not report mean changes in haemoglobin values with the standard deviation for the change.

Meta-regression was used to assess the impact of the following variables on treatment effect: mean baseline age of children (less than 12 months versus greater than 12 months), baseline haemoglobin concentrations (less than 110g/L versus greater than 110g/L), duration of the intervention (up to six months versus longer than six months), use of placebo versus other control group, geographical setting, and trial quality.

Results of the review
Twenty-one RCTs (n=3,869 patients) reported in 20 publications were included in the review. Sample sizes ranged from 53 to 638. Follow-up ranged from four to 15 months. Eleven trials were described as having the highest quality based on their Jadad score.

There was no statistically significant difference between intervention and control groups in change in haemoglobin concentrations (pooled WMD 0.8g/L; 95% CI -0.6 to 2.2; 21 RCTs). None of the sensitivity analyses resulted in a statistically significant effect of supplementation being detected. Meta-regression revealed no impact on treatment effect of any of the variables assessed.

The results of zinc supplementation 10 trials in malnourished children or those with underlying illnesses were mixed; one showed a significant positive effect in anaemic children without malaria, while one reported a significant adverse effect of supplementation in severely anaemic children.

Authors' conclusions
Zinc supplementation at doses typically used in randomised trials was a safe intervention with regard to haemoglobin concentration. There may be some benefits in children with severe anaemia or zinc deficiency; these benefits warrant further evaluation.

CRD commentary
The review question and the inclusion criteria were clear. However, despite the criterion for enrolled children to be healthy, several trials had mean baseline levels of haemoglobin below the commonly accepted cut-off for diagnosis of anaemia. The authors searched several relevant databases and other sources without language restrictions, reducing the chances of language or publication biases or the omission of relevant trials. The authors reported using methods designed to reduce reviewer error and bias in the selection of studies, but not at other stages of the review process.

An acceptable tool was used to assess the validity of the included trials, but reporting of the result of this assessment was very limited. The decision to use meta-analysis appeared reasonable; steps were taken to assess and explore statistical and clinical heterogeneity between trials.

The authors' conclusions appear reasonable with regard to the safety of zinc supplementation in healthy children, as they were robust to the exclusion of trials containing anaemic children, but those relating to benefits in children with anaemia or zinc deficiency relate to work outside the systematic review and could not be assessed. Given concerns over the application of inclusion criteria and the poor reporting of aspects of the review, it is difficult to determine the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for investigation of potential haematological benefits of zinc supplementation among children with increased zinc requirements.

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