Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review concluded that iron supplementation safely improved haematologic and non-haematologic outcomes among primary school aged children in low or middle income settings, and was well-tolerated. The authors’ conclusions may be affected by potential biases in the evidence, and some results were derived from a small subset of studies; the reliability of the conclusions is uncertain.

Authors’ objectives
To assess the benefits and safety of daily iron supplementation in primary-school-aged children.

Searching
Nine databases were searched including MEDLINE, EMBASE, ProQuest Digital Theses and WHO regional databases to July 2013. An example search strategy was available in an online appendix. References of retrieved articles and previous systematic reviews were also searched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that evaluated daily (five or more days a week) iron supplementation compared to control in primary-school-aged children (five to 12 years) were eligible for inclusion. Studies that did not specifically recruit children within five to 12 years were included if: the mean or median age was between five and 12 years old; more than 75% of children were five to 12 years old; most of the studies recruitment age overlapped five to 12 years. Studies of only children with a known developmental disability or a condition that substantially altered iron metabolism, including severe anaemia, were excluded. The primary outcomes were cognitive performance, physical growth, safety (as defined in review), haemoglobin, iron indices, prevalence of anaemia and iron deficiency. Secondary outcomes were the effects of iron on other micronutrients and physical performance.

All studies except two were conducted in low or middle income settings. Iron supplementation (ferrous sulphate) dose varied between studies. Some studies included concurrent anthelmintic therapy, levamisole, folate, mebendazole, zinc, albendazole, and multi-vitamins. Control groups included anthelmintic therapy, placebo, no intervention, zinc, folate, or were just reported as “control”.

Three reviewers selected studies for inclusion. Discrepancies were resolved through discussion.

Assessment of study quality
Study quality was assessed using the Cochrane Risk of Bias assessment tool. The authors did not state how many reviewers assessed quality.

Data extraction
Data were extracted to calculate mean differences between outcomes or mean changes from baseline for continuous data using the same scale, or standardised mean differences (SMD) if using a different scale. Risk Ratios were calculated for dichotomous data. Corresponding 95% confidence intervals were also calculated. Studies with a co-intervention were included in the analysis providing this was applied identically in the control arm. Studies with separate intervention arms were analysed separately.

Two reviewers independently extracted data which was checked by a third reviewer. Discrepancies were resolved through discussion.

Methods of synthesis
Pooled standardised mean differences, mean differences and risk ratios with their 95% confidence intervals were calculated using a random-effects model when at least two studies provided data. Statistical heterogeneity was assessed
using $X^2$ and $I^2$. Substantial heterogeneity was defined as $I^2$ greater than 50%. A range of subgroup analyses (reported in paper) were conducted for outcomes which had five or more studies. Sensitivity analyses were conducted removing studies with a high risk of bias from the analysis. Publication bias was assessed for outcomes which included 10 or more trials.

**Results of the review**

Thirty-two studies (7,089 children) were included in the review. Only four studies were considered to be at low overall risk of bias. The duration of the interventions ranged from four weeks to one year.

**Cognition:** Compared to control, iron supplementation significantly improved global cognitive scores (SMD 0.50, 95% CI 0.11 to 0.90; nine RCTs; $I^2=93\%$). Subgroup analysis also reported a significant beneficial effect among children who were anaemic at baseline (SMD 0.29, 95% CI 0.07 to 0.51; six studies; $I^2=22\%$), but there were no significant differences among children without anaemia (four studies; $I^2=0\%$).

There were no significant differences between iron supplementation and control for global intelligence quotient scores (five RCTs; $I^2=97\%$). Subgroup analysis found that children with anaemia at baseline had significant improvements in their intelligence quotient after supplementation (MD 4.55, 95% CI 0.16 to 8.94; three studies; $I^2=28\%$), but results were not significant for non-anaemic children (two RCTs; $I^2=0\%$).

Compared to control, iron supplementation produced a superior performance on the maze test (MD 1.30, 95% CI 0.90 to 1.70; four RCTs; $I^2=0\%$) and clerical task scores (SMD 0.44, 95% CI 0.14 to 0.75; four RCTs; $I^2=30\%$). There were no other significant differences reported for the remaining cognitive tests.

**Growth:** There were no significant differences between control and iron supplementation for absolute height (five RCTs) but there was a difference for height for age (z score) for children who received iron supplementation compared to those who received the control (MD 0.09, 95% CI 0.01 to 0.17; six RCTs; $I^2=10\%$). Results were similar for the sensitivity analysis including studies with a low risk of bias.

**Weight:** There were no significant differences in absolute weight between iron supplementation and control groups (five RCTs), although one study reported children with iron deficiency anaemia had a significant improvement in weight for age score compared to control but this effect was not reported for children without anaemia.

**Haematologic and iron indices:** Compared to control, iron supplementation significantly reduced the prevalence of iron deficiency (RR 0.21, 95% CI 0.07 to 0.63; four RCTs; $I^2=85\%$) and decreased the risk of anaemia (RR 0.50, 95% CI 0.39 to 0.64; seven RCTs; $I^2=85\%$)

**Safety:** There were no significant differences between groups for malaria infection (four RCTs), or for gastrointestinal adverse events (four RCTs).

Other results were reported in the review

**Authors’ conclusions**

The evidence suggested that iron supplementation safely improved haematologic and non-haematologic outcomes among primary-school-aged children in low- or middle-income settings, and was well-tolerated.

**CRD commentary**

The review question was clear with defined inclusion criteria. Several relevant sources were searched and efforts were made to locate unpublished data. Efforts were made to reduce the potential for language and publication bias. Study quality was assessed and the results were used to inform the analysis; few studies were at low risk of bias. Methods to reduce reviewer error and bias were used for study selection and data extraction, but it was unclear whether similar methods were used for assessing quality. The methods of analysis appeared appropriate, but there was significant statistical heterogeneity for a number of outcomes. There was wide variation between studies for intervention, control, duration and outcomes.

The authors’ conclusions regarding improvement of haematologic and non-haematologic outcomes reflect the evidence presented. The evidence on safety is based on a subset of studies which, combined with potential bias in the studies,
means the reliability of the conclusions is uncertain.

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

**Practice:** The authors stated that routine daily iron supplementation was likely to benefit cognitive performance in primary-school-aged children in developing settings where anaemia was prevalent and testing haemoglobin before iron supplementation may not have been feasible. In developed settings, the data support ensuring that anaemia was detected and treated. Reductions in the prevalence of anaemia and iron deficiency reported in the review should guide the targets of anaemia-control programs.

**Research:** The authors stated that further RCTs evaluating the non-Haematologic effects of iron, particularly outcomes such as cognitive performance, growth and safety, were needed.

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