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Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials

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Abstract

Objective: To evaluate the effect of iron supplementation on mental and motor development in children through a systematic review of randomised controlled trials (RCTs).

Data sources: Electronic databases, personal files, hand search of reviews, bibliographies of books, abstracts and proceedings of international conferences.

Review methods: RCTs with interventions that included oral or parenteral iron supplementation, fortified formula milk or cereals were evaluated. The outcomes studied were mental and motor development scores and various individual development tests employed, including Bayley mental and psychomotor development indices and intelligence quotient.

Results: The pooled estimate (random effects model) of mental development score standardised mean difference (SMD) was 0.30 (95% confidence interval (CI) 0.15 to 0.46, $P < 0.001$; $P < 0.001$ for heterogeneity). Initial anaemia and iron-deficiency anaemia were significant explanatory variables for heterogeneity. The pooled estimate of Bayley Mental Development Index (weighted mean difference) in younger children (<27 months old) was 0.95 (95% CI −0.56 to 2.46, $P = 0.22$; $P = 0.016$ for heterogeneity). For intelligence quotient scores (≥8 years age), the pooled SMD was 0.41 (95% CI 0.20 to 0.62, $P < 0.001$; $P = 0.07$ for heterogeneity). There was no effect of iron supplementation on motor development score (SMD 0.09, 95% CI −0.08 to 0.26, $P = 0.28$; $P = 0.028$ for heterogeneity).

Conclusions: Iron supplementation improves mental development score modestly. This effect is particularly apparent for intelligence tests above 7 years of age and in initially anaemic or iron-deficient anaemic subjects. There is no convincing evidence that iron treatment has an effect on mental development in children below 27 months of age or on motor development.

Keywords
Anaemia
Cognition
Iron deficiency
Iron supplementation
Mental development
Meta-analysis
Motor development
Randomised controlled trials

Animal studies have provided a number of possible mechanisms through which iron deficiency can leave an imprint on the developing brain[1–4]. Most observational studies in children have found associations between iron-deficiency anaemia (IDA) and poor cognitive and motor development and behavioural problems[5,6]. Longitudinal studies consistently indicate that children who were anaemic in infancy continue to have poorer cognition, school achievement and more behaviour problems into middle childhood[6]. However, the possible confounding effects of environmental factors, particularly poor socio-economic background, prevent causal inferences from being made. Furthermore, there is no convincing evidence that iron therapy can significantly improve psychomotor development and cognitive function in children under the age of 3 years with IDA[7]. This may be related to confounding by environmental factors and a possible irreversible effect of iron deficiency on the developing brain, particularly on the dopamine receptors and the myelin tissue[3,4]. It is important to evaluate the effect of iron administration on mental and motor development in children, including those in older age groups, to provide clarity about realistic expectations from iron supplementation and fortification efforts. We therefore conducted a systematic review to determine the effect of iron supplementation on mental and motor development in children.

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Methods

Searching

We searched computerised bibliographic medical databases, including Medline (1966 to March 2003), the Cochrane controlled trials register, Embase, IBIDS and Healthstar. We also reviewed reference lists of identified articles and hand searched reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings. Donor agencies, 'experts' and authors of recent iron supplementation trials were contacted to identify any additional or ongoing trials. The title and abstract of the trials identified in the computerised search were scanned to exclude studies that were obviously irrelevant. We reviewed the full texts of the remaining studies and identified trials that fulfilled the inclusion criteria. To avoid publication bias, we included published and unpublished trials.

Selection criteria

To be included, trials had to:

- be randomised placebo-controlled trials – except for those in which iron was given parenterally, in which case trials did not have to be placebo-controlled because it would be difficult to administer a similar placebo;
- investigate iron supplementation through the oral or parenteral route or as formula milk or cereals fortified with iron; and
- evaluate one or more developmental indicators (psychomotor development, cognition, mental development, intelligence quotient (IQ), school performance) as an outcome measure.

We also included studies in which other micronutrients and drugs were simultaneously administered if the only difference between the study and the control groups was iron supplementation.

Validity assessment

We assessed the quality of trials using recommended criteria[8,9]. Concealment of allocation was classed as adequate, unclear, inadequate, or not used. To assess attrition we classified studies by percentage of participants lost to follow-up ($<3\%$, 3–9.9%, 10–19.9% and $\geq 20\%$). Blinding was classified as double blinding, single blinding, no blinding, or unclear.

Data abstraction

We used pre-formed questionnaires to abstract data. The data included in this review were derived from the published papers or were provided by the authors. If required, and wherever possible, we contacted the authors for clarifications. T.G. abstracted all data.

Quantitative data synthesis

In studies with two or more iron intervention groups (different dosage or administration regimes) and a single control group, the sample size of the control group was divided equally between the number of intervention groups while retaining the same value for the change in outcome and its standard deviation (SD). This was done to avoid multiple counting of the control group (Oxman AD, personal communication, 2003; Deeks J, personal communication, 2003). Thus, some trials contributed more than one analytic component for statistical computations.

In computing pooled estimates, we required sample size, mean change in development score from the beginning to the end of the intervention and the SD of this change in the intervention and control groups. The following principles were used for derivations if actual variables were not stated.

1. In a group, the lower of the two stated sample sizes at the beginning or end of a trial was assumed to be the sample size for the change.
2. Wherever feasible, SD was back-calculated from the stated standard errors, t or P values.
3. Wherever not stated, the mean change in development score was computed as the difference of mean post- and pre-intervention scores.
4. Wherever not stated, the mean age of subjects was computed as the average of the stated range.

The SD for the change in development scores was available or could be back-calculated from only a few studies. For the rest, this SD was computed assuming correlations of 0.5, and 0 (independent) between the pre- and post-test variances[10]. Considering the number of assumptions and computations involved, and to be confident about the interpretation, three types of pooled estimates were calculated for each development score. In two, the change SD for values that were missing or could not be back-calculated were computed with the assumption of a correlation (P) of 0.5 or of independence. For the third, the post-intervention scores and their respective SDs were used.

The presence of publication bias in the extracted data was evaluated by funnel plots[11]. We used the METABIAS command in STATA software to perform statistical tests for funnel plot asymmetry[12]. The pooled estimates of the weighted mean difference (WMD) of the evaluated change in outcome score between the control and intervention group were calculated by both fixed effects and random effects model assumptions using the METAN command in STATA software[12]. Where different outcome scoring scales were used, the standardised-weighted mean difference (SMD) was used. We report primarily random effects estimates because most of the pooled results obtained were statistically heterogeneous.

We carried out pre-specified stratified analyses for quality of methods; age of subjects; route of iron

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administration (parenteral, oral supplement or food fortification); duration of supplementation; baseline haemoglobin (Hb) concentration in the supplemented group; and iron status of the study population. The contribution of these variables to heterogeneity was also explored by meta-regression using the METAREG command in STATA software with the restricted maximum likelihood option[12].

Results

Trial flow

We identified 32 randomised controlled trials that were potentially eligible[13–40]. Fifteen studies were ineligible (Fig. 1). We therefore evaluated 17 trials in this systematic review: 16 published and one unpublished (Kimmons G, Moffatt MEK, Longstaffe S, Whalen-Besant J. Short term effects of intra-muscular iron on the behaviour of iron-deficient children: a clinical trial).

Study characteristics

Table 1 depicts the baseline characteristics of the included trials. The studies were almost equally distributed between developed and developing countries (seven in Asia, three in Europe, three in North America, two in South America, one in Africa, location of one not clear). Most of the studies (11/17) were conducted in infants and toddlers, while in six trials older children were evaluated. In four studies the intervention lasted less than 2 weeks, while nine trials intervened for 4 months or longer. In most reports the subjects received iron supplements in the form of oral medicinal iron (12/17), two studies used fortified foods and three trials administered iron parenterally. In younger children, the developmental aspect studied were mainly the Bayley indices for mental and psychomotor development (9/17). Other studies used motor and language scores; discrimination learning, oddity learning and Peabody Picture Vocabulary Tests (PPVT); cognition score, visual recall, mazes, clerical task; Denver Development Screening Test (DDST); and IQ and school performance. The studies were grouped and analysed for two parameters, namely mental/intelligence scores and motor development indices. In addition, to retain a certain degree of homogeneity, individual analyses were also done for Bayley's indices, IQ scores, psychomotor scores and school performance.

Quantitative data synthesis

Mental development

Mental development score (MDS). This nomenclature refers to a logical combination of different tests that assess the same aspect of mental development, namely the Bayley Mental Development Index (MDI), Stanford Binet Test, PPVT, IQ and cognition scores. Fifteen studies (Table 1) were included in this analysis.

The funnel plot was symmetrical (Fig. 2) with no evidence of publication bias by Egger ($P = 0.694$) or

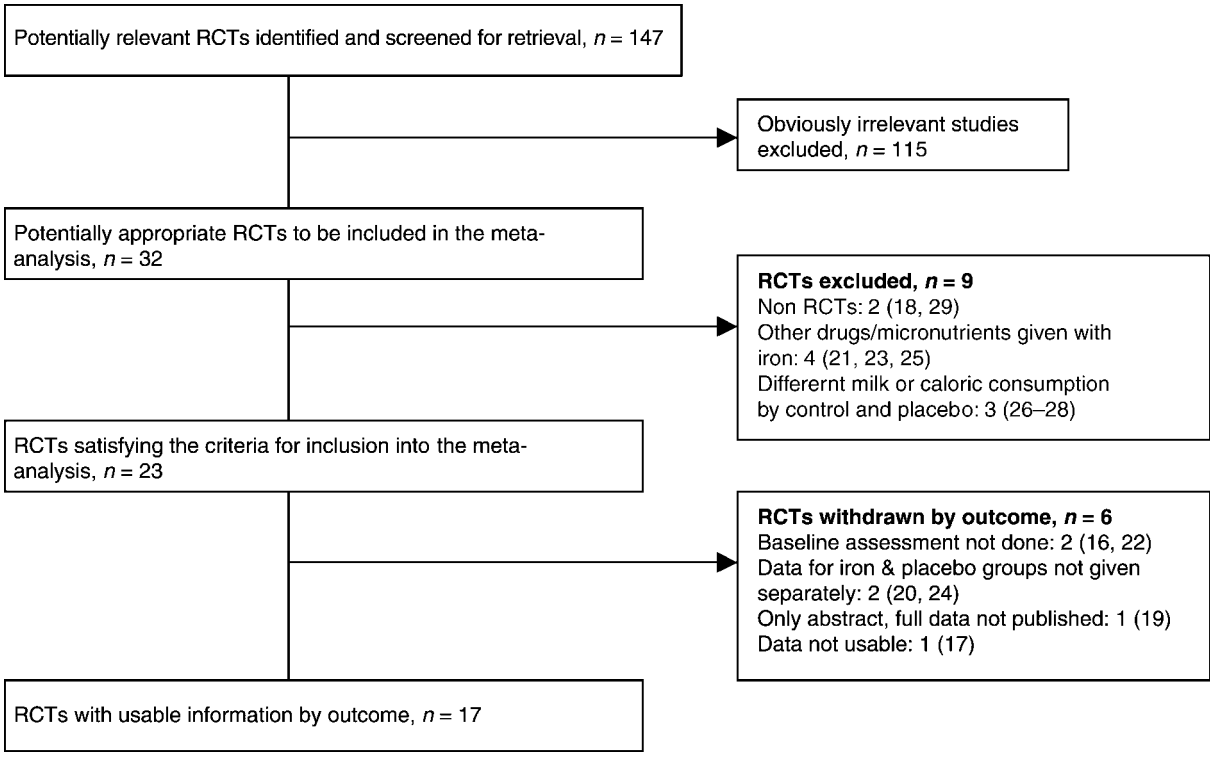

Fig. 1 Flow chart depicting the trial flow for selection of randomised controlled trials (RCTs) to be included in the meta-analysis (reference numbers in parentheses)

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Table 1 Characteristics of the selected trials

Study	Location	Age group	Sample size	Parameters	Methods of randomisation, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Iron supplementation
Oski and Honig (1978)[13]	USA, North America	9–26 months	T b = 24 Fe b = 12 Pl b = 12	Bayley MDI, Bayley PDI	Not mentioned, B, A, D	**1.** Anaemic **2.** Free from intercurrent illness **3.** No recognisable chronic illness **4.** Blood Pb $<30\,\mu g\,dl^{-1}$	Parenteral Duration of obs: 5–8 days
Lozoff *et al.* (1982)[30]	Guatemala, South America	6–24 months	T = 64 Fe = 31 Pl = 33	Bayley MDI, Bayley PDI	Not mentioned, B, D, D	**1.** Residents of a socio-economically homogeneous settlement in Guatemala city **2.** Hb <10.5 or $>12.0\,g\,dl^{-1}$ **3.** No birth complications, acute or chronic illness, neonatal distress, congenital anomalies, developmental retardation, generalised malnutrition, Fe therapy during the previous months **4.** Mature babies **5.** BW >5 lb	Oral (ferrous ascorbate) Dose: $5\,mg\,kg^{-1}\,day^{-1}$ Duration of suppl: 1 week Duration of obs: 1 week
Driva *et al.* (1985)[31]	Greece, Europe	3–25 months	T b = 40 Fe b = 20 Pl b = 20 T e = 40 Fe e = 20 Pl e = 20	Bayley MDI, Bayley PDI	Not mentioned, B, A, A	Children with Fe def	Parenteral Dose: 50 mg Duration of obs; 10 days
Soemantri *et al.* (1985)[32]	Indonesia, Asia	10–11 years	T = 119 Fe = 59 Pl = 60	IQ, school performance	Not mentioned, B, A, D	**1.** Above 80th centile of wt and ht **2.** Above 85th centile for MAC of Indonesian standards **3.** Negative parasite egg count on stool examination **4.** No evidence of haematological-related disease, other severe illness, severe physical handicap and neurological abnormalities **5.** Consent of parents **6.** IQ >75	Oral Dose: $2\,mg\,kg^{-1}\,day^{-1}$ Duration of suppl: 3 months Duration of obs: 3 months
Aukett *et al.* (1986)[33]	UK, Europe	17–19 months	T b = 110 Fe b = 54 Pl b = 56 T e = 97 Fe e = 48 Pl e = 49	DDST	Not mentioned, A, D, A	**1.** Resident of catchment areas of 4 clinics in Birmingham **2.** Hb = 8–11 $g\,dl^{-1}$	Oral Dose: $24\,mg\,day^{-1}$ Duration of suppl: 2 months Duration of obs: 2 months

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Table 1 *Continued*

Study	Location	Age group	Sample size	Parameters	Methods of randomisation, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Iron supplementation
Dienard *et al.* (1986)[14]	USA, North America	18–60 months	T = 45 Fe = 22 Pl = 23	Bayley MDI/ Stanford Binet scores	Alternately, D, A, D	**1.** Gestational age >38 weeks **2.** BW >2.5 kg **3.** Wt, ht, HC within 2SD of NCHS standards **4.** No evidence of a chronic condition such as haemoglobinopathy, liver disease or CNS disorder	Oral Dose: 6 mg kg^{-1} day^{-1} Duration of suppl: 6 months Duration of obs: 6 months
Pollitt *et al.* (1989)[15]	Thailand, Asia	9–12 years	T = 1358 Fe = 679 Pl = 679	IQ, language and maths	Not mentioned, B, D, A	School selection criteria: **1.** Located in non-malarial area **2.** >150 children/school **3.** Access to main roads Subject selection criteria: **1.** Absence of AE Bart or Hb H disease **2.** Absence of abnormal Hb **3.** Aged 108–144 months	Oral Dose: 4 mg kg^{-1} day^{-1} Duration of suppl: 4 months Duration of obs: 4 months
Soewondo *et al.* (1989)[34]	Indonesia, Asia	<5 years	T = 127 Fe = 51 Pl = 76	Discrimination learning, three oddity learning tasks, PPVT	Not mentioned, B, B, D	**1.** Female head of household works as a tea picker **2.** Husband is present in the household **3.** At least one pre-school child present **4.** Family lives inside the plantation	Oral Dose: 50 mg day^{-1} Duration of suppl: 2 months Duration of obs: 2 months
Seshadri and Gopaldas, (1989)[21], C	India, Asia	8–15 years	T = 48 Fe 1 = 16 Fe 2 = 16 Pl = 16	Total cognition score, visual recall, digit span, mazes, clerical task	Not mentioned, B, A, A	Students of the required age at a free school in Vadodara	Oral Dose: 30, 40 mg day^{-1} Duration of suppl: 4 months Duration of obs: 4 months
Seshadri and Golpadas (1989)[21], D	India, Asia	8–15 years	T = 130 Fe = 65 Pl = 65	Total cognition score, visual recall, digit span, mazes, clerical task	Not mentioned, B, D, A	**1.** Age 8–15 years **2.** Family income <$500 per month **3.** Parents gave informed consent for the study	Oral Dose: 60 mg day^{-1} Duration of suppl: 4 months Duration of obs: 8 months

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Table 1 *Continued*

Study	Location	Age group	Sample size	Parameters	Methods of randomisation, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Iron supplementation
Walter *et al.* (1989)[35]	Chile, South America	12 months	T = 196 Fe = 102 Pl = 94	Bayley MDI, Bayley PDI	Not mentioned, B, A, A	**1.** Residents of a well-defined geographical area **2.** Informed consent available from parents	Oral Dose: 45 mg day^{-1} Duration of suppl: 10 days Duration of obs: 10 days
Soemantri (1989)[36]	Indonesia, Asia	8.1–11.6 years	T = 130 Fe = 71 Pl = 59	IQ, language score, maths score, biology score, social science score	Not mentioned, B, A, A	**1.** >80th percentile of wt and ht **2.** > 85th percentile of MAC of Indonesian growth standards **3.** Negative parasite egg count after deworming **4.** No evidence of acute or chronic illness, clinical signs of malnutrition, physical handicap, mental retardation or neurological handicap **5.** Consent of parents to participate in the study **6.** IQ >75 **7.** Absence of acute or severe morbidity	Oral Dose: 2 mg kg^{-1} day^{-1} Duration of suppl: 3 months Duration of obs: 6 months
Idjradinata and Pollitt (1993)[37]	Indonesia, Asia	12–18 months	T b = 126 Fe b = 63 Pl b = 63 T e = 119 Fe e = 60 Pl e = 59	Bayley MDI, Bayley Motor DI	Random numbers table, B, B, D	BW >2.5 kg, singleton pregnancy, no major congenital anomalies, no jaundice treated with phototherapy, no hospital admission, no supplementation with other micronutrients, no chronic illness, no clinically identified neuromotor delay, no folic acid def, Hb >8 g dl^{-1}, no signs of abnormal Hb or thalassaemia, wt, length and HC within 2SD of NCHS	Oral (ferrous sulphate) Dose: 3 mg kg^{-1} day^{-1} Duration of suppl: 4 months Duration of obs: 4 months

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Table 1 *Continued*

Study	Location	Age group	Sample size	Parameters	Methods of randomisation, allocation concealment, follow-up, blinding*	Eligibility and exclusion criteria	Iron supplementation
Moffatt *et al.* (1994)[38]	Canada, North America	0–2 months	T e = 154 Fe e = 77 Pl e = 77	Bayley MDI, Bayley PDI, IBR	Not mentioned, A, D, A	**1.** Switched from breast to bottle feeding before 2 months of age **2.** Not fed cow's milk formula for more than 2 weeks **3.** BW > 2.5 kg **4.** No chromosomal anomaly **5.** Gestation > 34 weeks **6.** Apgar score > 5 **7.** No significant perinatal illness requiring prolonged treatment in NICU	Fortified Dose: 12.8 mg l^{-1} Duration of suppl: 15 months Duration of obs: 15 months
Morley *et al.* (1999)[39]	UK, Europe	9 months	T b = 327 Fe b = 162 Pl b = 165 T e = 268 Fe e = 133 Pl e = 135	Bayley MDI, Bayley PDI	Permuted blocks of random length, A, D, D	**1.** Healthy term infants **2.** BW > 2500 g **3.** Singleton or sole survivor from multiple pregnancy **4.** No disease or impairment known to affect growth or development **5.** No evidence of mental or neurosensory impairment **6.** No history of transfusion or Fe supplementation **7.** First language English	Fortified formula Dose: 1.2 mg l^{-1} Duration of suppl: 9 months Duration of obs: 9 months
Stoltzfus *et al.* (2001)[40]	Zanzibar, Africa	6–59 months	T b = 614 Fe b = 307 Pl b = 307 T e = 359 Fe e = 183 Pl e = 176	Language and motor score	Not mentioned, B, D, A	Residents of Kengja village with age of 3–56 months	Oral Dose: 10 mg day^{-1} Duration of suppl: 12 months Duration of obs: 12 months
Kimmons *et al.* (unpublished)	Not known	6–24 months	T = 34 Fe = 17 Pl = 17	Bayley MDI, Bayley PDI	Random numbers table, A, D, D		Parenteral

T – total; b – beginning of study; Fe – iron; Pl – placebo/control; e – end of study; MDI – Mental Development Index; PDI – Psychomotor Development Index; IQ – intelligence quotient; DDST – Denver Development Screening Test; PPVT – Peabody Picture Vocabulary Test; DI – development index; IBR – infant behaviour record; Hb – haemoglobin; BW – birth weight; def – deficiency; wt – weight; ht – height; MAC – mid upper arm circumference; HC – head circumference; SD – standard deviation; NCHS – National Center for Health Statistics; CNS – central nervous system; NICU – neonatal intensive-care unit; obs – observation; suppl – supplementation.

* Allocation concealment: A – adequate; B – unclear; C – inadequate; D – not used. Completeness of follow-up based on percentage of excluded participants: A – < 3%; B – 3–9.9%; C – 10–19.9%; D – ≥ 20%. Blinding: A – double blinding; B – single blinding; C – no blinding; D – unclear.

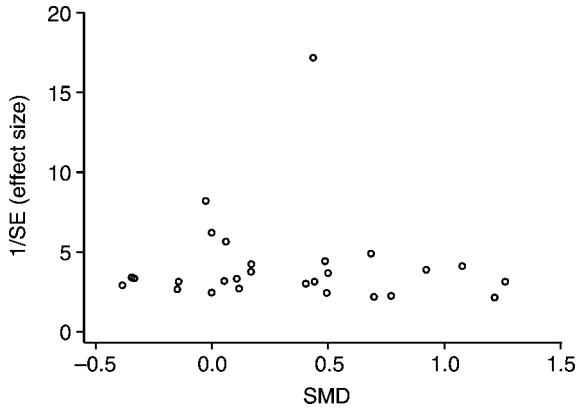

Fig. 2 Funnel plot of extracted studies for mental development score with unknown standard deviations derived under the assumption $P = 0.5$. SE – standard error; SMD – standardised mean difference

Begg ($P = 0.453$) methods. We collected data on 2827 children, 1412 of whom received iron and 1415 placebo (Table 2). The pooled estimate (SMD) of the post–pre test difference in MDS following iron supplementation was 0.30 (95% confidence interval (CI) 0.15 to 0.46; $P < 0.001$ (Fig. 3, Table 3); test for heterogeneity $Q = 72.05$, $P < 0.001$). The results were similar when SDs were calculated assuming $P = 0.5$, assuming independence and with post-test scores. Sensitivity analysis suggested that greater benefits were associated with oral route of supplementation, longer duration of iron therapy (>1 month), older age (>5 years) and lower baseline Hb and iron status. Meta-regression did not show any consistent association between the effect on MDS and duration of supplementation or age; however, lower baseline Hb and initially iron-deficient anaemic subjects were significant predictors of a positive effect of iron supplementation (Table 4).

Individual mental development tests (Table 5). Eight studies (references 13, 30, 31, 35, 37–39 and Kimmons *et al.*, unpublished) on younger children (<27 months of age) assessed Bayley MDI. The pooled estimate (WMD) was 0.95 (95% CI −0.56 to 2.46) and was not statistically significant ($P = 0.217$). On stratified analysis, iron-deficient anaemic children showed greater improvement in MDI scores vis-à-vis the control group (WMD = 3.77, 95% CI −0.50 to 8.04), but the difference was not statistically significant ($P = 0.08$). On meta-regression, when controlled for all other variables, IDA (vs. others) was a significant predictor of a beneficial response (WMD = 2.76, 95% CI 0.26 to 5.25, $P = 0.03$). On combining a trial[14] using both the Bayley MDI and the Stanford Binet Test with these eight studies, the pooled estimate was not statistically significant (SMD = 0.12, 95% CI −0.07 to 0.30, $P = 0.219$).

Four trials[15,21,36] evaluated IQ scores in children aged 8 years or more. The pooled SMD was 0.41 (95% CI 0.20 to 0.62), which was significant ($P < 0.001$). Children with initial anaemia (Hb < 11 g dl^{-1}) and IDA had a greater improvement, but this was not confirmed on meta-regression.

Two trials[21] reported the effect of iron supplementation on the individual components of the total cognition score used. The response to iron supplementation on each of these components was pooled and all four parameters (digit span, visual recall, mazes and clerical tests) showed an effect by one or more of the computational methods employed; however, the effect was consistently significant for mazes only. The studies evaluating the effect of iron supplementation on linguistic (three trials)[15,36,40] and mathematical (two trials)[15,36] capabilities did not show any significant benefit of iron supplementation.

Motor development

Among the 10 trials evaluating motor development (references 13, 30, 31, 33, 35, 37–40 and Kimmons *et al.*, unpublished), eight used the Bayley Psychomotor Development Index (PDI), one assessed psychomotor development through DDST[33] and one used a physical activity score[40]. The funnel plot (Fig. 4) was symmetrical with no evidence of publication bias by Begg ($P = 0.921$) and Egger ($P = 0.826$) tests. We collected data on 1246 children; 630 received iron and 616 placebo. The pooled SMD with missing change SDs calculated with the assumption $P = 0.5$ (Fig. 5) was 0.09 (95% CI −0.08 to 0.26, $P = 0.28$; test for heterogeneity $Q = 25.69$, $P = 0.028$). Comparable pooled estimates were obtained with SDs computed under the assumption of independence (0.09, 95% CI −0.08 to 0.26, $P = 0.305$; test for heterogeneity $Q = 25.49$, $P = 0.03$) and with post-test scores (0.12, 95% CI −0.08 to 0.32, $P = 0.24$; test for heterogeneity $Q = 28.92$, $P = 0.007$). Sensitivity and meta-regression (Table 6) analyses indicated that quality of the study, route of supplementation, duration of supplementation, baseline Hb and iron status were not significant predictors of SMD. Similarly, there was no benefit of iron supplementation on psychomotor development and specifically Bayley PDI scores (Table 5).

Discussion

The results from our analysis of these studies show that iron supplementation improves the mental development score of children marginally (SMD 0.30; 95% CI 0.15 to 0.46) but significantly ($P < 0.001$). The benefits were greater among initially anaemic or iron-deficient anaemic subjects and these traits were significant explanatory variables for heterogeneity. In younger children (<27 months old) invariably Bayley MDI was evaluated, which did not show any significant improvement with iron supplementation but there was a suggestion of benefit in those with initial IDA. In the four trials involving children over 7 years old, iron administration resulted in a significant improvement in

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Table 2 Data extracted from included studies with missing change standard deviation (SD) computed with the assumption $P = 0.5$

		Change in iron supplement group			Change in placebo group		
Author (reference)	Outcome	Number	Mean	SD	Number	Mean	SD
Mental development score							
Kimmons (unpublished)	Bayley MDI	17	4.10	3.90	17	5.60	3.90
Oski (13)	Bayley MDI	12	13.58	15.15	12	6.08	15.15
Lozoff 1 (30)	Bayley MDI	12	5.50	7.40	12	5.50	7.40
Lozoff 2 (30)	Bayley MDI	19	5.50	7.40	21	5.10	7.40
Driva (31)	Bayley MDI	20	7.00	9.50	20	2.80	9.50
Soemantri B1 (32)	IQ	43	3.64	4.00	35	−0.67	4.00
Soemantri B2 (32)	IQ	16	−0.29	4.00	25	0.28	4.00
Dienard (14)	Bayley MDI and Stanford Binet Test	22	1.50	16.50	23	7.00	16.50
Walter 1 (35)	Bayley MDI	24	8.60	5.40	15	6.70	3.20
Walter 2 (35)	Bayley MDI	66	8.90	3.40	61	8.70	3.20
Walter 3 (35)	Bayley MDI	12	8.70	3.50	18	8.30	3.30
Seshadri Ca (21)	Total cognition score	16	2.88	3.61	8	0.09	3.61
Seshadri Cb (21)	Total cognition score	16	4.82	3.89	8	0.09	3.89
Seshadri D1 (21)	Total cognition score	36	6.00	5.74	45	3.20	5.74
Seshadri D2 (21)	Total cognition score	10	5.70	3.36	10	3.35	3.36
Soemantri 1 (36)	IQ	37	1.50	6.38	35	0.41	6.38
Soemantri 2 (36)	IQ	34	1.05	6.79	24	−0.10	6.79
Pollitt 1 (15)	IQ	51	4.00	5.84	50	0.00	5.84
Pollitt 2 (15)	IQ	23	4.00	5.80	24	6.00	5.80
Pollitt 3 (15)	IQ	605	5.00	2.29	605	4.00	2.29
Soewondo 1 (34)	PPVT	27	6.70	8.60	43	−1.23	8.60
Soewondo 2 (34)	PPVT	24	6.05	8.60	33	1.75	8.60
Idjradinata 1 (37)	Bayley MDI	24	19.30	14.90	23	0.50	14.90
Idjradinata 2 (37)	Bayley MDI	14	5.30	14.90	14	7.50	14.90
Idjradinata 3 (37)	Bayley MDI	22	3.70	14.90	22	2.10	14.90
Mofatt (38)	Bayley MDI	77	−1.20	13.00	77	−1.20	13.00
Morley (39)	Bayley MDI	133	0.20	11.59	135	0.50	11.59
Language							
Soemantri 1 (36)	Language	37	−2.27	6.98	35	1.48	6.98
Soemantri 2 (36)	Language	34	12.55	3.52	24	4.62	3.52
Pollitt 1 (15)	Language	50	5.85	4.31	51	5.96	4.31
Pollitt 2 (15)	Language	24	1.48	7.39	23	0.96	7.39
Pollitt 3 (15)	Language	605	6.30	1.92	605	4.50	1.92
Stoltzfus (40)	Language	183	3.70	5.80	176	3.70	5.80
Mathematics							
Soemantri 1 (36)	Mathematics	37	4.48	4.22	35	4.50	4.22
Soemantri 2 (36)	Mathematics	34	9.40	3.24	24	1.30	3.24
Pollitt 1 (15)	Mathematics	50	0.00	3.73	51	7.91	3.73
Pollitt 2 (15)	Mathematics	24	4.16	7.79	23	7.50	7.79
Pollitt 3 (15)	Mathematics	605	5.25	2.12	605	5.80	2.12
Visual recall							
Seshadri Ca (21)	Visual recall	16	1.65	1.28	8	0.10	1.28
Seshadri Cb (21)	Visual recall	16	1.38	1.61	8	0.10	1.61
Seshadri D1 (21)	Visual recall	36	0.56	2.91	45	0.76	2.91
Seshadri D2 (21)	Visual recall	10	0.70	1.36	10	0.75	1.36
Digit span							
Seshadri Ca (21)	Digit span	16	0.81	1.81	8	0.10	1.81
Seshadri Cb (21)	Digit span	16	1.16	1.73	8	0.10	1.73
Seshadri D1 (21)	Digit span	36	0.88	1.52	45	0.42	1.52
Seshadri D2 (21)	Digit span	10	1.32	1.07	10	0.37	1.07
Mazes							
Seshadri Ca (21)	Mazes	16	2.88	3.61	8	0.09	3.61
Seshadri Cb (21)	Mazes	16	4.82	3.89	8	0.09	3.89
Seshadri D1 (21)	Mazes	36	6.00	5.74	45	3.20	5.74
Seshadri D2 (21)	Mazes	10	5.70	3.36	10	3.35	3.36
Clerical tasks							
Seshadri Ca (21)	Clerical tasks	16	0.91	1.55	8	0.11	1.55
Seshadri Cb (21)	Clerical tasks	16	0.84	1.33	8	0.11	1.33
Seshadri D1 (21)	Clerical tasks	36	1.93	1.84	45	0.77	1.84
Seshadri D2 (21)	Clerical tasks	10	1.97	1.51	10	0.87	1.51
Motor development scale							
Kimmons (unpublished)	Bayley PDI	17	0.20	9.73	17	3.30	9.73

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Table 2 *Continued*

Author (reference)	Outcome	Change in iron supplement group			Change in placebo group		
		Number	Mean	SD	Number	Mean	SD
Oski (13)	Bayley PDI	12	11.00	21.22	12	4.17	21.22
Lozoff 1 (30)	Bayley PDI	12	0.50	7.40	12	5.70	7.40
Lozoff 2 (30)	Bayley PDI	17	−1.60	7.40	18	1.30	7.40
Driva (31)	Bayley PDI	20	0.80	9.50	20	3.50	9.50
Aukett (33)	DDST	48	4.00	2.60	49	3.20	2.30
Walter 1 (35)	Bayley PDI	24	6.70	6.90	15	5.10	2.90
Walter 2 (35)	Bayley PDI	66	5.60	2.90	61	5.40	3.50
Walter 3 (35)	Bayley PDI	12	5.60	3.20	18	4.40	4.30
Idjradinata 1 (37)	Bayley PDI	24	23.50	14.27	23	5.10	14.27
Idjradinata 2 (37)	Bayley PDI	14	4.90	14.27	14	3.10	14.27
Idjradinata 3 (37)	Bayley PDI	22	3.40	14.27	22	2.40	14.27
Mofatt (38)	Bayley PDI	77	−2.10	12.63	77	−4.10	12.63
Morley (39)	Bayley PDI	133	−0.10	8.96	135	0.00	8.96
Stoltzfus (40)	Motor score	132	4.70	5.03	123	4.60	5.03

MDI – Mental Development Index; IQ – intelligence quotient; PPVT – Peabody Picture Vocabulary Test; PDI – Psychomotor Development Index; DDST – Denver Development Screening Test.

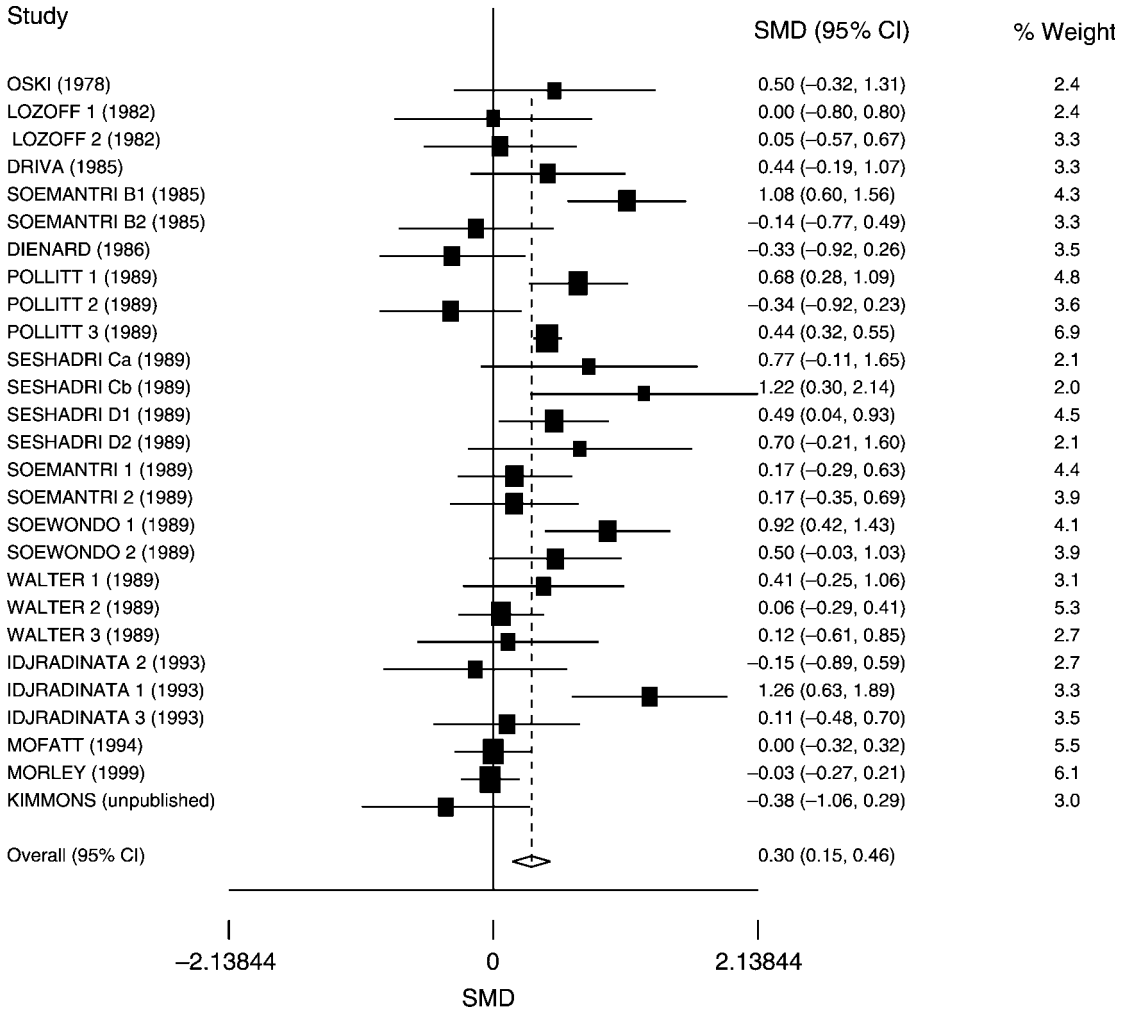

Fig. 3 Forest plot for mental development score with unknown standard deviations derived under the assumption $P = 0.5$. SMD – standardised mean difference; CI – confidence interval

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Table 3 Sensitivity analyses of pooled estimates of mental development score standardised mean difference

Stratification variable	No. of analytic components	Random effects model (95% CI)	*P*-value	Test for heterogeneity (*P*-value)
All				
SD by $P = 0.5$	27	0.30 (0.15, 0.46)	< **0.001**	72.05 (<0.001)
SD by independence	27	0.25 (0.12, 0.38)	< **0.001**	51.65 (0.002)
Post-test score and SD	27	0.19 (0.04, 0.34)	**0.013**	68.74 (<0.001)
Supplementation route				
Fortification	2	−0.02 (−0.21, 0.17)	0.866	0.02 (0.898)
Oral	22	0.36 (0.20, 0.53)	< **0.001**	52.10 (<0.001)
Parenteral	3	0.17 (−0.39, 0.74)	0.551	3.9 (0.142)
Duration of supplementation				
< 1 month	8	0.12 (−0.08, 0.33)	0.243	4.93 (0.669)
> 1 month	19	0.36 (0.17, 0.55)	< **0.001**	62.97 (<0.001)
Mean age				
< 24 months	13	0.15 (−0.04, 0.34)	0.128	19.98 (0.067)
< 60 months	16	0.21 (0.01, 0.41)	**0.043**	33.77 (0.004)
> 60 months	11	0.44 (0.21, 0.66)	< **0.001**	24.65 (0.006)
Allocation concealment				
Adequate	3	−0.04 (−0.23, 0.14)	0.643	1.06 (0.588)
Others	24	0.37 (0.21, 0.53)	< **0.001**	52.17 (<0.001)
Attrition				
< 10%	17	0.37 (−0.15, 0.59)	< **0.001**	36.41 (0.003)
> 10%	10	0.22 (−0.02, 0.46)	0.069	35.58 (<0.001)
Blinding				
Double blind	15	0.36 (0.19, 0.53)	< **0.001**	29.16 (0.010)
Others	12	0.21 (−0.09, 0.51)	0.178	36.72 (<0.001)
Mean baseline Hb				
$< 11\ g\,dl^{-1}$	14	0.49 (0.23, 0.74)	< **0.001**	39.82 (<0.001)
$> 11\ g\,dl^{-1}$	13	0.14 (−0.06, 0.34)	0.181	31.43 (0.002)
Iron deficiency status				
Deficient, anaemic	11	0.50 (0.25, 0.75)	< **0.001**	21.57 (0.017)
Deficient, non-anaemic	4	−0.11 (−0.36, 0.14)	0.386	2.12 (0.548)
Deficient, ± anaemic	15	0.31 (0.06, 0.56)	**0.014**	41.34 (<0.001)
Replete	8	0.33 (0.11, 0.55)	**0.003**	11.40 (0.122)

CI – confidence interval; SD – standard deviation; Hb – haemoglobin.
Except the all category, these calculations were performed with SD calculated under the assumption $P = 0.5$.

Table 4 Meta-regression analyses for mental development score standardised mean difference (SMD)

	Univariable analysis		Controlling for all variables	
Study characteristic	SMD (95% CI)	*P*-value	SMD (95% CI)	*P*-value
Study quality				
Allocation concealment (not adequate vs. adequate)	0.46 (0.03, 0.89)	**0.035**	0.53 (−0.17, 1.22)	0.136
Attrition (>10% vs. <10%)	−0.16 (−0.49, 0.18)	0.367	0.06 (−0.29, 0.41)	0.742
Blinding (not double blind vs. double blind)	−0.17 (−0.50, 0.17)	0.333	−0.12 (−0.46, 0.22)	0.478
Unit increase in duration of iron supplementation (months)	−0.01 (−0.07, 0.05)	0.797	0.01 (−0.06, 0.08)	0.775
Unit increase in mean age (months)	0.00 (−0.00, 0.01)	0.060	0.00 (−0.00, 0.00)	0.536
Unit increase in mean baseline Hb status ($g\,dl^{-1}$)	−0.11 (−0.23, 0.01)	0.069	−0.14 (−0.03, −0.25)	**0.012**
Iron deficiency status* (deficient, anaemic vs. others)	0.33 (0.02, 0.64)	**0.036**	0.30 (0.09, 0.51)	**0.005**

CI – confidence interval; Hb – haemoglobin.
*For the multivariable model, mean baseline Hb status was replaced by a dichotomous variable (deficient and anaemic = 1, others including unknown status = 0).

the pooled IQ scores. There was no effect of iron supplementation on motor development.

Our conclusion that mental development scores improved following iron supplementation was based on a large spectrum of sensitivity analyses. Significant explanatory variables could be identified to explain heterogeneity, specifically initial iron status and Hb. None of the analyses showed evidence of publication bias, and omitting one study at a time (data not shown) did not reveal an overwhelming effect of any study.

Seven limitations merit consideration. First, the review attempted to combine all studies examining mental or motor development irrespective of age, instrument used, setting or the specific aspect of development evaluated. However, the majority of the mental development scores, including Bayley MDI, Stanford Binet score, IQ and cognition score, assess general intelligence or overall mental development in children. Hence, we believe that combining these studies is a logical summary of the mental development effect for guiding

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Table 5 Pooled estimates of individual mental and motor development tests

Stratification variable	No. of analytic components	Random effects model (95% CI)	*P*-value	Tests for heterogeneity (*P*-value)
Bayley MDI (WMD)				
SD by $P = 0.5$	13	0.95 (−0.56, 2.46)	0.217	24.72 (0.016)
SD by independence	13	1.06 (−0.54, 2.66)	0.196	24.56 (0.017)
Post-test scores and SD	13	1.67 (−1.14, 4.49)	0.244	32.48 (0.001)
Bayley MDI and Stanford Binet test score (SMD)				
SD by $P = 0.5$	14	0.12 (−0.07, 0.30)	0.219	21.94 (0.056)
SD by independence	14	0.12 (−0.06, 0.30)	0.187	21.05 (0.072)
Post-test scores and SD	14	0.13 (−0.08, 0.35)	0.221	28.78 (0.007)
IQ (SMD)				
SD by $P = 0.5$	9	0.41 (0.20, 0.62)	< **0.001**	14.43 (0.071)
SD by independence	9	0.30 (0.20, 0.40)	< **0.001**	7.40 (0.494)
Post-test scores and SD	9	0.25 (−0.07, 0.57)	0.122	34.36 (<0.001)
Digit span (WMD)				
SD by $P = 0.5$	4	0.68 (0.20, 1.16)	**0.006**	0.99 (0.803)
SD by independence	4	0.69 (−0.01, 1.38)	0.052	0.49 (0.922)
Post-test scores and SD	4	0.37 (−0.24, 0.97)	0.234	4.52 (0.211)
Visual recall (WMD)				
SD by $P = 0.5$	4	0.66 (−0.24, 1.56)	0.152	6.46 (0.091)
SD by independence	4	0.74 (−0.15, 1.62)	0.103	3.54 (0.315)
Post-test scores and SD	4	0.88 (0.07, 1.68)	**0.033**	7.15 (0.067)
Mazes (WMD)				
SD by $P = 0.5$	4	3.06 (1.61, 4.52)	< **0.001**	1.28 (0.734)
SD by independence	4	3.17 (1.27, 5.06)	**0.001**	0.85 (0.837)
Post-test scores and SD	4	1.24 (0.61, 1.88)	< **0.001**	0.36 (0.948)
Clerical task (WMD)				
SD by $P = 0.5$	4	0.99 (0.46, 1.53)	< **0.001**	0.48 (0.923)
SD by independence	4	0.96 (0.24, 1.68)	**0.009**	0.28 (0.964)
Post-test scores and SD	4	0.34 (−0.31, 0.99)	0.302	4.64 (0.200)
Language score (SMD)				
SD by $P = 0.5$	6	0.42 (−0.18, 1.02)	0.166	121.86 (<0.001)
SD by independence	6	0.30 (−0.14, 0.74)	0.180	64.52 (<0.001)
Post-test scores and SD	6	0.57 (−0.10, 1.23)	0.096	146.34 (<0.001)
Mathematics score (WMD)				
SD by $P = 0.5$	5	−0.67 (−5.04, 3.69)	0.762	200.31 (<0.001)
SD by independence	5	−0.62 (−5.04, 3.79)	0.782	99.89 (<0.001)
Post-test scores and SD	5	−0.16 (−2.76, 2.44)	0.905	81.98 (<0.001)
Bayley PDI (WMD)				
SD by $P = 0.5$	13	0.52 (−1.22, 2.27)	0.558	28.50 (0.005)
SD by independence	13	0.51 (−1.36, 2.38)	0.595	28.10 (0.005)
Post-test scores and SD	13	1.47 (−1.35, 4.29)	0.308	33.28 (0.001)
Bayley PDI and DDST (SMD)				
SD by $P = 0.5$	14	0.10 (−0.09, 0.30)	0.297	25.40 (0.020)
SD by independence	14	0.10 (−0.10, 0.29)	0.317	25.21 (0.022)
Post-test scores and SD	14	0.11 (−0.12, 0.34)	0.341	28.62 (0.004)

CI –confidence interval; MDI – Mental Development Index; WMD – weighted mean difference; SD – standard deviation; SMD – standardised mean difference; IQ – intelligence quotient; PDI – Psychomotor Development Index; DDST – Denver Development Screening Test.

policy. A similar logic was used for motor development. To retain purity in the evaluated outcomes, we also conducted separate stratified analyses for specific individual tests.

Second, the sensitivities of the mental and motor development tests were different and this variability could not be quantified in the analytical process. DDST was used to assess the psychomotor development of children[33]. This test is a screening tool for single-time assessment of development; it is not designed to assess psychomotor development or the change in psychomotor development over a period of time with accuracy or a high degree of sensitivity. The IQ scales used in older children may have been more sensitive, and may explain the different results across the different age groups. Nevertheless, the contribution of this factor to differences in pooled estimates is speculative.

Third, most of the included trials did not control for differences in socio-economic status and the extent of stimulation provided to the children. This is important, because lower cognition scores in iron-deficient children have often been attributed to other confounding environmental factors such as poverty, lack of stimulation, undernutrition, maternal factors and worm infestation[5–7]. Because the trials included were randomised and controlled, most of these factors would have been controlled for.

Fourth, we could not confidently differentiate the therapeutic from the preventive effects of iron supplementation as few studies provided relevant data or were

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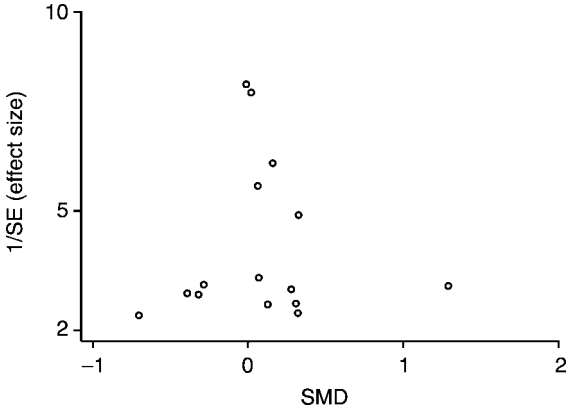

Fig. 4 Funnel plot for motor development scores with unknown standard deviations derived under the assumption $P = 0.5$. SE – standard error; SMD – standardised mean difference

designed as preventive interventions. An approximation of the preventive or therapeutic role can be inferred by relating the outcome to iron status.

Fifth, it was assumed that all cases of anaemia were attributable to iron deficiency. Iron deficiency is usually the most common cause of anaemia in childhood[41], but its contribution is variable in different countries depending upon the prevalence of hookworm infestation and malaria[42]. Among the studies included, only 10 determined the iron status of the children.

Sixth, the iron supplement dose could not be directly related to the observed effect because the majority of the trials did not provide these data. Thus, we assumed that the fortification trials used the lowest dose, parenteral studies the maximum dose, and oral iron supplementation studies a level in between.

Finally, in the absence of actual data on the variability of the change in outcome scores, several imputations were made based on pre-specified assumptions. The sensitivity analyses suggested that these imputations were robust because the quantification of the findings with various assumptions was invariably synchronous.

Like an earlier systematic review restricted to children with IDA below 3 years of age[7], we found no evidence of a beneficial effect of iron supplementation on motor development, even in iron-deficient and anaemic children. Nevertheless, because of the relatively small number of children included in these studies, the confidence intervals around the effects of treatment are wide and the results could be compatible with moderate positive or adverse effects of short-term iron therapy[7]. Three other possible explanations exist for this finding. First, iron deficiency may cause irreversible structural brain changes, particularly in younger children. Evidence from animal studies provides support of this possibility[1–4]. Second, the tests evaluated (for example, Bayley PDI) may not be sufficiently sensitive measures of motor development, particularly in younger subjects. Third, the duration of iron supplementation in several trials may have been too short to correct the iron deficiency (8/13 studies evaluating Bayley indices intervened for less than 1 month).

An approximation of the effect size of the mental development score can be derived by relating the

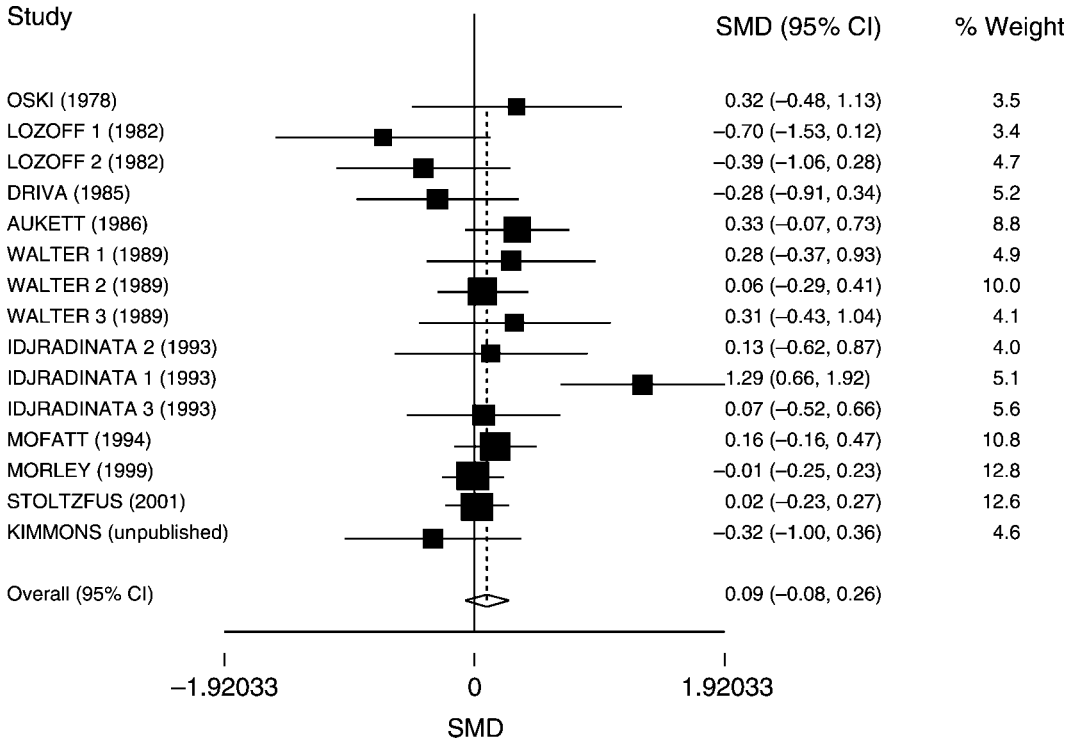

Fig. 5 Forest plot for motor development score with unknown standard deviations derived under the assumption $P = 0.5$. SMD – standardised mean difference; CI – confidence interval

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Table 6 Meta-regression analyses for motor development score standardised mean difference (SMD)

	Univariable analysis		Controlling for all variables	
Study characteristic	SMD (95% CI)	*P*-value	SMD (95% CI)	*P*-value
Study quality				
Allocation concealment (not adequate vs. adequate)	0.06 (−0.29, 0.41)	0.745	−0.32 (−1.31, 0.65)	0.519
Attrition (>10% vs. <10%)	−0.26 (−0.59, 0.08)	0.132	−0.69 (−1.47, 0.08)	0.080
Blinding (not double blind vs. double blind)	−0.13 (−0.47, 0.21)	0.448	−0.10 (−0.56, 0.35)	0.661
Unit increase in duration of iron supplementation (months)	0.01 (−0.03, 0.05)	0.769	0.02 (−0.05, 0.09)	0.607
Unit increase in mean age (months)	−0.00 (−0.03, 0.02)	0.854	−0.01 (−0.04, 0.03)	0.698
Unit increase in mean baseline Hb status ($g\,dl^{-1}$)	−0.02 (−0.15, 0.10)	0.719	−0.05 (−0.24, 0.13)	0.568
Iron deficiency status* (deficient, anaemic vs. others)	0.09 (−0.25, 0.43)	0.585	0.27 (−0.27, 0.82)	0.327

CI – confidence interval; Hb – haemoglobin.
* For the multivariable model, mean baseline Hb status was replaced by a dichotomous variable (deficient and anaemic = 1, others including unknown status = 0).

standardised mean differences to actual mean differences whenever feasible. Thus, for Bayley MDI, a standardised mean difference of 0.147 was equivalent to a mean difference of 0.949 (a conversion factor of 6.5). Similarly, for IQ scores a standardised mean difference of 0.41 was equivalent to a mean difference of 1.96 (a conversion factor of 5). Extrapolating to mental development score on a scale of 100, a reasonable estimate of standardised mean difference of 0.30 would be between 1.5 to 2 points, which is 'modest'.

A significant improvement was evident in intelligence tests conducted in children over 7 years old, whereas no benefit was documented in Bayley MDI amongst those below 27 months of age. These differences could be real. However, another review[43] has attributed this differential benefit to better designed studies, increased sensitivity of the instruments used and the possibility of a transitory effect of iron deficiency on these tests. Animal studies indicate that adverse effects of iron deficiency on neurotransmitter systems, such as monoamine oxidase, can be reversed by supplementation[44]. Conversely, lack of benefit in Bayley MDI scores could reflect irreversible effects of iron deficiency on rapidly developing brain. In animal studies, dietary iron deficiency during the period of maximal brain growth leads to irreversible effects[3,4,45–47].

The improvement in intelligence scores in older children, and particularly in those who were iron-deficient and anaemic, suggests a causal role of iron in mental development. Furthermore, the reversibility of the cognitive deficit, even if partial and restricted to a subset, lends support to advocacy for public health programmes to control iron deficiency.

The documentation of a significant benefit in mental development score in iron-sufficient children suggests a possible preventive role. Suitably designed trials are required to critically evaluate the role of preventive supplementation, particularly in younger children. It has been hypothesised that iron supplementation could benefit specific components of mental development with no demonstrable evidence on the total score[29,40]. We cannot address this issue from the available data.

Conclusion

Most observational studies have found associations between IDA and poor mental and motor development in children. Conflicting data exist regarding the possibility of improved mental and motor development with iron administration, resulting in confusion about realistic expectations from iron supplementation and fortification efforts.

Our meta-analysis indicates that iron supplementation improves mental development score, but the effect is modest (SMD of 0.3, equivalent to 1.5 to 2 points on a scale of 100). This effect is particularly apparent for intelligence tests above 7 years of age, and in initially anaemic or iron-deficient anaemic subjects. There is no convincing evidence that iron treatment has an effect on mental development in children below 27 months of age, or on motor development.

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Competing interests: H.P.S.S. is an honorary member of the International Nutritional Anaemia Consultative Group (INACG) Steering Committee that is managed by

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