Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials

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Summary

Background About 47% of preschool children worldwide are anaemic. Daily oral iron supplementation is a commonly recommended intervention for treatment and prevention of anaemia, but the efficacy and safety of iron supplementation programmes is debated. Thus, we systematically reviewed the evidence for benefit and safety of daily iron supplementation in children aged 4–23 months.

Methods We searched Scopus and Medline, from inception to Feb 5, 2013, WHO databases, theses repositories, grey literature, and references. Randomised controlled trials that assigned children 4–23 months of age to daily oral iron supplementation versus control were eligible. We calculated mean difference (MD) or standard MD (SMD) for continuous variables, risk ratios for dichotomous data, and rate ratios for rates. We quantified heterogeneity with the I^2 test and synthesised all data with a random-effects model. This review is registered with the International Prospective Register of Systematic Reviews, number CRD42011001208.

Findings Of 9533 citations identified by the search strategy, 49 articles from 35 studies were eligible; these trials included 42 306 children. Only nine studies were judged to be at low risk of bias. In children receiving iron supplements, the risk ratio for anaemia was 0·61 (95% CI 0·50–0·74; 17 studies, n=4825), for iron deficiency was 0·30 (0·15–0·60; nine studies, n=2464), and for iron deficiency anaemia was 0·14 (0·10–0·22; six studies, n=2145). We identified no evidence of difference in mental (MD 1·65, 95% CI –0·63 to 3·94; six studies, n=1093) or psychomotor development (1·05, –1·36 to 3·46; six studies, n=1086). We noted no significant differences in final length or length-for-age, or final weight or weight-for-age. Children randomised to iron had slightly lesser length (SMD –0·83, –1·53 to –0·12; eight studies, n=868) and weight gain (–1·12, –1·19 to –0·33) over the course of the studies. Vomiting (risk ratio 1·38, 95% CI 1·10–1·73) and fever (1·16, 1·02–1·31) were more prevalent in children receiving iron.

Interpretation In children aged 4–23 months, daily iron supplementation effectively reduces anaemia. However, the adverse effect profile of iron supplements and effects on development and growth are uncertain. Adequately powered trials are needed to establish the non-haematological benefits and risks from iron supplementation in this group.

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Introduction

More than 1·6 billion people worldwide are anaemic and the prevalence is highest (47·4%) in preschool children,[1] especially those aged 4–23 months. Iron deficiency is thought to be the commonest cause of anaemia worldwide.[1] Complex factors interact to cause iron deficiency in children aged 4–23 months: inadequate iron stores attributable to low birthweight and prematurity, increased requirements during rapid growth and erythropoiesis, inadequate iron content and availability from complementary foods (introduced at 4–6 months of age),[2] and blood loss due to parasitic infection.[3] Beyond anaemia, iron deficiency in early childhood has been associated with many adverse effects, especially potentially irreversible cognitive deficits associated with impairment to CNS structural and metabolic development.[4] Iron supplementation programmes are premised on the assumption that iron will benefit anaemia and also non-haematological outcomes.[5]

The importance of prevention of undernutrition during gestation and the first 2 years (first 1000 days) of life for optimum development has been re-emphasised.[6] Daily iron supplementation is a widely recommended strategy for anaemia control (including by WHO[7]) although these recommendations are not based on a systematic review of this specific intervention. In the past decade, randomised controlled trials and previous systematic reviews have reported uncertain benefits and safety of iron supplementation in young children.[8–10] Understanding of the risks and benefits of daily iron supplementation is crucial to develop an appropriate evidence base for anaemia control policy. This systematic review and meta-analysis aims to comprehensively assess the effect of daily iron supplementation in children aged 4–23 months on important haematological and non-haematological outcomes and adverse effects.

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Methods

Search strategy and selection criteria

We searched Scopus (comprises Embase and Medline) and Medline (separately; from inception to Feb 5, 2013), Cochrane Controlled Clinical Trials Register, Proquest Digital Theses, Australian Digital Theses Database, and OpenSigle (in March, 2012). We also searched WHO regional databases (AIM, AFROMED, LILACS, IMSEAR, WPRIM, and IMEMR; from inception to April 4, 2012). We reviewed references of identified articles and previous systematic reviews. We applied no language restrictions. We searched the WHO International Clinical Trials Registry Platform in March, 2013, to identify ongoing or unpublished potentially eligible trials. The Scopus search strategy is presented in appendix p 2.

See Online for appendix

Randomised controlled trials assigning community or outpatient, otherwise well children aged 4–23 months to daily oral iron supplements versus control were eligible. Studies that combined iron supplements with a second intervention were eligible when the co-intervention was applied identically (without iron) in the control group (studies comparing multiple micronutrients containing iron with control were thus ineligible). When a study did not specifically recruit children aged 4–23 months, it remained eligible when the mean or median age was within 4–23 months, when at least 75% of participants were within the designated age range, or when most of the study's designated recruitment age range overlapped 4–23 months.

Data extraction and management

Two authors independently screened the titles and abstracts identified by the search and excluded those for which title and abstract indicated clear ineligibility. Full-text studies were screened for eligibility against the inclusion criteria by two authors independently. Data were extracted in duplicate by different authors independently. One author then entered data into Review Manager software (RevMan, version 5.1) and a second author checked entries for accuracy. Discrepancies were resolved through discussion.

Assessment of risk of bias in included studies

Two authors independently assessed risk of bias using the Cochrane instrument,[11] according to established criteria (appendix pp 3–4). Discrepancies were resolved through discussion. We did a sensitivity analysis including only studies judged at low overall risk of bias (appendix pp 18–20).[12] We used funnel plots to assess potential publication bias for outcomes with more than ten trials.

Outcomes

We selected outcomes to inform guidelines for anaemia control[13] by assessing potential benefits and risks relevant to implementation of public health anaemia control programmes in low-income and middle-income countries. Primary outcomes were: haemoglobin (g/L), anaemia (defined by study investigators), iron status (iron indices, including ferritin), iron deficiency (defined by study investigators), iron deficiency anaemia (IDA, defined by study investigators), cognitive and psychomotor development, physical growth, and safety (ie, gastrointestinal effects, infections such as malaria, mortality). Secondary outcomes included effects of iron on other micronutrients (eg, zinc, vitamin A).

Synthesis of results

We did meta-analysis for outcomes reported by at least two trials. For continuous data measured on the same scale, mean difference (MD) was estimated. Data using different scales were combined with standardised MD (SMD).[14] When, for particular outcomes, some studies reported endpoint data only and others reported change from baseline only, these were combined using MD when the same scale had been used.[14] When studies reported both endpoint and change from baseline data for the same outcome, endpoint data were used. For dichotomous data, we calculated risk ratios. For rates, we calculated rate ratios. We extracted 2×2 factorial studies as two separate experiments (iron supplementation *vs* control, iron supplementation plus co-intervention *vs* co-intervention alone); these data were entered into the meta-analysis separately.

We quantified heterogeneity with the I^2 test; we deemed substantial heterogeneity to exist when I^2 exceeded 50%. For each outcome, subgroup analysis was done to explain potential methodological or clinical heterogeneity.[14] Subgroups included baseline anaemia and iron status, dose and duration of supplementation, present breastfed status, and malaria endemicity of the study setting (appendix p 1). We compared effect sizes in subgroups when at least three studies were included per stratum, using the adapted χ^2 p and I^2 statistics of Borenstein.[15] We drew forest plots to present the effect size and relative weighting for each study and the overall calculated effect size. In view of potential heterogeneity, all data were synthesised with a random-effects model, with calculation of the τ^2 value.[14] This review is registered at the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42011001208.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The search identified 9533 papers. We did not identify any ongoing or unpublished studies through WHO ICTRP. The outcome of papers that underwent full-text review is presented in appendix pp 6–12. After screening, 49 papers relating to 35 trials were eligible, of which

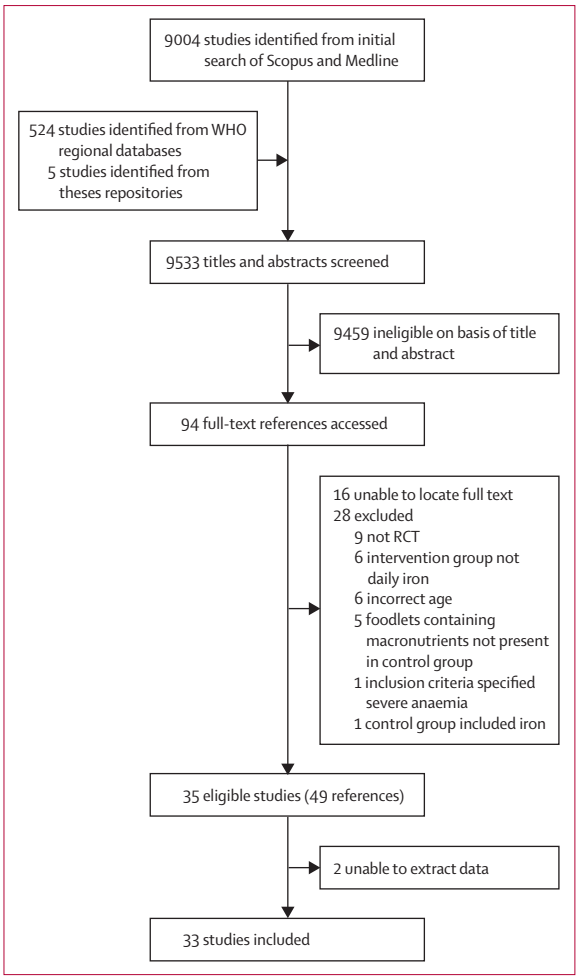

Figure 1: **Study flow diagram**
RCT=randomised controlled trial.

33 contained data that could be extracted (figure 1). These 33 trials included 42 015 children, with 21 175 randomised to iron supplementation and 21 089 to control. Excluding the large studies by Sazawal and colleagues[10] and Tielsch and colleagues[16] (32 976 children; appendix p 21), which used cluster randomisation, 9039 children were included, 4690 randomised to iron supplements and 4350 to control.

Appendix pp 13–17 show characteristics of included studies. Iron was generally provided as ferrous salts, including ferrous sulfate in 22 studies (six studies did not specify preparation). Only one study reported quality control testing of supplements.[17] Nine studies were judged at low overall risk of bias (appendix pp 18–20) for sensitivity analysis.

Findings for meta-analysis of primary outcomes are summarised in the table. Appendix pp 28–41 detail all results including, for outcomes containing six or more studies, subgroup analysis.

Iron supplementation increased haemoglobin and ferritin and reduced the prevalence of anaemia, iron deficiency, and IDA (table, appendix pp 22–24). We identified no evidence of publication bias for effects of iron on haemoglobin, ferritin, and anaemia (appendix pp 25–26). As shown in appendix pp 27–31, these

	Number of trials	Number of participants	Measure of difference (95% CI)	p value for effect	I^2
Haematology					
Haemoglobin (g/L)	26	5479	MD 7·22 (4·87 to 9·57)	<0·0001	94%
Mean cell volume (fL)	10	1434	MD 2·81 (1·20 to 4·42)	0·001	88%
Anaemia	17	4825	Risk ratio 0·61 (0·50 to 0·74)	<0·0001	86%
Iron indices					
Ferritin (ng/mL)	23	4236	MD 21·42 (17·25 to 25·58)	<0·0001	98%
Transferrin saturation (%)	7	774	MD 6·00 (2·65 to 9·35)	0·0004	81%
Transferrin receptor	3	837	SMD –0·99 (–1·60 to –0·39)	0·001	94%
Serum iron (mcg/dL)	4	210	MD 3·56 (–1·79 to 8·91)	0·19	79%
Erythrocyte protoporphyrin	4	747	SMD –0·32 (–0·61 to –0·03)	0·03	72%
Iron deficiency (ferritin)	9	2464	Risk ratio 0·30 (0·15 to 0·60)	0·0006	94%
Iron deficiency anaemia	6	2145	Risk ratio 0·14 (0·10 to 0·22)	<0·0001	0%
Other micronutrients					
Serum zinc (μmol/L)	6	1988	MD –0·70 (–1·37 to –0·03)	0·04	85%
Retinol (μmol/L)	3	429	MD –0·07 (–0·15 to 0·01)	0·02	68%
Development					
Bayley's mental development index (score)	6	1093	MD 1·65 (–0·63 to 3·94)	0·16	66%
Bayley's psychomotor development index (score)	6	1086	MD 1·05 (–1·36 to 3·46)	0·39	67%
Growth					
Weight (kg)	8	2702	MD –0·02 (–0·09 to 0·05)	0·56	25%
Weight for age (Z-score)	8	3237	MD –0·02 (–0·08 to 0·03)	0·43	0%
Change in weight	8	868	SMD –1·12 (–1·91 to –0·33)	0·0005	96%
Length (cm)	7	2470	MD –0·13 (–0·33 to 0·07)	0·20	0%
Length for age (Z-score)	8	3237	MD 0·01 (–0·04 to 0·06)	0·71	4%
Change in length	8	868	SMD –0·83 (–1·53 to –0·12)	0·02	95%
Weight for length (Z-score)	5	2763	MD 0·03 (–0·06 to 0·12)	0·50	46%
Stunting	3	1504	Risk ratio 1·10 (0·92 to 1·32)	0·29	0%
Wasting	3	1504	Risk ratio 1·03 (0·65 to 1·64)	0·89	0%
Adverse effects					
Vomiting	3	1020	Risk ratio 1·38 (1·10 to 1·73)	0·006	1%
Diarrhoea (prevalence)	6	1697	Risk ratio 1·03 (0·86 to 1·23)	0·78	0%
Diarrhoea (incidence)	5	..	Rate ratio 0·98 (0·88 to 1·09)	0·69	0%
Constipation	2	570	Risk ratio 0·54 (0·05 to 5·83)	0·49	77%
Any side-effects	3	912	Risk ratio 1·10 (0·98 to 1·25)	0·12	0%
Fever (prevalence)	4	1318	Risk ratio 1·16 (1·02 to 1·31)	0·02	0%
Fever (incidence)	2	..	Rate ratio 1·08 (0·79 to 1·47)	0·63	0%
Acute respiratory infection	2	944	Risk ratio 1·04 (0·92 to 1·19)	0·51	0%
Lower RTI (incidence)	3	..	Rate ratio 1·00 (0·89 to 1·12)	0·96	0%
Clinical malaria	3	..	Rate ratio 0·91 (0·71 to 1·17)	0·47	53%
All malaria episodes	2	..	Rate ratio 0·81 (0·64 to 1·03)	0·08	0%
Malaria parasitaemia	2	..	Rate ratio 0·96 (0·81 to 1·15)	0·68	0%
Outpatient attendances	2	..	Rate ratio 1·00 (0·88 to 1·15)	0·97	0%
Mortality	2	..	Rate ratio 1·10 (0·91 to 1·34)	0·33	0%

MD=mean difference. SMD=standard MD. RTI=respiratory tract infection.

Table: **Summary of findings**

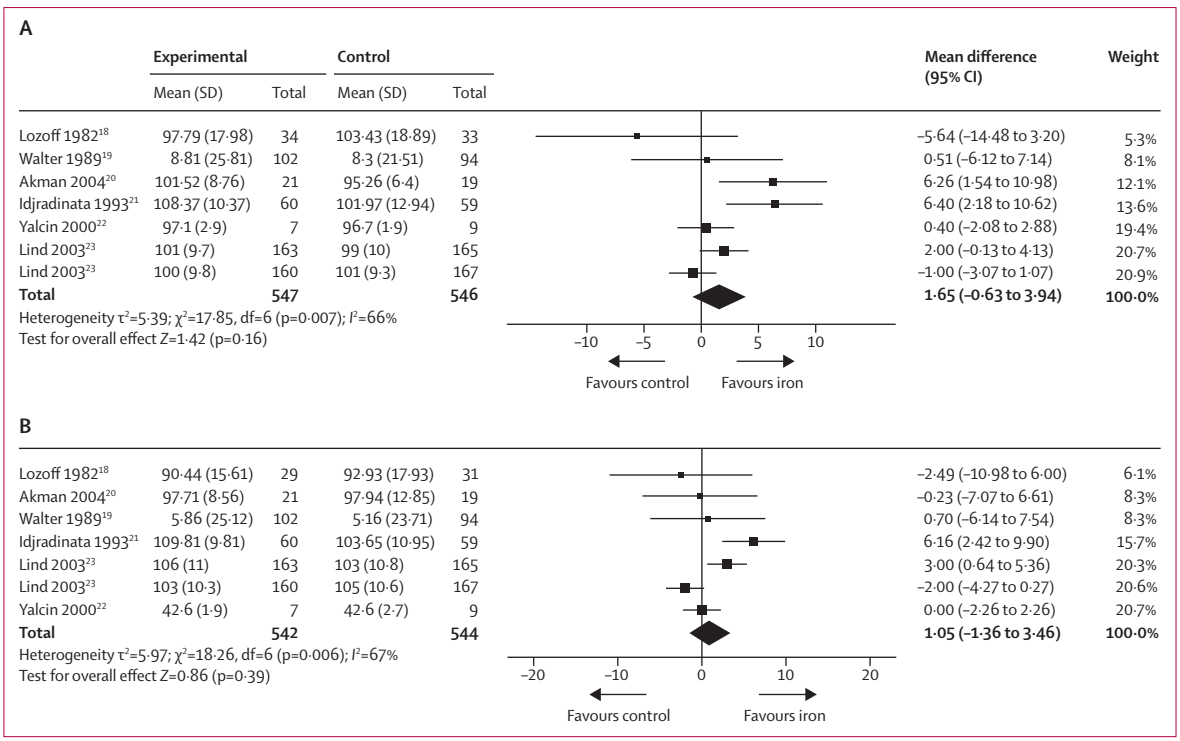

Figure 2: **Forest plots for effect of daily iron supplementation on development**
(A) Bayley's mental development index. (B) Bayley's psychomotor development index. *Inverse variance, random effects.

improvements tended to be greatest in children with baseline anaemia or iron deficiency, although most studies did not stratify inclusion by these disorders. Nevertheless, we also noted significant benefits in children with unknown baseline anaemia and iron status. Longer duration (>3 months vs <1 month) of supplementation seemed to have a greater effect on ferritin and transferrin saturation but not on haematological indices. When only trials at low risk of bias were included (haemoglobin, seven trials; ferritin, five trials; anaemia, seven trials; iron deficiency, four trials; IDA, three trials), significant improvements in these outcomes were still noted (data not shown).

Cognitive development was reported using Bayley's mental development index in six studies.[18–23] We identified no significant difference in Bayley's mental development index in children receiving iron compared with control (figure 2A). When only studies at low risk of bias (two trials[21,23]) were included, MD was 2·05 (95% CI −1·46 to 5·55; p=0·25). Subgroup analysis did not show evidence of benefit on mental development index from iron supplementation in children who were anaemic (MD 4·46, 95% CI −9·32 to 18·24; p=0·53); however, there was evidence of a beneficial effect in children with iron deficiency at baseline (MD 5·90, 95% CI 1·81 to 10·00; p=0·005; appendix p27). A further two studies measured cognitive development by different methods. Siegel[24] and Surkan and colleagues[25] reported no difference from iron supplementation in Fagan intelligence scale, or attainment of cognitive or motor milestones in Nepalese children, respectively. Pongcharoen and colleagues[26] could not identify any evidence of long-term cognitive improvement (measured by the Wechsler Intelligence Scale for Children, Raven's Colored Progressive Matrices, or school performance) in Indonesian children randomised to iron with zinc versus zinc alone at 4–6 months of age.

We identified no significant difference in Bayley's Psychomotor Development Index in children receiving iron supplements (figure 2B).[18–23] When only studies at low risk of bias (two trials[21,23]) were included, MD was 2·21 (95% CI −2·29 to 6·71; p=0·34). Aukett and colleagues[27] noted no benefit in psychomotor development measured by the Denver development scale in children with anaemia randomised to iron versus control (MD 0·80, 95% CI −0·18 to 1·78; p=0·11).

Physical growth was reported in different studies as length and weight at the end of the intervention; change in length and weight over the duration of the study; and as *Z* scores for weight-for-age, length-for-age, or weight-for-length, at study endpoint. No studies reported absolute, normalised, or change in length or weight in children who were anaemic or iron deficient. We identified no differences between children randomised to iron or control in final length, length-for-age *Z* score, final weight, weight-for-age *Z* score, or weight-for-length *Z* score (figures 3, 4), with much the same results when only studies at low risk of bias were included (data not shown).

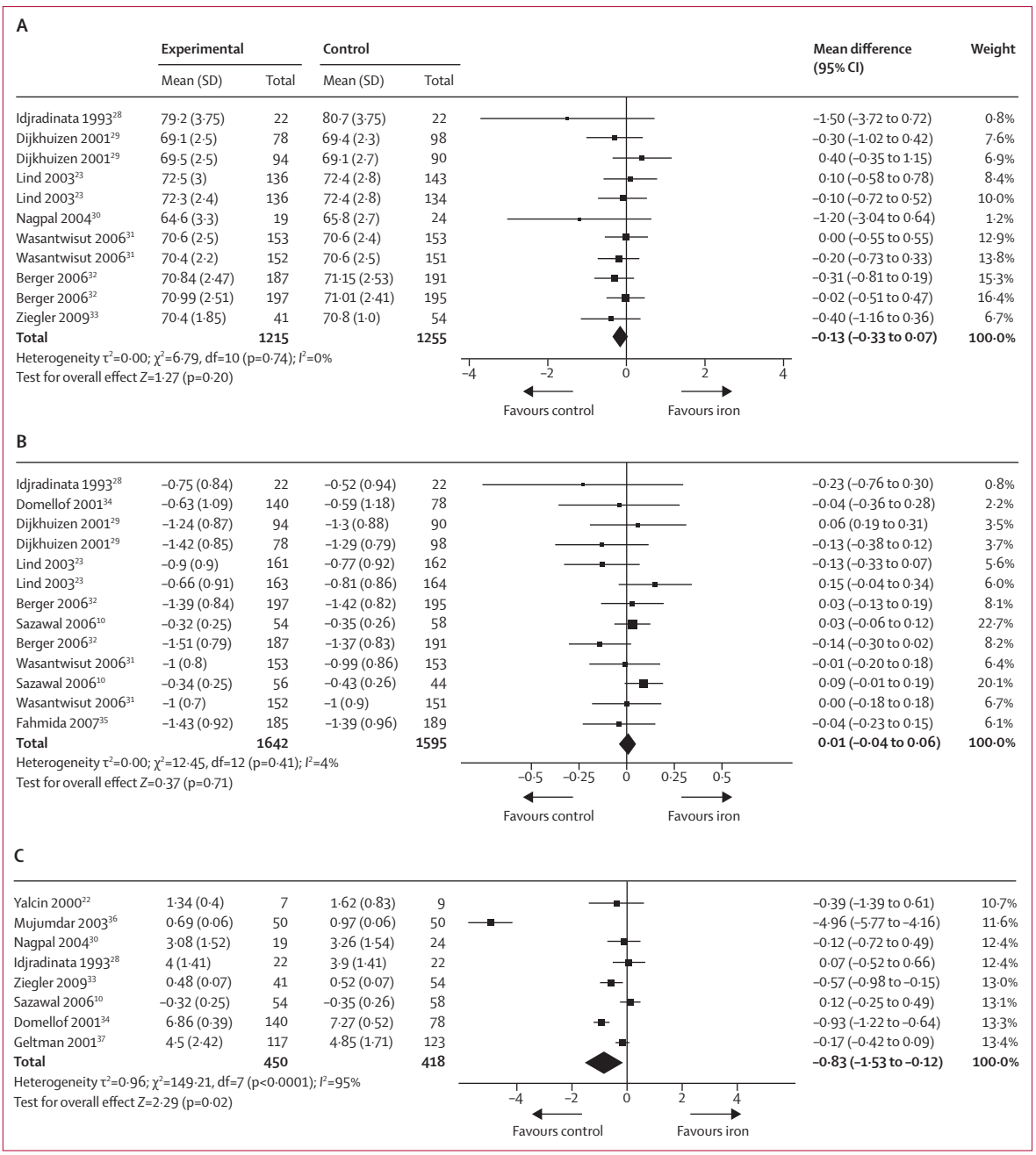

Figure 3: **Forest plots for effects of daily iron supplementation on growth**
(A) Final length. (B) Final length for age. (C) Length gain.

When growth was reported as change from baseline, children who received iron supplementation had significantly reduced length gain (figure 3C) and weight gain (figure 4C) compared with control. Subgroup analysis showed that children receiving more than 3 months of iron supplementation had reduced weight gain (SMD –2·39, 95% CI –4·37 to –0·41; p=0·02). When only the two studies[10,28] at low risk of bias were included, SMD for weight gain was –0·21 (95% CI –0·61 to 0·19; p=0·31), and SMD for length gain was 0·10 (–0·21 to 0·42; p=0·52). One study, by Majumdar and colleagues,[36] contributed effect estimates for both change in weight and length that were substantially more negative than other studies; however, even when this study was excluded, we noted an adverse effect from iron on weight gain (–0·32, –0·62 to –0·02; p=0·03); MD for length gain was –0·30 (–0·64 to 0·04; p=0·09).

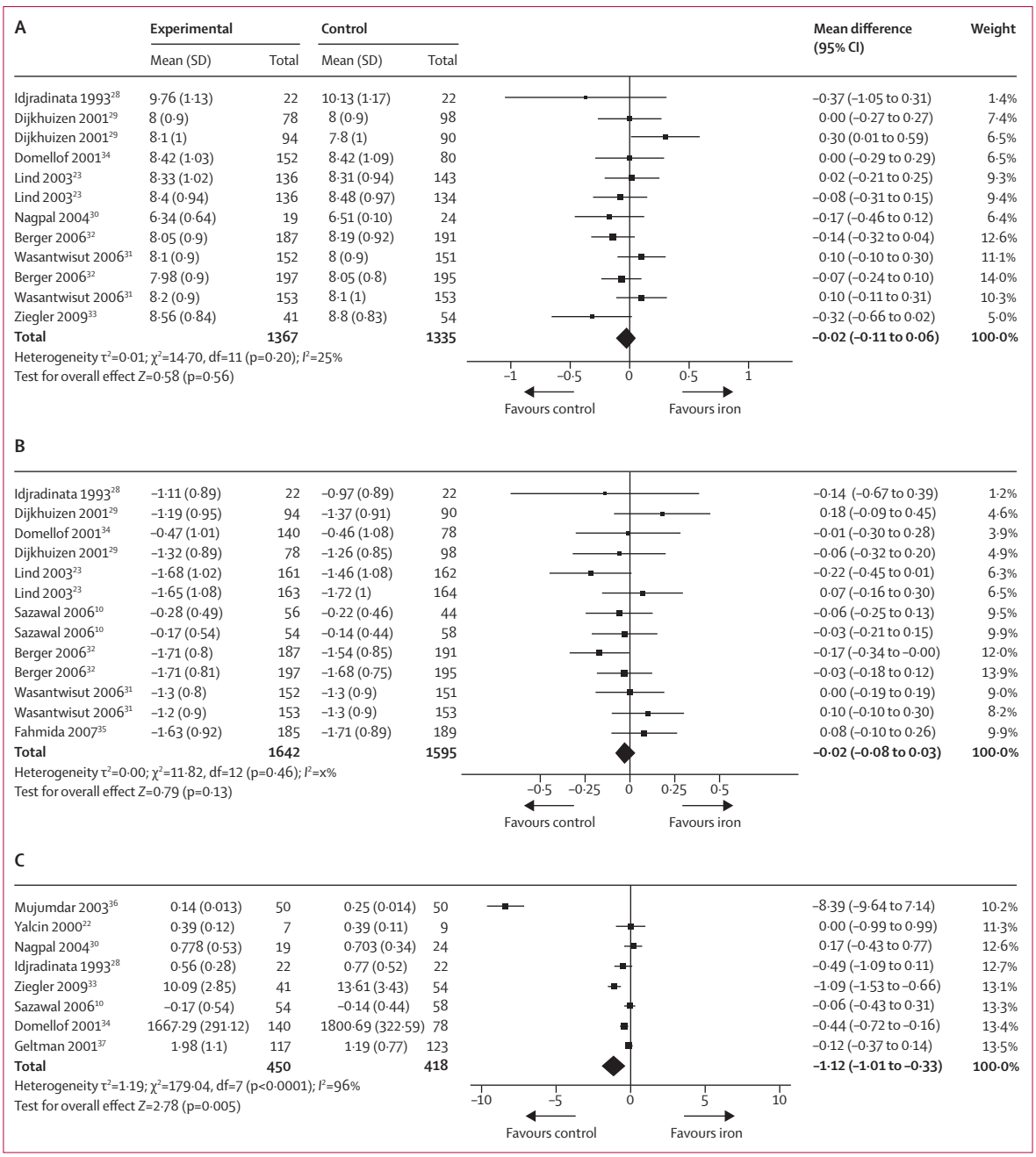

Figure 4: **Forest plots for effects of daily iron supplementation on growth**
(A) Final weight. B) Final weight for age. (C) Weight gain. *Inverse variance, random effects.

Safety outcomes are summarised in the table. Iron supplementation increased the risk of vomiting; the effect was still noted when only data from the one trial at low risk of bias was included: risk ratio 1·35 (95% CI 1·00–1·83; p=0·05). We identified no effect from iron supplementation on constipation, or prevalence or incidence of diarrhoea, nor did iron affect mortality (appendix pp 39–40). Children randomised to iron had an increased prevalence of fever. When only studies at low risk of bias (two trials) were included, the risk ratio was 0·99 (0·76–1·30; p=0·95). Iron supplementation did not affect incidence of fever. There was no effect from iron supplementation on incidence of lower respiratory infections. Berger and colleagues[32] noted no evidence of an effect from iron supplementation on prevalence of respiratory infections (risk ratio 1·05, 95% CI 0·92–1·20; p=0·45).

Malaria-related outcomes were reported in four studies.[10,38–40] Meta-analysis showed that clinical malaria,

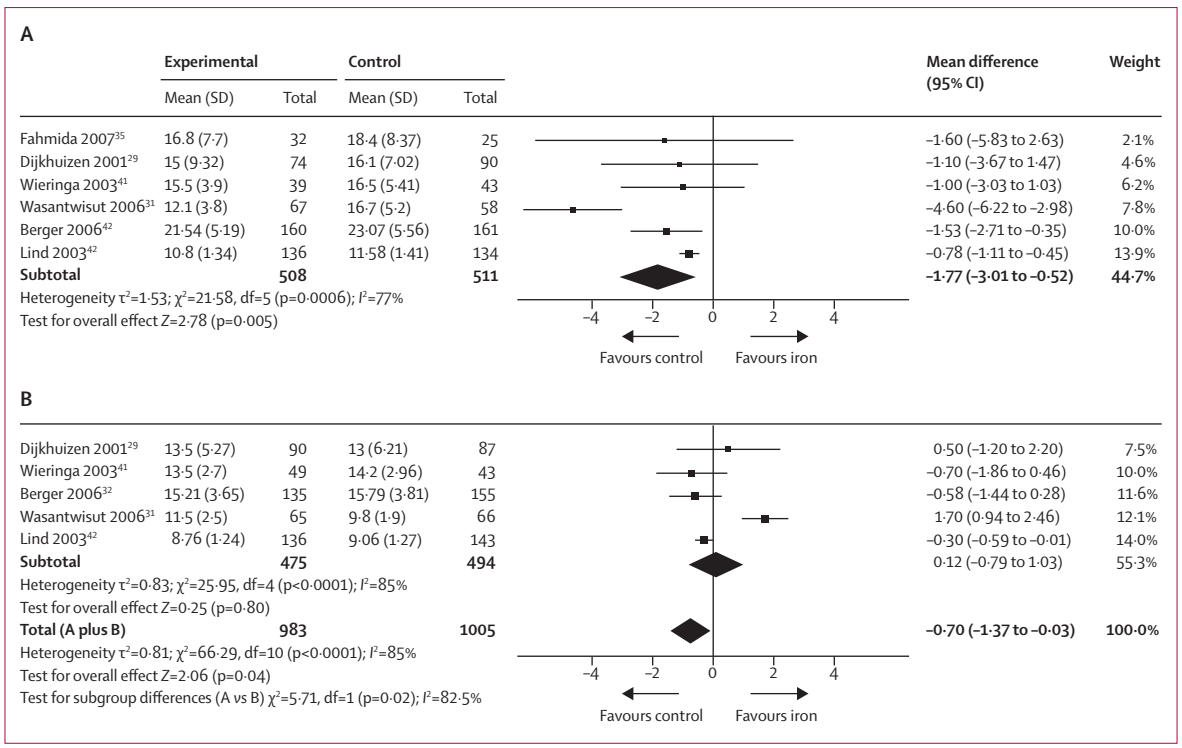

Figure 5: **Forest plots for effects of daily iron supplementation on zinc concentrations**
(A) Iron plus zinc versus zinc alone. (B) Iron alone versus control, and overall. *Inverse variance, random effects.

parasitaemia, and parasite densities were not affected by iron supplementation. Further descriptions of the findings of these trials are included in the appendix p 21.

Children randomised to iron had lower zinc concentrations than control children[29,31,32,35,41,42] (MD −0·70 (95% CI −1·37 to −0·03; p=0·04). When only the four trials[32,31,35,42] at low risk of bias were included, MD was −0·80 (95% CI −1·65 to 0·04; p=0·06). Post-hoc subgroup analysis to compare the MD in trials comparing iron versus control, with the MD in trials comparing combined iron and zinc versus zinc alone, showed that children supplemented with iron and zinc in combination had reduced zinc concentrations compared with children receiving zinc alone (six studies, MD −1·77, 95% CI −3·01 to −0·52; p=0·005, I^2=77%; figure 5A), but children given iron alone did not have lower zinc concentrations compared with those receiving control (five studies, MD 0·12, −0·79 to 1·03; p=0·80, I^2=85%), test for subgroup difference p=0·01 (figure 5B).

Meta-analysis of adherence was not possible because of differences in reporting between studies. Adherence was not reported in 11 studies. Another 11 studies showed no difference in adherence between iron and control groups. Six studies administered all doses under supervision to ensure adherence. Two studies reported poorer adherence in children randomised to iron (appendix pp 18–20)

Discussion

Our study shows that daily iron supplementation improves haemoglobin and iron indices and substantially reduces the risk of anaemia, iron deficiency, and especially IDA in children aged 4–23 months. However, benefits to development and growth from daily iron supplementation in this age group are unclear. Participants of included studies were at high risk of anaemia (ie, 44% prevalence of anaemia at endpoint in the control group of the meta-analysis), iron deficiency (32% prevalence at endpoint in control group), and IDA (20% prevalence in control group). Most studies were done in low-income or middle-income settings. Our findings are thus relevant to anaemia control programmes in developing countries.

IDA is an important medical problem in young children (panel[3,43–49]), associated with symptoms including lethargy, irritability, pica, and poor oral intake. We identified a clear improvement in haemoglobin (MD 7·22 g/L, 26 studies) and reduction in the prevalence of anaemia (risk ratio 0·61, 17 studies; table) in children receiving daily iron supplementation. Gera and colleagues[43] identified a similar effect of iron on haemoglobin (MD 7·4 g/L) but did not do meta-analysis for anaemia, instead estimating that between 37·9% and 62·3% of baseline anaemia is amenable to control by iron, less so in malaria-endemic areas. Likewise, we noted a smaller effect from iron on anaemia in

***Panel:* Research in context**

We searched PubMed up to April 10, 2013, without language restriction, for systematic reviews assessing iron administration in children. We identified nine previous systematic reviews. A series of reviews assessed effects of iron in children on haemoglobin (but not anaemia),[43] cognitive and motor development,[45] growth,[46] exercise performance,[47] and risk of infectious disease.[48] These reviews combined age ranges of children and iron administration routes. Effects of iron on development in non-anaemic iron-deficient children have also been reviewed,[49] with authors finding data inadequate to draw conclusions. The effect of intermittent (1–3 times per week on non-consecutive days) iron[13] and multiple-micronutrient[44] supplementation on nutritional and developmental outcomes in children has also been assessed, with few data for non-haematological outcomes. Finally, a review examined the effects of daily iron supplementation in children aged 2–5 years.[55] As far as we are aware, the effects of daily iron supplementation have not been assessed by systematic review in children of this age group.

Interpretation

Daily iron improves haemoglobin and iron stores, and reduces the risk of anaemia, iron deficiency, and iron deficiency anaemia. However, only very few trials, recruiting relatively few children, have adequately studied non-haematological outcomes associated with iron supplementation in children with anaemia. There is inadequate evidence that iron improves cognitive development in this age group, although we noted a small benefit (non-statistically significant). High quality, suitably powered trials are needed to establish the risks and non-haematological benefits from iron in this population. Health worker and parental monitoring of children receiving daily iron is advisable.

malaria-endemic areas (risk ratio 0·70) than non-endemic areas (0·40; appendix p 28). De-Regil and colleagues[44] showed that multiple-micronutrient fortification reduced anaemia by 31% and iron deficiency by 51% in children younger than 2 years (six studies), whereas intermittent iron in children younger than 12 years reduced anaemia by 49% and iron deficiency by 76% (ten studies).[12] We conclude that iron supplementation can be expected to halve the prevalence of anaemia in young children (with greater reductions in the prevalence of iron deficiency [risk ratio 0·30] and IDA [0·14]; table). These estimates should guide realistic targets for anaemia control programmes.

Previous systematic reviews have failed to identify evidence of benefit from iron on mental development in young children.[45,50–52] Although we retrieved and included additional trials compared with previous reviews, we were also unable to find a beneficial overall effect, perhaps attributable to several reasons. First, individual trials and the overall meta-analysis might be underpowered to find a significant difference; a trial powered to identify a 1·6% improvement in Bayley's mental development index (as recorded in our meta-analysis) would need about 1300 children per group. Of 1093 children included in studies measuring Bayley's mental development index, only 113 children known to be anaemic and 241 known to be iron deficient were recruited. Second, tests for cognitive development in children of this age used in included studies might be insensitive to small changes.[53] Third, iron deficiency might cause an irreversible cognitive deficit in children that is refractory to iron supplementation. Finally, iron might not affect cognitive development in children; however, this conclusion would be in contradiction with data from animal studies[54] and benefits from iron noted in children aged 2–5 years (preschool)[55] and schoolchildren.[45] We did identify evidence with subgroup meta-analysis to suggest a beneficial effect from iron in iron deficient children. This effect was generated by the study by Akman and colleagues,[20] which did not use a placebo in the control group and is therefore at high risk of bias, and the combined iron deficiency anaemia and non-anaemic iron deficiency subgroups of the study by Idjradinata and colleagues;[28] of which only the iron deficiency anaemia subgroup showed evidence of benefit from iron. The inability to definitively quantify cognitive benefits from iron supplements affects the risk–benefit analysis needed for appropriate guideline development.

Our finding that daily iron supplementation impaired length gain and weight gain over the duration of follow-up (even though we noted no differences in final weight or length) raises concern. Changes from baseline scores are perhaps more valuable than comparison of final values, because they account for between-person baseline variability. Sachdev and colleagues[46] likewise noted no evidence of benefit on growth in children receiving iron, and identified evidence to suggest impairment in linear growth in children receiving iron for longer than 6 months or from developed countries. One potential mechanism for this finding is that children given iron might have gastrointestinal symptoms (including vomiting as noted in our meta-analysis), impairing appetite and oral intake. The scarcity of data for the effects of iron supplementation on growth in children who are anaemic or iron deficient limits the conclusions that can be drawn from these findings.

Although children receiving iron and zinc had lower zinc concentrations than children receiving zinc alone, these children still had higher absolute zinc concentrations (weighted mean 15·7 μmol/L) than children receiving iron alone (weighted mean 12·4 μmol/L) or control (12·4 μmol/L). Thus, coadministration of iron might impair efficacy of zinc supplementation but does not seem to affect de-novo zinc concentrations.

We did not identify evidence that daily oral iron supplementation increased malaria (although few studies were done in malaria-endemic areas or specifically reported malaria-related outcomes), diarrhoea, or respiratory infection, but we did identify evidence that iron increased fever. A systematic review[56] reported that iron did not increase the risk of clinical malaria, excluding sites where services did not provide for malaria surveillance and treatment, but did increase risk of parasitaemia. Taken together with our finding that iron increased vomiting, these data reinforce the need for health worker monitoring of children receiving iron supplements.

We have improved on previous systematic reviews by using a more comprehensive search strategy, enabling us to include more studies than previous meta-analyses; by

specifically assessing daily iron supplementation, a widely recommended and implemented intervention strategy;[57] and by comprehensively summarising the evidence for this intervention for a range of clinically important outcomes, in the age group in which anaemia control is deemed perhaps both most important[3] and also most problematic. Our conclusions are limited by quality of included trials. Few studies reported methodology for randomisation and concealment of allocation, and only nine studies were considered at low risk of bias. It is possible that a larger number of studies had appropriately prevented bias but had not reported these methods. Reporting of adherence and supplement quality control was also suboptimum. There remains a paucity of high quality randomised controlled trials reporting non-haematological outcomes.

Our systematic review was done in the context of growing uncertainty about the safety and optimum approach for iron supplementation to young children in low-income settings, prompted by data from high quality, adequately powered trials. Results of a randomised controlled trial[9] of home-based iron-containing multiple micronutrient fortification (not eligible for this review) showed that although micronutrients alleviated iron deficiency and anaemia, there was an increase in diarrhoea (including bloody diarrhoea) and respiratory illness in children randomised to intervention. Results of a randomised controlled trial[58] in Tanzanian children showed an increase in malarial episodes in iron-deficient children receiving micronutrients. A large randomised controlled trial[10] (included in this review) identified an increase in malaria and infection-related morbidity and mortality in Tanzanian children randomised to iron-folic acid.[10] Thus an urgent need exists to clarify the net benefits and risks of iron supplementation to preschool children. Our findings confirm the benefit of iron supplementation for control of anaemia. However, benefits on cognitive development and growth remain uncertain. Our data can inform the design of well-conducted, adequately powered trials that are still needed to define the benefits and safety of iron supplementation in children of this age group.

Contributors

S-RP and B-AB designed the study; S-RP, EH, and KK screened studies for eligibility and extracted data from studies; S-RP and EH analysed data; S-RP wrote the paper and had full access to all the data in the study and had final responsibility for the decision to submit for publication; all authors read and approved the final paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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