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

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Abstract

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

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

Review methods: RCTs evaluating change in anthropometry with interventions that included oral or parenteral iron supplementation, or iron-fortified formula milk or cereals, were analysed.

Results: Twenty-five trials (26 cohorts) had relevant information. There was no evidence of publication bias. The pooled estimates (random effects model) did not document a statistically significant ($P > 0.05$) positive effect of iron supplementation on any anthropometric variable (weight-for-age, weight-for-height, height-for-age, mid upper-arm circumference, skinfold thickness, head circumference). Significant heterogeneity was evident, and its predictors included greater weight-for-age in supplemented children in malaria hyperendemic regions and greater weight-for-height for children above 5 years of age, but a negative effect on linear growth in developed countries and with supplementation for 6 months or longer.

Conclusions: This review did not document a positive effect of iron supplementation on the physical growth of children. The identified predictors of heterogeneity should be considered as exploratory and requiring confirmation, not conclusive.

Keywords
Anaemia
Anthropometry
Growth
Height-for-age
Iron deficiency
Iron supplementation
Meta-analysis
Randomised controlled trials
Weight-for-age
Weight-for-height

According to estimates of the World Health Organization, more than one-third of the world's population is anaemic; nearly two billion individuals are affected[1]. The problem is of more serious concern and magnitude in infants and children. Global estimates suggest that this malady afflicts 46% of school-going children, the problem being even more severe in the developing nations where the prevalence estimates range between 52 and 63%[2]. Recent estimates from India documented an anaemia prevalence of 74% in children aged between 9 and 36 months[3].

The aetiology of anaemia is multifactorial[4–6]; however, from a public health perspective, iron deficiency is believed to be the most important causal factor[6]. Consequently, in public health terminology, the terms 'anaemia', 'iron-deficiency anaemia' and 'iron deficiency' are often used interchangeably. Nevertheless, it is important to be aware that anaemia is multifactorial in aetiology and that its reliability as an indicator of iron deficiency will vary across different epidemiological settings. Currently there are no global data for iron deficiency that are based on direct indicators. Using anaemia as an indirect indicator, it is likely that iron deficiency is a major public health problem, particularly in infants and children.

Several observational studies have documented a relationship between iron-deficiency anaemia and impaired physical growth[7,8]. The proposed mechanisms through which iron deficiency may impair growth include its effect on immunity, appetite, thermogenesis and thyroid hormone metabolism[9,10]. The presence of several confounders, however, precludes causal inferences from these observational studies: (1) coexistent parasitic infections such as malaria and hookworm, which cause iron deficiency, may also impact on growth; (2) children who grow rapidly may have more depleted iron stores while those with slow growth may appear iron-replete; and (3) concomitant deficiencies of other micronutrients such as zinc may also have an effect on physical growth.

The evidence from well-designed intervention trials is conflicting. Some studies have shown significant improvement in physical growth with iron supplementation[11],

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while other investigators found no such benefit[12]. Another interesting dimension has been added to the controversy by the possibility of a detrimental effect of iron supplementation on physical growth in iron-replete children[13]. We therefore conducted a systematic review to evaluate the effect of iron supplementation on various anthropometric parameters in children and identify any effect predictors.

Methods

Searching

Computerised bibliographic medical databases, including Medline (1966 to March 2003), the Cochrane controlled trials register, Embase, IBIDS and Healthstar, were searched using the keywords 'iron' and 'child'. Reference lists of identified articles and hand-searched reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings were also reviewed. 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. Full texts of the remaining studies were reviewed and trials that fulfilled the inclusion criteria identified. To avoid publication bias, both published and unpublished trials were included.

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 could be non placebo-controlled because it would be difficult to administer a similar placebo; had to investigate iron supplementation through the oral or parenteral route or as formula milk or cereals fortified with iron; had to evaluate one of the anthropometric parameters as an outcome measure; and duration of supplementation had to be 2 months or more, since less lengthy interventions were considered too short to exhibit an effect on physical growth. Studies in which other micronutrients and drugs were simultaneously administered were included if the only difference between the study and the control group was iron supplementation.

Validity assessment

Trial quality was assessed (A, B, C or D) using recommended criteria[14,15]. Concealment of allocation was classed as adequate, unclear, inadequate or not used. To assess attrition, studies were classified by percentage of participants lost to follow-up (<3%, 3–9.9%, 10–19.9% and >20%). Blinding was classified as double blinding, single blinding, no blinding and unclear.

Data abstraction

Preformed questionnaires were used 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, the authors were contacted 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.

To compute pooled estimates, sample size, mean change in anthropometric parameters from the beginning to the end of the intervention and the SD of this change in the intervention and control group were required. 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, SDs were back-calculated from the stated standard errors, t or p values; (3) wherever not stated, the mean change in anthropometry was computed as the difference of mean post- and pre-intervention scores; and (4) wherever not stated, the mean age of subjects was computed as the average of the stated range.

The SD for the change in the physical growth parameters was available or could be back-calculated from some studies. For the rest this SD was computed assuming correlations (p) of 0.5 and 0 (independent) between the pre- and post-test variances[16]. Considering the number of assumptions and computations involved, and to be confident about the interpretation, four types of pooled estimates were calculated. In the first, the available change values were used. In the second and third, the SD of the change for values that were missing or could not be back-calculated was computed with the assumption of a correlation $p = 0.5$ or of independence. For the fourth, the post-intervention scores and their respective SDs were used.

The presence of publication bias in the extracted data was evaluated by funnel plots[17]. The METABIAS command in STATA software was used for statistical testing of funnel plot asymmetry[18]. The pooled estimates of the weighted mean difference of each of the anthropometric parameters' change between the control and intervention groups were calculated by both fixed effects and random effects model

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assumptions using the METAN command in STATA software[18]. Random effects estimates are mainly reported here because most of the pooled results obtained were statistically heterogeneous.

Pre-specified stratified analyses were carried out for: (1) methodological quality; (2) age of the subjects; (3) route of iron administration (parenteral, oral supplement or food fortification); (4) dose of iron supplementation; (5) frequency of oral supplementation per week for oral route; (6) duration of supplementation; (7) baseline haemoglobin of the supplemented group; (8) location of study population; (9) malarial endemicity of the study area; and (10) baseline anthropometry of the study population. The contribution of these variables to heterogeneity was also explored by meta-regression using the METAREG command in STATA with the restricted maximum likelihood option[18]. A variable was considered to be an important explanatory factor if statistical significance was consistently documented in the stratified analyses and in the meta-regression. A greater credence was attached to the meta-regression results, particularly those controlling for all variables.

Results

Trial flow

A total of 40 studies (38 published[9,11–13,19–52] and two unpublished) were identified to be potentially eligible for inclusion in the systematic review. After thorough scrutiny, 15 of these trials were excluded due to specific reasons (Fig. 1). Thus, 25 trials were included in the systematic review, of which 23 were published in various indexed journals while two were unpublished (Agarwal D, Sachdev HPS, Mallika V, Singh T. Iron supplementation in breast fed, full term, low birth weight infants; Nagpal J, Sachdev HPS, Mallika V, Singh T. Iron supplementation with complementary feeding in predominantly breastfed infants). One study publication had data from two separate cohorts[52], which for analytic purposes were taken as two separate trials.

Baseline characteristics of the studies

Table 1 depicts the baseline characteristics of the analysed trials. Most of the cohorts were from the developing countries (13 were from Asia, four were from Europe, two were from North America, three were from South America and four were from Africa). Most of the studies were conducted in infants and toddlers (12 in infants below 2 years of age and eight in preschool children), while only six trials evaluated older children. In eight studies, supplementation was done for 3 months or less; in 10 studies the duration of supplementation was for more than 3 but less than 6 months; while eight investigations followed up the subjects for longer than 6 months. In most of the studies the subjects received iron supplementation in the form of oral medicinal iron (20/26) while in six trials fortified foods were used. No trial used the parenteral mode of administration. The anthropometric parameters evaluated included weight-for-age, weight-for-height, height-for-age, mid upper-arm circumference, head circumference and skinfold thicknesses.

Quantitative data synthesis

Weight-for-age

All 26 cohorts were included in this analysis. The funnel plot (Fig. 2) was symmetrical indicating the absence of publication bias, which was confirmed using Egger's (weighted regression) method (P for bias = 0.190) and Begg's (rank correlation) method (continuity corrected $P = 0.202$).

'Weight-for-age' was reported as 'Z-scores' or percentages of a reference population or actual weights; standardised weighted mean differences (SMDs) were therefore used for computing the pooled estimates.

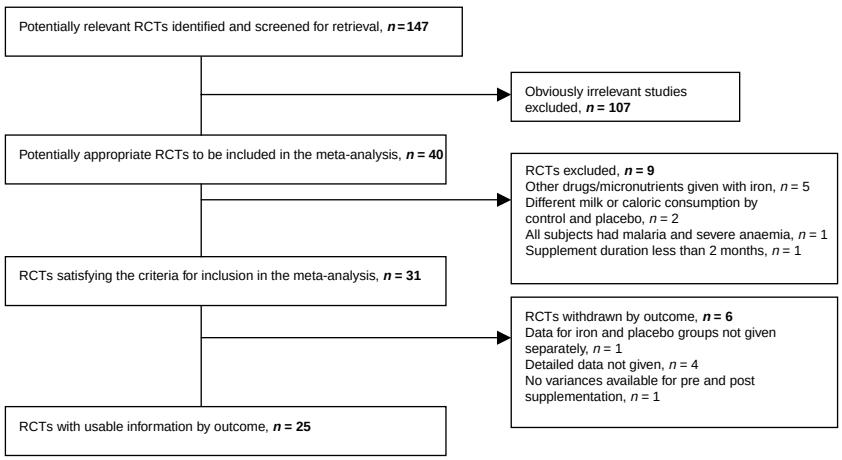

Fig. 1 Flow-chart depicting the selection of randomised controlled trials (RCTs) for inclusion in the meta-analysis

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Table 1 Baseline characteristics of the studies included

Study	Location	Age group	Sample size	Methods*	Eligibility and exclusion criteria	Iron supplementation
Periera *et al.* (1978)[33]	India, Asia	2–5 yrs	T = 24 Fe = 12 Pl = 12	Height, Hb and serum iron paired; B; A; D	Pre-school children living in a residential home, in apparent good health *Exclusion*: Children with tuberculosis and other chronic diseases	Oral Dose: 20 mg day^{-1} Duration of suppl: 7 mo Duration of obs: 7 mo
Periera *et al.* (1979)[34]	India, Asia	2–5 yrs	T = 44 Fe = 22 Pl = 22	Height, Hb and serum iron paired; B; A; D	Pre-school children living in a residential home, in apparent good health *Exclusion:* Children with tuberculosis and other chronic diseases	Fortified Duration of suppl: 5 mo Duration of obs: 5 mo
Chwang *et al.* (1988)[35]	Indonesia, Asia	8.2–13.5 yrs	T = 119 Fe = 59 Pl = 60	Not mentioned; B; A; A	**1.** No evidence of haematological related disease (thalassaemia, malaria and helminthiasis), nephritis, nephrosis, meningitis, encephalitis, measles, chickenpox or other severe illness, nutritional deficiency symptoms, physical handicaps, neurological abnormalities **2.** Negative egg count in stool examination after deworming treatment **3.** > 80th percentile of median W/H and >85th percentile of the median arm circumference for Indonesian growth curves of the respective measures	Oral Dose: 2 mg kg^{-1} day^{-1} Duration of suppl: 3 mo Duration of obs: 3 mo
Latham *et al.* (1990)[36]	Kenya, Africa	Mean = 8 yrs	T = 55 Fe = 29 Pl = 26	Paired groups randomised; B; C; A	All children attending the lowest grades (1 & 2) *Exclusion:* **1.** Evidence of *Schistostoma* infection using reagent strips **2.** Absence on the day of first examination **3.** Clinical evidence of serious disease or malnutrition **4.** Hb <8 g dl^{-1} **5.** Heavy infections with hookworm (>10 000 eggs/g stool) **6.** Parental or child objection for inclusion into the study	Oral Dose: 80 mg day^{-1} Duration of suppl: 8 mo Duration of obs: 8 mo
Javaid *et al.* (1991)[37]	Pakistan, Asia	4 mo	T = 129 Fe = 87 Pl = 42	Unclear; B; D; D	Birth weight >2.5 kg	Fortified Duration of suppl: 8 mo Duration of obs: 8 mo
Angeles *et al.* (1993)[40]	Indonesia, Asia	2–5 yr	T = 80 Fe = 40 Pl = 40	Unclear; B; B; A	W/A *Z*-score between −2 and −3, Hb = 8–11 g dl^{-1}, SF <12 μg dl^{-1}	Oral Dose: 30 mg day^{-1} Duration of suppl: 2 mo Duration of obs: 2 mo

Table 1. *Continued*

Study	Location	Age group	Sample size	Methods*	Eligibility and exclusion criteria	Iron supplementation
Bhatia *et al.* (1993)[38]	India, Asia	3–5 yrs	T = 156 Fe = 84 Pl = 72	Cluster randomisation; B; A; D	Children from four Balwadis	Oral Dose: 40 mg day^{-1} Duration of suppl: 6 mo Duration of obs: 6 mo
Brunser *et al.* (1993)[39]	Chile, South America	3 mo	T = 400 Fe = 200 Pl = 200	Random numbers table; A; D; A	Birth wt ≥2.5 kg, W/A ≥80% or 50th centile, Hb ≥10.5 g dl^{-1}	Fortified Duration of suppl: 6 mo Duration of obs: 6 mo
Idjradinata *et al.* (1994)[13]	Indonesia, Asia	12–18 mo	T = 119 Fe = 60 Pl = 59	Random numbers table; B; B; D	Birth wt >2.500 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 sulfate) Dose: 3 mg kg^{-1} day^{-1} Duration of suppl: 4 mo Duration of obs: 4 mo
Lawless *et al.* (1994)[9]	Kenya, Africa	6–11 yrs	T = 86 Fe = 44 Pl = 42	Stratified randomisation (by gender and initial Hb value); C; A; A	Hb ≥8 g dl^{-1} *Exclusion:* Heavy hookworm infection, blood in the urine indicative of *S. haematobium*, dislike of uji, absence at the time of interval exams	Oral Dose: 60 mg day^{-1} Duration of suppl: 3 mo Duration of obs: 3 mo
Hemminki *et al.* (1995)[41]	Hungary, Europe	<45 days	T = 322 Fe = 164 Pl = 158	Unclear; A; B; D	Birth wt ≥2.5 kg *Exclusion:* Critically ill, malformations, child cared for outside home, consultation with private physician	Fortified Duration of suppl: 10.5 mo Duration of obs: 10.5 mo
Palupi *et al.* (1997)[42]	Indonesia, Asia	2–5 yrs	T = 194 Fe = 96 Pl = 98	Unclear; B; B; A	Registered at village health centre	Oral Dose: 15 mg week^{-1} Duration of suppl: 2 mo Duration of obs: 2 mo
Gill *et al.* (1997)[43]	UK, Europe	6 mo	T = 252 Fe = 192 Pl = 60	Not mentioned; B; D; A	Healthy term infants receiving cow's milk or infant formula *Exclusion:* **1.** Totally or partially breast-fed **2.** Receiving or had previously received non-dietary iron supplements or blood transfusion **3.** Suffering from severe or chronic disease, haematological disorders, malnutrition or congenital anomalies which interfered with growth or feeding **4.** Identified as being iron-deficient at entry reflected by Hb <11 g dl^{-1} or SF <10 μg l^{-1} **5.** < 2.5 kg at birth	Fortified Duration of suppl: 9 mo Duration of obs: 9 mo

Table 1. *Continued*

Study	Location	Age group	Sample size	Methods*	Eligibility and exclusion criteria	Iron supplementation
Rosado *et al.* (1997)[12]	Mexico, North America	1.5–3 yrs	T = 219 Fe = 109 Pl = 110	Stratified randomisation (by age and sex); B; C; A	Age as stated	Oral Dose: 20 mg day^{-1} Duration of suppl: 12 mo Duration of obs: 12 mo
Morley *et al.* (1999)[44]	UK, Europe	9 mo	T = 327 Fe = 162 Pl = 165	Permuted blocks of random length; A; D; D	**1.** Healthy term infants **2.** Birth wt >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 iron supplementation **7.** First language English	Fortified formula Dose: 1.2 mg l^{-1} Duration of suppl: 9 mo Duration of obs: 9 mo
Rahman *et al.* (1999)[45]	Bangladesh, Asia	2–48 mo	T = 349 Fe = 172 Pl = 177	Block randomisation of four homogeneous clusters; A; C; A	*Exclusion:* Critically ill, congenital malformations, metabolic disorders	Oral Dose: 15 mg day^{-1} Duration of suppl: 15 mo Duration of obs: 15 mo
Aguayo (2000)[46]	Bolivia, South America	6–11.9 yrs	T = 64 Fe = 33 Pl = 31	Assorted random digits; B; C; A	Hb >14.4 g dl^{-1}	Oral Dose: 3 mg kg^{-1} day^{-1} Duration of suppl: 18 weeks Duration of obs: 18 weeks
Mwanri *et al.* (2000)[47]	Tanzania, Africa	9–12 yrs	T = 136 Fe = 68 Pl = 68	Not mentioned; B; A; A	Children who had attended school for 2 years or more Children who were not ingesting any supplements Informed consent available	Oral Dose: 60 mg day^{-1} Duration of suppl: 3 mo Duration of obs: 3 mo
Dossa *et al.* (2001)[48]	Benin, Africa	3–5 yrs	T = 136 Fe = 68 Pl = 68	Not mentioned; B; D; A	Absence of acute disease	Oral Dose: 60 mg day^{-1} Duration of suppl: 3 mo Duration of obs: 3 mo
Geltman *et al.* (2001)[49]	USA, North America	5–7 mo	T = 240 Fe = 117 Pl = 123	Not mentioned; A; D; A	Infants identified through clinics *Exclusion:* Premature birth, haematological or gastrointestinal abnormalities, previous supplement use	Oral Dose: 2 mg kg^{-1} day^{-1} Duration of suppl: 3 mo Duration of obs: 3 mo
Dijkhuizen *et al.* (2001)[50]	Indonesia, Asia	4 mo	T = 478 Pl = 238 Fe = 240	Block randomisation; A; D; A	Infants identified by volunteers *Exclusion:* Severe or chronic illness, severe clinical malnutrition, congenital anomalies	Oral Dose: 1.5 mg kg^{-1} day^{-1} Duration of suppl: 6 mo Duration of obs: 6 mo

Table 1. *Continued*

Study	Location	Age group	Sample size	Methods*	Eligibility and exclusion criteria	Iron supplementation
Sungthong *et al.* (2002)[51]	Thailand, Asia	6–13 yrs	T = 510 Fe = 268 Pl = 242	Simple random allocation; A; A; A	*Exclusion:* **1.** Severe malnutrition (W/H less than 3rd centile for Thai reference) **2.** Chronic illness such as thalassaemia, haemolytic disease **3.** High iron storage (SF $>100\ \mu g\,l^{-1}$) **4.** Physical handicaps **5.** No baseline laboratory assessment	Oral Dose: 60 mg daily/weekly Duration of suppl: 4 mo Duration of obs: 4 mo
Dewey *et al.* (2002)[52]	Sweden, Europe and Honduras, South America	4 mo	T = 147 Fe = 70 Pl = 77	Not mentioned; A; B/C; A	Breast-fed infants	Oral Dose: $1\ mg\,kg^{-1}\,day^{-1}$ Duration of suppl: 5 mo Duration of obs: 5 mo
Agarwal *et al.*. (1999)†	India, Asia	50–80 days	T = 73 Fe = 37 Pl = 36	Computer-generated random numbers; A; C; A	Gestation ≥37 weeks, birth wt <2.5 kg *Exclusion:* Twins, congenital malformations, received blood, adverse neonatal event requiring admission in nursery, sampling prior to recruitment >10 ml, significant current morbidity, maternal antepartum haemorrhage	Oral Dose: $3\ mg\,kg^{-1}\,day^{-1}$ Duration of suppl: 2 mo Duration of obs: 2 mo
Nagpal *et al.* (2000)‡	India, Asia	4–6 mo	T = 100 Fe = 49 Pl = 51	Computer-generated random numbers; A; D; A	Gestation ≥37 weeks, birth wt ≥2.5 kg, breast-fed *Exclusion:* Twins, congenital malformations, received blood or iron, adverse neonatal event requiring admission in nursery, sampling prior to recruitment >10 ml, significant current morbidity	Oral Dose: $2.5\ mg\,kg^{-1}\,day^{-1}$ Duration of suppl: 2 mo Duration of obs: 2 mo

yrs – years; mo – months; T – total; Fe – iron group; Pl – placebo group; Hb – haemoglobin; W/H – weight-for-height; W//A – weight-for-age; SF – serum ferritin; wt – weight; HC – head circumference; SD – standard deviation; NCHS – National Center for Health Statistics; suppl – supplementation; obs – observation.

* Method of randomisation; allocation concealment (A – adequate, B – unclear, C – inadequate, D – not used); follow-up (attrition rate: A – < 3%, B – 3–9.9%, C – 10–19.9%, D – 20% and above); blinding (A – double blinding, B – single blinding, C – no blinding, D – unclear).

† Agarwal D, Sachdev HPS, Mallika V, Singh T. Iron supplementation in breast fed, full term, low birth weight infants, unpublished.

‡ Nagpal J, Sachdev HPS, Mallika V, Singh T. Iron supplementation with complementary feeding in predominantly breastfed infants, unpublished.

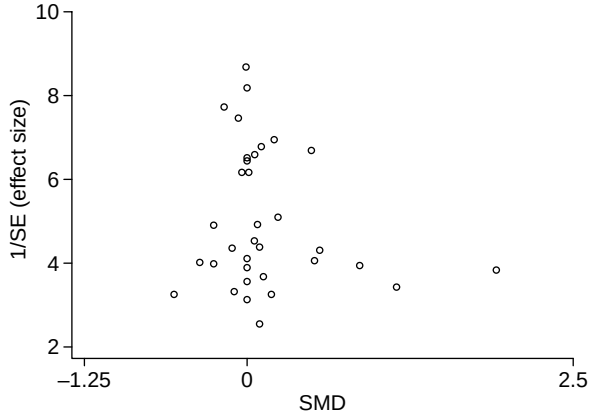

Fig. 2 Funnel plot of weight-for-age with unknown standard deviations derived with the assumption $p = 0.5$. SE – standard error; SMD – standardised mean weighted difference

This systematic review provides pooled data on 4327 children, 2329 of whom received iron while 1998 constituted the placebo group (Table 2). The pooled standardised mean estimate of the change (pre- to post-test difference) was significant when assuming $p = 0.5$ (SMD = 0.13; 95% confidence interval (CI) = 0.01, 0.25; $P = 0.04$; test for heterogeneity = 109.25, $P < 0.001$) (Fig. 3). However, the results were not statistically significant when the SDs were calculated by the independence assumption, with the post-test scores or with the analytic components where actual SDs were available (Table 3).

On sensitivity analysis, the change in weight-for-age was greater (non-overlapping confidence intervals) in studies conducted in malarial hyperendemic regions (Table 4). On meta-regression, residence in malarial hyperendemic region was a significant predictor of heterogeneity on both univariable analysis and when controlling for all variables (Table 5).

Weight-for-height

Seven studies assessed the effect of iron supplementation on weight-for-height. All of them were published in indexed journals and were from developing countries (three from Asia, three from Africa and one from Mexico). The duration of supplementation was <3 months in three trials, 6 months in one study and longer in the rest. The route of administration was oral medicinal iron in all seven trials. There was no evidence of publication bias.

The seven included trials provided data on 1246 children, of which 626 received iron whereas 620 constituted the control group. The pooled mean estimate of the standardised difference in change in weight-for-height between the iron and control groups was not statistically significant (SMD = 0.21; 95% CI = −0.09, 0.52; $P = 0.170$; test for heterogeneity = 5.40, $P < 0.001$) (Fig. 4 and Table 3). The results were identical when the SDs were calculated by various methods.

On sensitivity analysis, the effect size was greater (non-overlapping confidence intervals) in children above 5 years of age (Table 4). Age was a significant predictor on both univariable and multivariable meta-regression analyses (Table 5).

Height-for-age

A total of 23 (24 study populations) trials were available for this analysis. Most of the studies were from the developing countries (12 were from Asia, three were from Europe, two were from North America, three were from South America and four were from Africa). Most of the studies were conducted in infants and toddlers (10 in infants below 2 years of age and eight in pre-schoolers), while only six trials evaluated older children. In eight studies, supplementation was done for 3 months or less; in nine trials the duration of supplementation was for more than 3 but less than 6 months; seven investigations followed up the subjects for longer than 6 months. In most of the studies the subjects received iron supplementation in the form of oral medicinal iron (20/24); in four trials fortified foods were used. There was no evidence of publication bias.

The 24 trials had evaluated the effect of supplementation on 3935 children of which 2132 received iron and 1803 received placebo. The pooled SMD of the change in height-for-age was not significant (SMD = 0.01; 95% CI = −0.10, 0.12; $P = 0.795$; test for heterogeneity = 72.37, $P < 0.001$) (Fig. 5 and Table 3). The results were identical when the SDs were calculated by various methods (Table 3).

Sensitivity analysis showed that iron supplementation had a negative impact on the linear growth of children from developed countries (SMD = −0.27; 95% CI = −0.49, −0.05; $P = 0.018$) while having no significant effect in developing countries. This association was also significant on univariable meta-regression (SMD = −0.35; 95% CI = −0.59, −0.12; $P = 0.003$). Supplementation for a longer period (>6 months) was associated with a significantly slower linear growth (SMD = −0.13; 95% CI = −0.24, −0.01; $P = 0.039$). Duration of supplementation was a significant explanatory variable on meta-regression, with both univariable analysis and when controlling for all variables. There was a significant negative association of baseline weight-for-age on univariable and multivariable meta-regression (Tables 4 and 5).

Mid upper-arm circumference

Eight trials evaluated the effect of iron supplementation on the mid upper-arm circumference in 1163 children, 538 of whom received iron and 525 received placebo. The pooled difference of the standardised mean change

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Table 2 Extracted data from included studies with missing change standard deviations (SDs) computed with the assumption $p = 0.5$

	Change in iron supplement group			Change in placebo group		
Author	Number	Mean	SD	Number	Mean	SD
Weight-for-age						
Idjradinata *et al.*	22	−0.14	0.23	22	0.05	0.42
Angeles *et al.*	39	0.17	0.33	37	0.21	0.36
Morley *et al.*	133	2.20	1.26	135	2.20	1.26
Dewey *et al.* 1	40	1.55	0.54	42	1.52	0.54
Dewey *et al.* 2	30	1.93	0.55	36	2.13	0.55
Geltman *et al.*	117	1.08	0.62	123	1.19	0.62
Mwanri *et al.* 1	34	0.70	0.58	34	0.20	0.58
Mwanri *et al.* 2	34	0.90	0.58	34	0.60	0.58
Sungthong *et al.* 1	139	−0.02	0.30	61	−0.02	0.20
Sungthong *et al.* 2	129	−0.02	0.20	61	−0.02	0.20
Latham *et al.*	29	1.60	2.80	26	−1.50	2.60
Brunser *et al.* 1	70	1.90	9.92	83	2.30	9.92
Brunser *et al.* 2	70	−2.70	8.63	83	−2.80	8.63
Dossa *et al.* 1	33	1.20	0.50	28	1.20	1.10
Dossa *et al.* 2	31	1.20	0.60	37	1.20	1.00
Aguayo	33	1.63	1.11	31	1.88	0.79
Rosado *et al.* 1	50	0.28	0.42	47	0.25	0.34
Rosado *et al.* 2	49	0.16	0.42	48	0.26	0.35
Dijkhuizen *et al.* 1	94	−1.13	0.92	90	−1.23	0.92
Dijkhuizen *et al.* 2	78	−1.26	0.86	98	−1.31	0.86
Rahman *et al.*	107	1.35	0.65	116	1.39	0.54
Lawless *et al.*	44	0.22	0.12	42	0.00	0.11
Chwang *et al.* 1	43	0.16	0.20	35	0.05	0.20
Chwang *et al.* 2	16	0.07	0.22	25	0.07	0.22
Javaid *et al.*	57	2.54	1.14	29	2.44	0.89
Bhatia *et al.* 1	56	1.00	1.69	49	0.60	1.69
Bhatia *et al.* 2	28	1.00	1.52	23	1.00	1.52
Palupi *et al.*	96	0.14	0.36	98	0.06	0.41
Gill *et al.*	192	3.20	0.20	60	3.10	0.20
Periera *et al.*	22	0.42	1.92	22	0.61	1.92
Periera *et al.* B	27	0.40	2.10	27	0.14	2.10
Hemminki *et al.*	157	6.50	1.01	145	6.51	1.12
Agarwal *et al.*	13	1.69	0.54	13	1.65	0.26
Nagpal *et al.*	19	0.78	0.53	24	0.70	0.34
Weight-for-height						
Angeles *et al.*	39	−0.06	0.46	37	0.21	0.51
Latham *et al.*	29	3.50	3.93	26	−0.20	3.11
Dossa *et al.* 1	33	−0.15	0.47	28	−0.09	0.57
Dossa *et al.* 2	31	−0.15	0.39	37	−0.24	0.48
Rosado *et al.* 1	50	0.36	0.42	47	0.29	0.41
Rosado *et al.* 2	49	0.19	0.56	48	0.25	0.42
Dijkhuizen *et al.* 1	94	−1.07	0.83	90	−1.11	0.83
Dijkhuizen *et al.* 2	78	−1.11	0.83	98	−1.08	0.83
Lawless *et al.*	44	0.43	0.22	42	0.10	0.21
Palupi *et al.*	96	0.12	0.49	98	0.03	0.56
Height-for-age						
Idjradinata *et al.*	22	−0.03	0.52	22	−0.02	0.52
Angeles *et al.*	39	0.37	0.41	37	0.07	0.23
Morley *et al.*	133	10.40	2.88	135	10.70	2.88
Dewey *et al.* 1	40	6.52	1.14	42	6.83	1.17
Dewey *et al.* 2	30	7.31	1.26	36	7.79	1.26
Geltman *et al.*	117	4.50	2.96	123	4.85	2.96
Mwanri *et al.* 1	34	0.40	0.36	34	0.10	0.34
Mwanri *et al.* 2	34	0.50	0.34	34	0.40	0.34
Sungthong *et al.* 1	139	−0.07	0.14	61	−0.05	0.15
Sungthong *et al.* 2	129	−0.03	0.15	61	−0.05	0.15
Latham *et al.*	29	3.20	0.92	26	3.20	0.76
Dossa *et al.* 1	33	0.17	0.36	28	0.16	0.42
Dossa *et al.* 2	31	0.12	0.23	37	0.13	0.44
Aguayo	33	2.35	0.94	31	2.11	1.03
Rosado *et al.* 1	50	0.02	0.42	47	0.13	0.41
Rosado *et al.* 2	49	0.07	0.42	48	0.16	0.35
Dijkhuizen *et al.* 1	94	−0.35	0.83	90	−0.42	0.83
Dijkhuizen *et al.* 2	78	−0.51	0.78	98	−0.59	0.78
Rahman *et al.*	107	6.01	1.47	116	6.18	1.58
Lawless *et al.*	44	−0.04	0.09	42	−0.08	0.08

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Table 2. *Continued*

Author	Change in iron supplement group			Change in placebo group		
	Number	Mean	SD	Number	Mean	SD
Chwang *et al.* 1	43	0.10	0.35	35	0.03	0.35
Chwang *et al.* 2	16	0.04	0.34	25	0.03	0.34
Bhatia *et al.* 1	56	1.60	5.06	49	2.10	5.06
Bhatia *et al.* 2	28	0.80	5.56	23	1.20	5.56
Palupi *et al.*	96	0.07	0.27	98	0.03	0.26
Gill *et al.*	192	11.30	0.28	60	11.50	0.28
Periera *et al.*	22	1.90	6.06	22	2.00	6.06
Periera *et al.* B	27	1.50	6.75	27	1.40	6.75
Hemminki *et al.*	157	24.40	3.76	145	24.90	3.26
Agarwal *et al.*	13	6.57	2.10	13	5.24	1.30
Nagpal *et al.*	19	3.08	1.52	24	3.26	1.54
Mid upper-arm circumference						
Idjradinata *et al.*	22	0.23	0.38	22	0.40	0.42
Morley *et al.*	133	0.40	1.45	135	0.50	1.45
Latham *et al.*	29	0.60	0.48	26	0.20	0.41
Dossa *et al.* 1	33	0.00	0.80	28	0.10	0.90
Dossa *et al.* 2	31	0.10	0.70	37	0.10	0.80
Aguayo	33	0.29	0.57	31	0.22	0.54
Rosado *et al.* 1	50	0.73	0.57	47	0.67	0.55
Rosado *et al.* 2	49	0.68	0.49	48	0.93	0.14
Chwang *et al.* 1	43	0.48	1.22	35	0.09	1.22
Chwang *et al.* 2	16	0.14	1.15	25	0.13	1.15
Bhatia *et al.* 1	56	0.00	0.73	49	0.00	0.73
Bhatia *et al.* 2	28	0.00	1.32	23	0.00	1.32
Head circumference						
Morley *et al.*	133	2.80	1.48	135	2.80	1.48
Dewey *et al.* 1	40	3.01	0.51	42	2.87	0.45
Dewey *et al.* 2	30	3.56	0.49	36	3.88	0.48
Agarwal *et al.*	13	3.75	1.00	13	4.50	1.40
Nagpal *et al.*	19	2.00	0.33	24	1.90	0.37
Triceps skinfold thickness						
Morley *et al.*	133	−1.90	2.49	135	−2.00	2.49
Latham *et al.*	29	0.70	0.81	26	0.00	0.82
Dossa *et al.* 1	33	−0.20	1.60	28	0.20	1.70
Dossa *et al.* 2	31	0.00	1.50	37	−0.60	1.30
Rosado *et al.* 1	50	0.46	1.70	47	0.33	1.85
Rosado *et al.* 2	49	0.74	1.89	48	0.59	2.08
Bhatia *et al.* 1	56	−0.10	1.20	49	0.10	1.20
Bhatia *et al.* 2	28	0.10	1.02	23	0.10	1.02
Subscapular skinfold thickness						
Morley *et al.*	133	−1.20	1.98	135	−1.10	1.98
Latham *et al.*	29	0.80	0.48	26	0.00	0.62

was 0.0 (95% CI = −0.20, 0.20), which was statistically not significant ($P = 0.991$) (Table 3).

Skinfold thicknesses

Triceps skinfold thickness. A total of five studies assessed the impact of iron supplementation on triceps skinfold thickness. There was no significant difference in the change in triceps skinfold thickness between the iron and control groups (SMD = 0.16; 95% CI = −0.12, 0.44; $P = 0.252$) (Table 3).

Subscapular skinfold thickness. Only two studies assessed the impact of iron supplementation on subscapular skinfold thickness in children. There was no significant effect of iron supplementation on subscapular skinfold thickness (Table 3).

Head circumference

Only four publications (five trials) assessed the impact of iron supplementation on head circumference in children. There was no significant effect of iron supplementation on head circumference (Table 3).

Discussion

This systematic review of largely heterogeneous data derived from randomised controlled efficacy trials did not document a positive effect of iron supplementation on the physical growth of children. A recent meta-analysis also concluded that iron interventions have no significant effect on children's weight or height, the results being similar across categories of age, duration of intervention, mode and dosage of intervention, and baseline anthropometric status[53].

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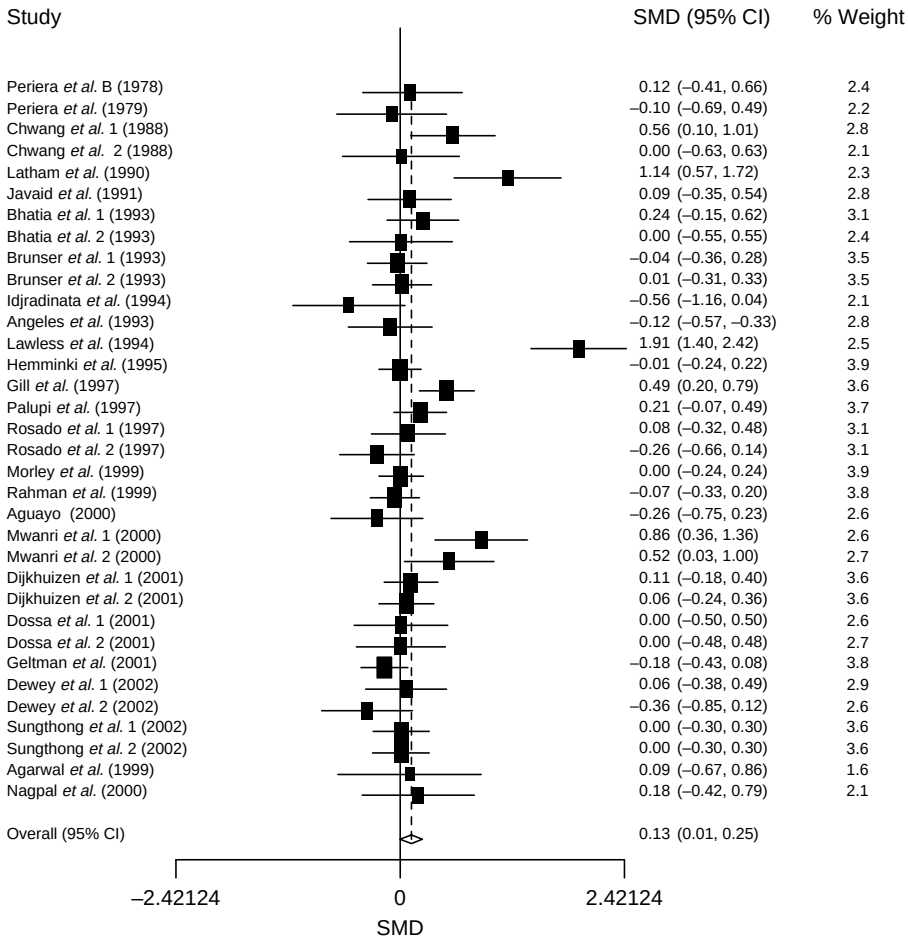

Fig. 3 Forest plot of weight-for-age with unknown standard deviations derived with the assumption $p = 0.5$. SMD – standardised mean weighted difference; CI – confidence interval

Strengths and limitations of the analysis

The main conclusion regarding the lack of effect of iron supplementation on physical growth following iron supplementation remained stable over a large spectrum of sensitivity analyses performed. Also influence analyses, i.e. the effect of omitting one study at a time (data not shown), did not reveal an overwhelming effect of any single trial. Consistent and statistically significant predictors of heterogeneity could be identified, i.e. residence in malarial hyperendemic region for weight-for-age, age above 5 years for weight-for-height, and residence in developed countries and supplementation for 6 months or longer for height-for-age. In view of the small sample sizes in the subgroups and the possibility of false positives due to multiple comparisons, these predictors of heterogeneity should be viewed only as possibilities and not conclusive.

Three limitations merit consideration. First, only a proportion of the included trials were of good quality as assessed by recommended criteria[14,15]. On analysis, the quality of the trials (allocation concealment and attrition rate) did not have a statistically consistent relationship with the pooled effect size. Second, compliance to the supplementation regimen and the bioavailability of the iron preparation used for supplementation[54,55] are potential explanatory variables for heterogeneity. Also, physical growth of an individual child can be influenced by several other proximate factors including energy and micronutrient adequacy and freedom from morbidity, particularly infections. Most of the included trials did not control for or provide information on all these factors. Even the baseline iron status was not reported in most of the studies, and haemoglobin was used as a proxy for this nutrient. However, the included trials were randomised and controlled, which should control for most of these factors. Finally, in the absence of actually stated data on the variability of the change in outcome scores, several imputations were made on the basis of pre-specified assumptions. The sensitivity analyses suggest that these imputations were robust since the interpretation and quantification with various assumptions were invariably synchronous.

A few interesting observations have emerged from this systematic review, which may have programmatic

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Table 3 Pooled analyses of effect of iron supplementation on anthropometric parameters

Stratification variable	No. of analytic components	Random effects model (95% CI)	*P*-value	Tests for heterogeneity (*P*-value)
Weight-for-age				
Change SDs available	22	0.13 (−0.05, 0.32)	0.145	95.14 (< **0.001**)
All				
SDs by $p = 0.5$	34	0.13 (0.01, 0.25)	**0.04**	109.25 (< **0.001**)
SDs by independence	34	0.11 (−0.01, 0.23)	0.062	101.40 (< **0.001**)
Post-test scores and SDs	32	0.07 (−0.00, 0.13)	0.057	32.18 (0.408)
Weight-for-height				
Change SDs available	8	0.27 (−0.14, 0.69)	0.188	52.27 (< **0.001**)
All				
SDs by $p = 0.5$	10	0.21 (−0.09, 0.52)	0.170	55.10 (< **0.001**)
SDs by independence	10	0.21 (−0.09, 0.52)	0.171	55.12 (< **0.001**)
Post-test scores and SDs	10	0.04 (−0.11, 0.20)	0.599	4.36 (0.110)
Height-for-age				
Change SDs available	21	0.06 (−0.07, 0.20)	0.385	48.20 (< **0.001**)
All				
SDs by $p = 0.5$	31	0.01 (−0.1, 0.12)	0.795	72.37 (< **0.001**)
SDs by independence	31	0.02 (−0.08, 0.12)	0.737	60.45 (**0.001**)
Post-test scores and SDs	29	0.08 (−0.01, 0.16)	0.066	35.12 (0.167)
Mid upper-arm circumference				
Change SDs available	7	−0.02 (−0.38, 0.33)	0.894	23.12 (< **0.001**)
All				
SDs by $p = 0.5$	12	0.00 (−0.20, 0.20)	0.991	25.65 (**0.007**)
SDs by independence	12	0.00 (−0.20, 0.19)	0.960	24.50 (**0.011**)
Post-test scores and SDs	12	0.12 (0.00, 0.25)	0.051	8.62 (0.657)
Triceps skinfold thickness				
Change SDs available	5	0.32 (−0.06, 0.71)	0.099	6.68 (0.154)
All				
SDs by $p = 0.5$	8	0.16 (−0.12, 0.44)	0.252	12.06 (0.099)
SDs by independence	8	0.20 (−0.09, 0.49)	0.178	10.25 (0.175)
Post-test scores and SDs	8	0.03 (−0.46, 0.53)	0.891	26.16 (< **0.001**)
Subscapular skinfold thickness				
Change SDs available	1	Not possible		
All				
SDs by $p = 0.5$	2	0.37 (−0.51, 1.25)	0.411	9.96 (**0.002**)
SDs by independence	2	0.40 (−0.47, 1.28)	0.368	5.80 (**0.016**)
Post-test scores and SDs	2	0.58 (−0.69, 1.85)	0.370	5.94 (**0.015**)
Head circumference				
Change SDs available	4	−0.08 (−0.36, 0.21)	0.599	12.11 (**0.007**)
All				
SDs by $p = 0.5$	5	−0.05 (−0.28, 0.17)	0.643	12.12 (**0.017**)
SDs by independence	5	−0.06 (−0.30, 0.18)	0.631	12.11 (**0.017**)
Post-test scores and SDs	5	−0.04 (−0.33, 0.25)	0.796	5.37 (0.251)

CI – confidence interval; SD – standard deviation.
Bold font indicates significant *P*-values.

implications and can provide direction for future research.

Since iron administration does not result in any significant change in physical growth, public health programmes of iron supplementation cannot be justified for improving childhood undernutrition. It would be pertinent to examine the finding of this review in the light of earlier literature. The role of iron in cell differentiation and somatic growth in the human body has largely been speculative. Observational studies had postulated a positive effect on physical growth due to indirect effects of iron supplementation – improvement in immunity leading to decreased incidence of infections[35], and improvement in listlessness leading to increased appetite and consequently the intake of energy[9]. However, a recent meta-analysis has shown that iron supplementation does not reduce the incidence of infections in children[56], and in fact there is a marginally increased risk of diarrhoea. Also, since most of the studies did not specifically estimate appetite and energy intake, the role of this factor still remains speculative. Most of the included studies were from developing countries, where food availability is marginal and feeding practices poor. In such a scenario, even improvement in the appetite and activity levels of the child may not translate into substantially increased energy intake, and therefore enhanced height and weight gain. A recent study from this setting[27] documented a significant increase in physical growth with combined energy and iron

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Table 4 Sensitivity analyses of pooled estimates for weight-for-age, weight-for-height and height-for-age

Stratification variable	No. of analytic components	Random effects model (95% CI)	*P*-value	Tests for heterogeneity (*P*-value)
Weight-for-age				
Setting				
Developed countries	5	0.01 (−0.23, 0.25)	0.933	14.75 (**0.005**)
Developing countries	29	0.16 (0.01, 0.30)	**0.031**	92.55 (< **0.001**)
Malaria hyperendemicity				
Yes	6	0.73 (0.15, 1.3)	**0.014**	40.40 (< **0.001**)
No	28	0.03 (−0.05, 0.10)	0.472	31.84 (< **0.001**)
Mean age				
< 24 months	14	0.02 (−0.09, 0.13)	0.734	19.34 (0.113)
< 60 months	25	0.03 (−0.05, 0.10)	0.549	25.29 (0.390)
> 60 months	9	0.51 (0.09, 0.94)	**0.018**	65.58 (< **0.001**)
Allocation concealment				
Adequate	13	−0.02 (−0.10, 0.06)	0.629	5.21 (0.950)
Others	21	0.24 (0.03, 0.45)	**0.024**	87.27 (< **0.001**)
Weight-for-height				
Mean age				
< 24 months	2	0.01 (−0.20, 0.21)	0.944	0.16 (0.690)
< 60 months	8	0.00 (−0.15, 0.15)	0.979	9.17 (0.241)
> 60 months	2	1.30 (0.82, 1.79)	< **0.001**	1.71 (0.190)
Mean baseline haemoglobin				
$< 11\,g\,dl^{-1}$	5	−0.08 (−0.34, 0.18)	0.556	7.05 (0.133)
$> 11\,g\,dl^{-1}$	4	0.67 (0.03, 1.30)	**0.040**	34.33 (< **0.001**)
Height-for-age				
Setting				
Developed countries	5	−0.27 (−0.49, −0.05)	**0.018**	12.68 (**0.013**)
Developing countries	26	0.09 (−0.02, 0.20)	0.120	42.52 (**0.016**)
Malaria hyperendemicity				
Yes	6	0.27 (0.0, 0.55)	**0.048**	9.57 (0.088)
No	25	−0.04 (−0.15, 0.07)	0.472	52.41 (**0.001**)
Frequency (per week)*				
7	21	0.00 (−0.12, 0.13)	0.979	33.05 (0.033)
< 7	6	0.21 (−0.03, 0.39)	**0.020**	8.14 (0.149)
Mean age				
< 24 months	11	−0.13 (−0.30, 0.03)	0.127	25.34 (**0.005**)
< 60 months	22	−0.06 (−0.18, 0.06)	0.308	47.56 (**0.001**)
> 60 months	9	0.21 (0.02, 0.41)	**0.031**	14.23 (**0.076**)
Duration of study				
< 6 months	17	0.15 (−0.01, 0.32)	0.073	39.17 (**0.001**)
> 6 months	14	−0.13 (−0.24, −0.01)	**0.039**	20.88 (0.075)

CI – confidence interval.
Only variables significant in at least one stratum are depicted; bold font indicates significant *P*-values.
Calculations performed using standard deviations calculated with the assumption $p = 0.5$.
* Analysis was restricted to oral supplementation route only.

supplementation, but this finding needs further validation. Another factor to be considered is the interaction with other micronutrients like zinc and vitamin A, which may have a role in physical growth. Iron supplementation in high doses could impair zinc absorption and nutriture[57], and a recent meta-analysis[58] has documented an increase in height and weight with zinc supplementation. There is thus a need for well-designed intervention studies to evaluate the role of micronutrient interactions in determining physical growth of children.

There was a suggestion of a detrimental effect of iron supplementation on linear growth in developed countries and with longer duration of supplementation. Individual studies have observed growth retardation in iron-sufficient children following iron therapy[13]. Children from developed countries and those receiving iron for prolonged periods (>6 months) are more likely to be iron-replete. However, this review failed to document an inverse association between baseline haemoglobin status and response. It is therefore important for future trials to relate growth data to iron status directly, in order confirm the possibility of a beneficial effect on anthropometry in iron-deficient children or of growth retardation in iron-sufficient children.

A surprising finding was a greater rise in weight in children residing in malaria hyperendemic areas. This finding must be interpreted with caution because the number of studies from these regions was few. It is possible that these children were initially severely undernourished and anaemic, and therefore most likely to benefit from iron supplementation. However, this possibility was not supported by sensitivity analyses and meta-regression. Two of these studies[47,48] had multiple intervention arms including vitamin A and

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Table 5 Meta-regression analyses for weight-for-age, weight-for-height and height-for-age (restricted maximum likelihood method)

	Univariable analysis		Controlling for all variables	
Study characteristic	SMD (95% CI)	*P*-value	SMD (95% CI)	*P*-value
Weight-for-age				
Allocation concealment (not adequate vs. adequate)	0.26 (0.01, 0.52)	**0.046**	0.12 (−0.17, 0.41)	0.416
Developed vs. developing country	−0.15 (−0.52, 0.21)	0.407	0.14 (−0.33, 0.61)	0.561
Malaria hyperendemic vs. not	0.69 (0.40, 0.99)	< **0.001**	0.57 (0.14, 1.00)	**0.009**
Unit increase in mean age (months)	0.00 (0.00, 0.01)	**0.005**	0.00 (−0.0, 0.00)	0.650
Unit increase in mean baseline height-for-age (*Z*-score)*	−0.10 (−0.44, 0.25)	0.588	1.00 (0.60, 1.40)	< **0.001**
Weight-for-height				
Malaria hyperendemic vs. not	0.70 (0.09, 1.32)	**0.025**	−1.47 (−3.27, 0.34)	0.111
Unit increase in mean age (months)	0.01 (0.01, 0.02)	< **0.001**	0.08 (0.01, 0.16)	**0.033**
Unit increase in mean baseline haemoglobin status ($g\,dl^{-1}$)	0.50 (−0.14, 1.15)	0.124	0.02 (−0.89, 0.95)	0.958
Height-for-age				
Study quality (attrition >10% vs. <10%)	−0.22 (−0.43, −0.01)	**0.045**	−0.05 (−0.36, 0.25)	0.724
Developed vs. developing country	−0.35 (−0.59, −0.12)	**0.003**	−0.28 (−0.84, 0.28)	0.331
Malaria hyperendemic vs. not	0.32 (0.03, 0.60)	**0.028**	0.24 (−0.14, 0.61)	0.214
Fortified food vs. oral iron	0.33 (0.05, 0.60)	**0.020**	−0.14 (−0.68, 0.40)	0.617
Unit increase in frequency of supplementation per week†	−0.03 (−0.09, 0.02)	0.229	−0.01 (−0.06, 0.05)	0.829
Unit increase in duration of iron supplementation (months)	−0.05 (−0.08, −0.02)	**0.001**	−0.05 (−0.10, −0.00)	**0.031**
Unit increase in mean age (months)	0.00 (0.00, 0.01)	**0.005**	−0.00 (−0.00, 0.00)	0.911
Unit increase in mean baseline weight-for-age (*Z*-score)‡	−0.16 (−0.32, −0.00)	**0.049**	−0.54 (−0.99, −0.10)	**0.017**

SMD – standardised mean weighted difference; CI – confidence interval.
Only statistically significant variables on meta-regression (univariable analysis or on controlling for all variables) or sensitivity analyses (at least one stratum) are depicted; bold font indicates significant *P*-values.
Calculations were performed using standard deviations calculated with the assumption $p = 0.5$.
* Analysis was restricted to those with data on baseline height-for-age (analytic components = 17). While controlling for other variables, frequency and mean iron dose were not considered.
† Analysis was restricted to oral supplementation route only (analytic components = 27).
‡ Analysis was restricted to those with data on baseline weight-for-age (analytic components = 16). While controlling for other variables, frequency and mean iron dose were not considered.

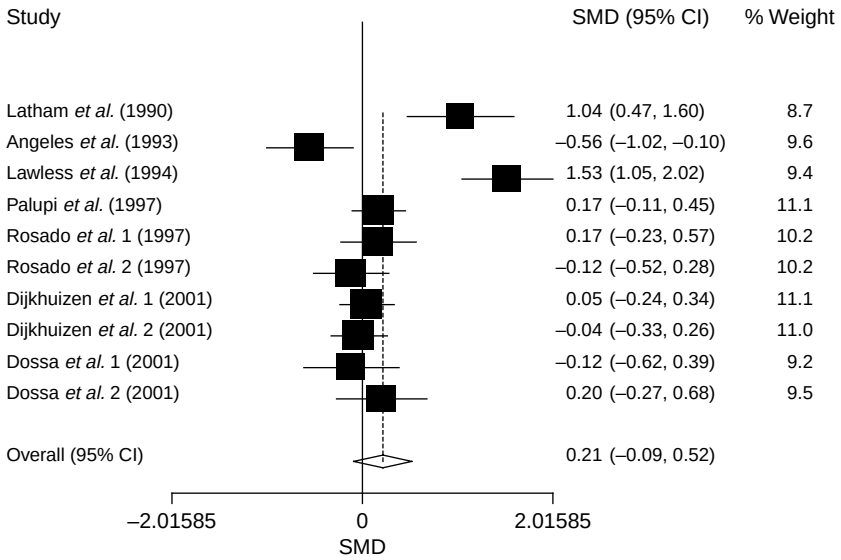

Fig. 4 Forest plot of weight-for-height with unknown standard deviations derived with the assumption $p = 0.5$. SMD – standardised mean weighted difference; CI – confidence interval

antihelmintic treatment, which may also have resulted in a positive interaction.

There was a greater rise in weight-for-height in children above 5 years of age. This finding could have resulted from fewer studies in older children, better designed trials in school-going children rather than the younger age group, and inclusion of adolescent children (>10 years old), as adolescence is considered be critical for iron nutriture and physical growth. However, the first two years of life also represent a critical period for iron nutriture and physical growth, and the review failed to document a significantly greater benefit in this age group.

In conclusion, this systematic review did not document a positive effect of iron supplementation on the physical

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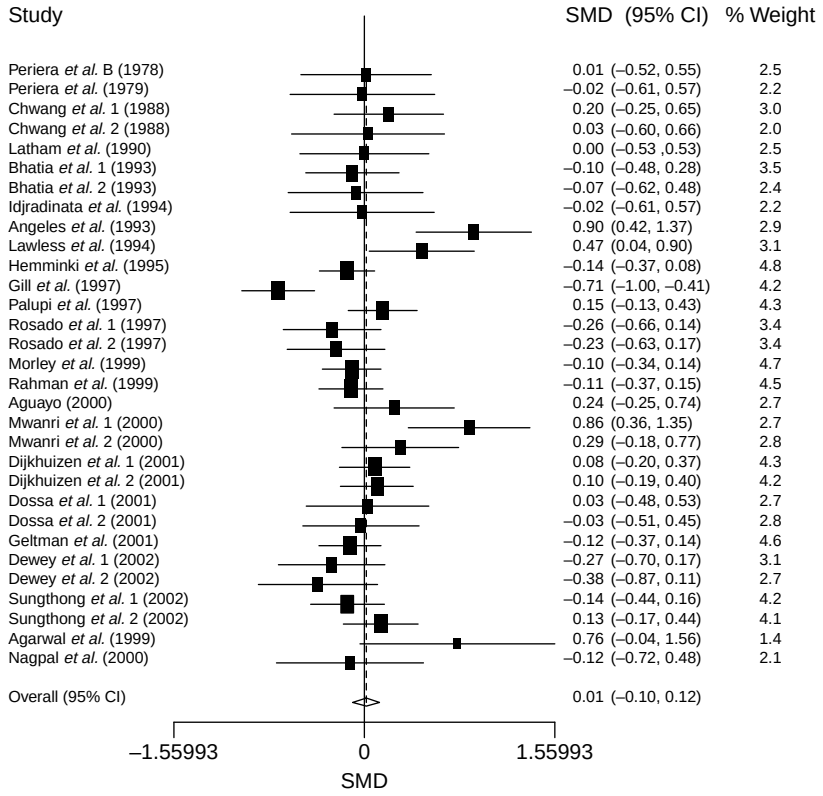

Fig. 5 Forest plot of height-for-age with unknown standard deviations derived with the assumption $p = 0.5$. SMD – standardised mean weighted difference; CI – confidence interval

growth of children. Significant heterogeneity was evident, and its predictors included greater weight-for-age in supplemented children in malaria hyperendemic regions and greater weight-for-height for children above 5 years of age, but a negative effect on linear growth in developed countries and with supplementation for 6 months or longer. However, these predictors of heterogeneity should be viewed only as exploratory and requiring confirmation, not as conclusive.

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Contributors: T.G. prepared the protocol, applied the search strategy, performed the retrieval of articles and extracted the data from the included studies. H.P.S.S. and P.N. developed the idea for the review, finalised the protocol and search strategy. H.P.S.S. performed the statistical analysis. All of the authors contributed to the drafting of the final version of the paper. H.P.S.S. and T.G. are the guarantors.

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