Special Article

NUTRITION REVIEWS

Effect of iron intervention on growth during gestation, infancy, childhood, and adolescence: a systematic review with meta-analysis

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To evaluate the effect of iron intervention on physical growth in fetuses, infants, children, and adolescents up to 18 years of age, a systematic review with meta-analysis of randomized controlled trials (RCTs) was conducted. Structured electronic searches were conducted to February 2010 using MEDLINE, Embase, and the Cochrane Library databases. RCTs that included iron-fortified foods, iron-fortified formula, or iron supplements and in which height, weight, mid-arm circumference (MAC), head circumference, birth weight, or length of gestation was evaluated were analyzed for inclusion. In total, 21 RCTs in infants, children, and adolescents and 7 studies in pregnant women met the inclusion criteria. The overall pooled result (random-effects model) showed no significant effects of iron intervention on any of the parameters measured. To accommodate wide heterogeneity, studies were stratified according to dose of iron, duration of intervention, age, and baseline iron status. However, only doses of 40–66 mg of supplemental iron and intervention in children ≥6 years of age showed a slight but significant association with weight and MAC.

INTRODUCTION

Iron deficiency (ID) is one of the most prevalent nutritional deficiencies worldwide and often leads to iron deficiency anemia (IDA). Although the etiology of anemia is multifactorial, ID is considered the most important causal factor.[1] According to the World Health Organization (WHO) estimates, anemia affects nearly 30% of the world's population (i.e., about 2 billion people), and approximately half of these cases result from ID.[2]

An inadequate dietary intake is the leading cause of IDA development, although other physiological and pathologic conditions, including impaired absorption or transport of iron, physiological losses, or chronic blood loss secondary to disease, could contribute as well.[3,4] Periods of rapid growth make infants and toddlers aged 6–24 months, as well as adolescents during puberty, a particular risk group for IDA.[5,6] Pregnant women are also at risk for IDA because of their increased nutritional needs. During pregnancy, IDA seems to exert adverse

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effects such as intrauterine growth restriction, preterm delivery, low birth weight (LBW), etc. on fetal growth and development.[7,8] Although iron status is strongly dependent on adequate iron intake,[9] it is still unclear whether prophylactic iron supplementation can reduce the rates of preterm delivery or LBW. Potentially harmful effects of routine iron supplementation during pregnancy in iron-sufficient women are still a matter of discussion because results related to clinical endpoints are conflicting.[10] Some authors reported that supplementation (30 mg/day) significantly increased birth weight and lowered the incidence of preterm delivery[11,12]; others found no effect of iron supplementation (20 mg/day) on clinical endpoints,[13] while Ziaei et al.[14] found that iron supplementation (50 mg/day) may have been associated with adverse effects in nonanemic women, since the incidence of small-for-gestational-age (SGA) newborns was significantly higher among iron-supplied pregnant women than among women who took no iron. Finally, the meta-analysis by Peña-Rosas and Viteri[9] suggested daily iron supplementation during pregnancy had no effect on the birth weight of newborns when compared with placebo or no treatment at all.

Several observational studies have also documented a relationship between IDA and impaired physical growth in infants and children.[15,16] The presence of several confounders, however, such as socioeconomic factors, concomitant deficiencies of other micronutrients, and coexistent parasitic infections, precludes convincing conclusions on a causal relationship.[17] Many intervention trials have addressed the effects of iron supplementation on growth, but the results have been contradictory. Iron supplementation in anemic[18] or malnourished children[19,20] improved growth in some studies. Other studies found no benefit of iron intake on growth,[21] although a higher intake affected iron status,[22–24] indicating that ID was not a growth-limiting factor in infants and young children. Moreover, two studies showed an adverse effect of iron supplementation on physical growth in iron-replete young children.[25,26] Therefore, to clarify the variable results obtained thus far, a systematic review with meta-analysis was conducted using pooled data from all available randomized control trials (RCTs) to ascertain if there is a significant effect of oral iron intervention on physical growth in infants, children, and adolescents and during pregnancy and to quantify the possible dose-response relationship.

METHODS

This systematic review is a part of the European Micronutrient Recommendations Aligned (EURRECA) network of excellence that aims to identify micronutrient requirements for optimal health in European populations (http://www.eurreca.org). The data reported in this review are a part of a wider review process to identify studies assessing the effect of iron intake on different status markers and health outcomes.

Search methods

Structured electronic searches were carried out over all years until February 2010 on MEDLINE®, Embase®, (both on Ovid), and the Cochrane Library CENTRAL database. The general search strategy included terms for [study designs in humans] AND [intake or status] AND [iron] AND [growth]. Both indexing and text terms were used, and each search strategy was further adapted for the individual databases searched. In addition, reference lists of collected papers and of published reviews were also screened for relevant studies. Four reviewers independently scanned identified titles and abstracts with 10% duplication (VV, CV, CB, and KF). The duplicate checks were performed first, and any discrepancies were discussed before screening the remainder of the references. Any potentially relevant references were collected as full-text papers.

Inclusion criteria

Studies included in the review met the following criteria: 1) the study investigated the effect of iron intervention from supplements, fortified foods, or natural dietary sources; 2) the study evaluated any parameters of physical growth, including height, weight, mid-upper-arm circumference (MAC), head circumference, or any markers of fetal growth, e.g., weight at birth or gestational age, as outcome measures; 3) the study comprised RCTs with an adequate control group that received placebo; 4) the study reported baseline data for the outcomes measured; and 5) the study participants were apparently healthy human infants, children, adolescents (from birth to 18 years of age at the time of the intervention), or pregnant women. Subjects with ID or anemia but who were otherwise healthy were also included. Further specific inclusion criteria were defined for trials in pregnant women: the intervention had to last at least 12 weeks, and the daily dose of iron from supplements and/or fortified foods was $\leq$100 mg/d elemental iron.

Selection of studies and data extraction

Full-text articles were assessed for inclusion by four independent reviewers (VV, CV, KF, and CB), with duplicate assessment of a random sample of 10% in order to harmonize the process. Only those papers meeting the inclusion criteria were included and extracted onto an Access (Microsoft, Redmond, Wash.) database. Information

pertaining to bibliographic and methodological details, population characteristics, intervention details (including duration, type. and dose of iron supplements), outcome data, and parameters for growth and standard deviations were collated. If standard deviations were not reported, they were calculated or estimated using methods described in the Cochrane Handbook.[27]

Assessment of internal validity of included studies

Assessment of validity specific to RCTs was carried out using the main data extraction form, as previously described.[28] This included assessment of the following indicators: 1) method of sequence generation and allocation, 2) blinding, 3) potential funding bias, 4) number of participants at start, 5) dropouts and dropout reasons, 6) dose check, 7) reporting of dietary intake data, 8) comparability and reproducibility of outcomes, and 9) similarity of most- and least-exposed groups at baseline. Based on these indicators, two reviewers (VV and CB) assessed the overall risk of bias. The criteria for evaluation of these indicators were adapted from the Cochrane Handbook.[27]

Data analysis

The effect of total iron intake (iron supplied plus dietary iron) on parameters of physical growth was investigated through meta-analyses of the intervention group versus the placebo group for all included studies. When dietary intake was not reported, the mean dietary iron intake from other comparable studies was used for calculation. For each individual study, a regression coefficient (β) and its standard error (SE[β]) were calculated for the effect measure of intake on parameters (weight, height, etc.), based on the assumption of a linear relation on the $\log_e$-$\log_e$ scale (natural logarithm of intake versus natural logarithm of parameters measured). The overall pooled β and SE(β) were calculated by meta-analysis using a random-effects model, which estimates the between-study variance using the methods of DerSimonian and Laird.[29] Residual heterogeneity among studies was evaluated using the I^2 statistic. Meta-analysis with regressions coefficients was carried out with RevMan 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

RESULTS

Selection of eligible papers

The literature search related to anthropometric parameters in infants, children, and adolescents yielded 434 references and, in pregnant women, an additional 265 references. Figure 1 shows a flowchart of studies assessed and excluded at various stages of the review. Of 434 studies in infants, children, and adolescents (right side of the Figure 1), 372 were excluded on the basis of titles and abstracts, while 60 were identified as potentially eligible and were collected as full-text articles. After detailed evaluation, 21 studies in infants, children, or adolescents met the inclusion criteria. The main reasons for exclusion were multiple supplementations where the effect could not be attributed solely to iron; the lack of an adequate control group; improper randomization or no RCT; and incomplete data.

Regarding studies in pregnant women, after excluding titles and abstracts very unlikely to be relevant, 160 studies were assessed for inclusion (Figure 1, left side). Of these, only 7 studies met the inclusion criteria and were included in the meta-analysis. Most of the excluded papers reported the effect of iron on other outcomes, supplied elemental iron in doses ≥100 mg/day, or were not RCTs (no or inadequate control groups, observational or metabolic studies).

Baseline characteristics and results of included trials

The key characteristics of the included RCTs assessing parameters of growth – height, weight, and mid-arm circumference in the infants, children, and adolescents group, head circumference in infants, and outcomes of interest in pregnant women (length of gestation and birth weight) – are presented in Tables 1 and 2.[11–14,19,21,25,26,30–50]

In 13 papers on infants, children, and adolescents, there were two or more substudies: the intervention group was divided according to baseline iron status,[31,32] according to two intervention groups,[33,35,36,38–42,45] or according to gender and doses of supplemented iron.[47] Furthermore, Dewey et al.[25] conducted two substudies in Sweden and Honduras. Thus, from 21 studies in infants, children, and adolescents, a total of 36 estimates were obtained from different population groups. For details, see Table 1.

Nine studies assessed physical growth in infants until 12 months of age, six studies were conducted in preschool children 1–5 years of age, and six studies were performed in children (≥6 years of age) and/or adolescents. All studies were performed in both sexes. Weight (kg) and height (cm) were measured in 19 studies, MAC (cm) in 8 studies, and head circumference (cm) in 2 studies on infants. Five of seven studies in pregnant women investigated the effects of iron supplementation of the length of gestation (weeks), a parameter related to both preterm delivery and SGA. Six trials examined the effects of iron supplementation on newborns' weight (g) at birth, a parameter linked to LBW and SGA (Table 2). A fortified food product was used in one study only,[35] while all other

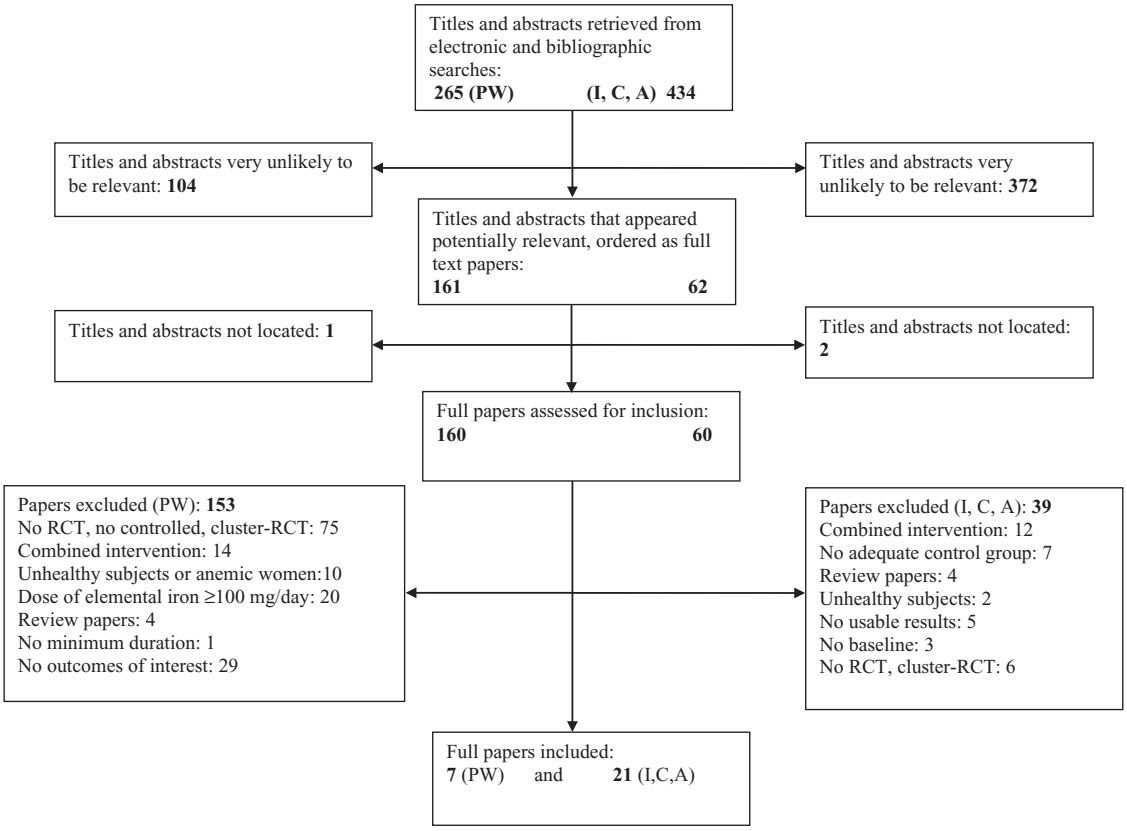

Figure 1 **Flowchart of the articles screened, assessed, and excluded at various stages for this review.**
Abbreviations: I,C,A, infants, children, adolescents; PW, pregnant women; RCT, randomized control trial.

RCTs provided oral iron supplements: ferrous sulfate alone; ferrous sulfate combined with zinc, vitamin C, retinyl acetate, or multivitamins; iron aminoates; or ferrous fumarate. Some authors reported doses of supplemented iron, but not the form of the supplement.

The doses of iron used for supplementation varied among studies and ranged from 7 mg to 66 mg of elemental iron daily. Additionally, Sungthong et al.[38] provided 60 mg of elemental iron 5 days per week to one study group and the same amount of iron once per week to the other group of participants. In several studies, the dose of iron provided to study participants differed, depending on body weight, with doses ranging from 1 mg/kg daily in infants[25,46] to 3 mg/kg daily[26,30] or weekly in children.[30] The duration of the interventions ranged from 6 weeks to 12 months in infants, children, and adolescents, and from 14 weeks to 26 weeks in pregnant women. Five studies were carried out in anemic children, seven studies in both anemic and nonanemic children or infants, and nine studies in nonanemic infants and children. At recruitment, all pregnant women were iron replete and were comparable for age. In the majority of the RCTs included, supplementation started in the first half of gestation (11–19 weeks). Only Makrides et al.[13] recruited pregnant women at week 20 of gestation (Table 2).

The quality of included trials was assessed using recommended criteria and is presented in the last column in Tables 1 and 2. Of the 28 studies included, 12 had a high risk of bias, 10 a moderate risk, and 6 a low risk. The most common reasons for a high risk of bias were lack of an adequate sequence generation and/or allocation, and inadequate information on study funders. In many cases, information provided on those criteria was insufficient.

Weight

Thirty-two data sets from 19 studies included in this review provided data on weight in infants, children, and adolescents related to iron supplementation. These studies evaluated data on 4,830 participants, 2,419 of whom received iron and 2,411 of whom constituted the control group. Duration of interventions varied from 6 weeks to 12 months. For further details on the characteristics of included studies, see Table 1.

The forest plot of weight response to iron intervention is shown in Figure 2. According to the results of the meta-analysis, the overall pooled estimate was 0.00 (95%

Table 1 **Summary of main characteristics and main results of included randomized control trials assessing anthropometric parameters in infants, children, and adolescents.**

Reference	Country	Population characteristics (no. of subjects, description, age group)	Intervention treatment[a] (no. of subjects at start/end of study)	Control treatment (no. of subjects at start/end of study)	Duration of intervention	Outcomes	Risk of bias
Aguayo (2000)[30]	Bolivia	Nonanemic children 6–11.9 yrs of age ($n = 73$)	Ferrous sulfate 3 mg/kg/bw ($n = 37/33$)	Placebo ($n = 36/31$)	18 wks	Height, weight, MAC	Moderate
Angeles et al. (1993)[19]	Jakarta	Anemic children 2–5 yrs of age ($n = 80$)	Ferrous sulfate 30 mg/d + 20 mg vitamin C ($n = 40/39$)	20 mg vitamin C ($n = 40/37$)	2 mos	Height, weight	Moderate
Bhatia & Seshadri (1993)[31]	India	Anemic & nonanemic children 3–5 yrs of age ($n = 156$)	Elemental iron 40 mg/d ($n = 84/84$)	Placebo ($n = 72/72$)	6 mos	Height, weight, MAC	High
Chwang et al. (1988)[32]	Indonesia	Anemic & nonanemic children 8.2–13.5 yrs of age ($n = 119$)	Ferrous sulfate 2 mg/kg/d ($n = 59/59$)	Placebo ($n = 60/60$)	12 wks	Height, weight, MAC	Moderate
Dossa et al. (2001)[33]	Benin	Stunted, anemic children 1.5–2.5 yrs of age ($n = 154$)	1st group: ferrous fumarate 66 mg/d ($n = 37/35$) 2nd group: ferrous fumarate + multivitamins 66 mg/d ($n = 40/39$)	1st group: placebo ($n = 39/39$ 2nd group: multivitamins ($n = 38/37$)	6 wks	Height, weight, MAC	High
Idjradinata et al. (1994)[26]	Indonesia	Iron-sufficient children 12–18 mos of age ($n = 47$)	Ferrous sulfate 3 mg/kg/d ($n = 24/22$)	Placebo ($n = 23/22$)	4 mos	Height, weight, MAC	Moderate
Lawless et al. (1994)[34]	Kenya	Anemic children 6–11 yrs of age ($n = 86$)	Ferrous sulfate 30 mg/d ($n = 44/44$)	Placebo ($n = 42/42$)	14 wks	Height, weight	Moderate
Longfils et al. (2008)[35]	Cambodia	Anemic subjects 9–21 yrs of age ($n = 140$)	1st group: ferrous sulfate + citrate 10 mg elemental iron ($n = 47/48$) 2nd group: NaFeEDTA 10 mg elemental iron ($n = 47/48$)	Placebo ($n = 45/46$)	21 wks	Height, weight	High
Mwanri et al. (2000)[36]	Tanzania	Anemic children 9–12 yrs of age ($n = 36$)	1st group: ferrous sulfate 40 mg 3×/wk + retinyl acetate ($n = 34/34$) 2nd group: ferrous sulfate 40 mg/d ($n = 34/374$)	1st group: retinyl acetate ($n = 34/34$ 2nd group: placebo ($n = 34/34$)	12 wks	Height, weight	Low
Palupi et al. (1997)[37]	Indonesia	Anemic & nonanemic children 2–5 yrs of age ($n = 299$)	Ferrous sulfate 30 mg/d ($n = 96/96$)	Placebo ($n = 98/98$)	9 wks	Height, weight	High
Rosado et al. (1997)[21]	Mexico	Anemic & nonanemic children 18–36 mos of age ($n = 108$)	Ferrous sulfate 20 mg/d ($n = 53/53$)	Placebo ($n = 55/55$)	12 mos	Height, weight, MAC	Moderate
Sungthong et al. (2002)[38]	Thailand	Anemic & nonanemic children 6–13 yrs of age ($n = 397$)	1st group: ferrous sulfate 60 mg 5×/wk ($n = 140/139$) 2nd group: ferrous sulfate 60 mg/wk ($n = 134/130$)	Placebo ($n = 123/122$)	16 wks	Height, weight	Low
Berger et al. (2006)[39]	Vietnam	Nonanemic, breastfed infants 4–7 mos of age ($n = 915$)	1st group: ferrous sulfate 10 mg/d 2nd group: iron 10 mg/d + zinc 10 mg/d	1st group: placebo 2nd group: zinc 10 mg/d	6 mos	Height, weight	Low
Dewey et al. (2002)[25]	Honduras, Sweden	Nonanemic, breastfed infants 4 mos of age ($n = 148$)	1st group: elemental iron 1 mg/kg/d Honduras, 4–9 mos 2nd group: Fe 1 mg/kg/d Sweden, 4–9 mos	1st group: placebo, Honduras 2nd group: placebo, Sweden	5 mos	HC	High
Dijkhuizen et al. (2001)[40]	Indonesia	Nonanemic infants 4 mos of age ($n = 478$)	1st group: iron 10 mg/d 2nd group: iron 10 mg/d + zinc 10 mg/d	1st group: placebo 2nd group: zinc 10 mg/d	6 mos	Height, weight	Low
Fischer Walker et al. (2009)[41]	Bangladesh	Nonanemic, breastfed infants 6 mos of age ($n = 645$)	1st group: elemental iron 20 mg/wk 2nd group: iron 20 mg/wk + zinc 20 mg/wk	1st group: placebo 2nd group: zinc 20 mg/wk	6 mos	MAC	High
Lind et al. (2004)[42]	Indonesia	Healthy infants, 40% anemic (Hb < 110 g/L), 8% anemic (Hb < 110 g/L + ferritin <12 µg/L) 6 mos of age ($n = 680$)	1st group: iron (ferrous sulfate) 10 mg/d 2nd group: iron 10 mg/d + zinc 10 mg/d	1st group: placebo 2nd group: zinc 10 mg/d	6 mos	MAC	Low
Smuts et al. (2005)[43] Corresponding study: de Romana et al. (2005)[44]	Indonesia, Peru, South Africa, Vietnam	Healthy infants, majority of whom were anemic 6–12 mos of age ($n = 571$)	Iron (elemental iron) 10 mg/d	Placebo	6 mos	Height, weight	Moderate
Wasantwisut et al. (2006)[45]	Thailand	Nonanemic infants 4–6 mos of age ($n = 675$)	1st group: iron (ferrous sulfate) 10 mg/d 2nd group: iron 10 mg/d + zinc 10 mg/d	1st group: placebo 2nd group: zinc 10 mg/d	6 mos	Height, weight	High
Yalçin et al. (2000)[46]	Turkey	Nonanemic infants 6 mos of age ($n = 24$)	Iron (ferrous sulfate) 1 mg/kg/d	Placebo	3 mos	Height, weight, HC	High
Ziegler et al. (2009)[47]	United States	Nonanemic, breastfed infants 4 mos of age ($n = 152$)	1st group: ferrous sulfate 7.5 mg/d 2nd group: ferrous sulfate 7 mg/d	Placebo	5 mos	Height, weight	High

[a] All dosages represent amount of elemental iron, regardless of the form of the iron supplement.
Abbreviations: bw, body weight; HC, head circumference; MAC, mid-arm circumference.

Table 2 **Summary of main characteristics and main results of included randomized control trials assessing birth weight and length of gestation in pregnant women.**

Reference	Country	Population characteristics and age group (no. of subjects)	Intervention treatment (no. of subjects at start/ end of study)	Control treatment (no. of subjects at start/ end of study)	Duration of intervention	Outcomes	Risk of bias
Cogswell et al. (2003)[11]	United States	Iron group: 24.3 ± 5.31 yrs; placebo group: 24.5 ± 5.1 yrs ($n = 275$)	Ferrous sulfate 30 mg/d ($n = 117/146$)	Placebo ($n = 96/129$)	26 wks	Length of gestation, birth weight	Low
Siega-Riz et al. (2006)[12]	Not stated	19–24 yrs ($n = 429$)	Ferrous sulfate 30 mg/ d + multivitamins ($n = 173/218$) ($n = 166/218$)	Multivitamins ($n = 172/211$) ($n = 168/211$)	14 wks	Length of gestation, birth weight	Moderate
Makrides et al. (2003)[13]	Australia	Iron group: 28.5 ± 5.0 yrs; control group: 28.0 ± 5.0 yrs ($n = 430$)	Ferrous sulfate 20 mg/d ($n = 216/216$)	Placebo ($n = 214/214$)	20 wks	Length of gestation, birth weight	Moderate
Ziaei et al. (2007)[14]	Iran	Iron group: 25.7 ± 4.6 yrs; control group: 25.7 ± 4.5 yrs ($n = 727$)	Ferrous sulfate 50 mg/d ($n = 370/375$)	Placebo ($n = 357/375$)	24 wks	Length of gestation	Moderate
Chan et al. (2009)[48]	China	31.3 ± 0.19 yrs ($n = 1,164$)	Ferrous sulfate 60 mg/d ($n = 392/565$)	Placebo ($n = 413/599$)	20 wks	Length of gestation	High
Milman (1994)[49]	Denmark	Age NA ($n = 120$)	Ferrous sulfate 66 mg/d ($n = 63/63$)	Placebo ($n = 57/57$)	24 wks	Birth weight	High
Paintin et al. (1966)[50]	United Kingdom	Iron group: 23.7 ± 2.9 yrs; control group: 23.9 ± 3.5 yrs ($n = 117$)	Iron aminoates 12 mg/d ($n = 60/60$)	Placebo ($n = 57/57$)	16 wks	Birth weight	High

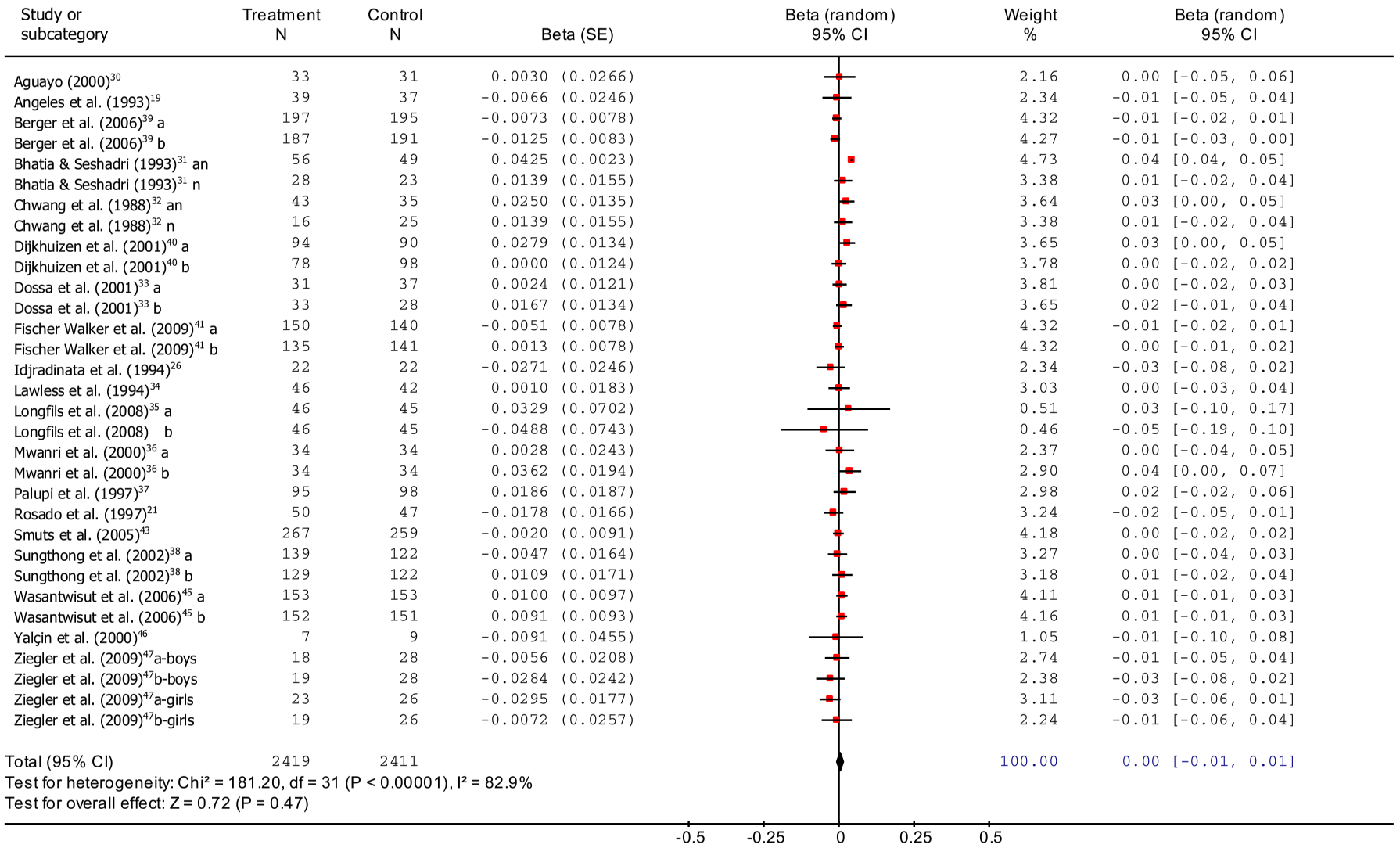

Figure 2 **Forest plot of the effect of iron supplementation on weight in infants, children, and adolescents.**
Abbreviations: an, anemic children; CI, confidence interval; n, nonanemic children; RCT, randomized control trial; SE, standard error; a, first intervention group; b, second intervention group. For details see Table 1.

CI −0.01, 0.01), demonstrating no significant effect of iron supplementation on weight in infants, children, and adolescents ($P = 0.47$). Test for heterogeneity among studies, describing the percentage of variation across the RCTs included, showed a large heterogeneity among the study groups, as shown by the I-squared statistic ($I^2 = 82.9\%$). Thus, studies were stratified according to dose of supplemental iron, age of participants, duration of intervention, and baseline characteristics of participants (anemic or nonanemic) to perform a sensitivity analysis. The results are summarized in Table 3.

Grouping estimates revealed that a small but significant effect of iron supplementation on weight was found in studies that used 40–66 mg/d elemental iron for supplementation (overall pooled β 0.02, 95% CI 0.00–0.03, $P = 0.02$, $I^2 = 71.3\%$), in studies with a duration of up to 12 weeks (overall β 0.01, 95% CI 0.00–0.03, $P = 0.01$, $I^2 = 0\%$), and in studies conducted in children ≥6 years of age (overall β 0.01, 95% CI 0.00–0.02, $P = 0.05$, $I^2 = 0\%$). It was difficult to stratify the studies according to baseline iron status, since most of the studies were carried out in both anemic and nonanemic children. Nevertheless, it was possible to extract 10 studies conducted in anemic children only (Table 3).

Height

The same 32 data sets that were included in the meta-analysis on the effect of iron supplementation on weight were also available for analysis of height in infants, children, and adolescents. The obtained results are displayed in Figure 3. They also indicate no influence of iron supplementation on height. The total pooled β was 0.00 (95% CI −0.00, 0.00) and test for heterogeneity revealed low heterogeneity among studies ($I^2 = 24.2\%$); thus, stratified analysis did not need to be performed.

Mid-arm circumference

A total of eight studies (with 13 data sets) were available for this analysis, including 1,830 children, of whom 925 received an oral iron supplement and 905 received a placebo. The duration of intervention ranged between 6 weeks and 6 months. The results of the meta-analysis of the effect of iron supplementation on MAC showed no significant relationship (Figure 4). Namely, the total pooled β was 0.00, with the 95% CI interval ranging from 0.00 to 0.01. A wide heterogeneity ($I^2 = 80.2\%$) was found across studies. Similar to the findings on weight, stratification of studies did not significantly change the results presented, and only doses of 40–66 mg of elemental iron per day, studies in children >6 years of age, and studies in anemic children showed a small but significant effect on MAC (Table 3).

Head circumference

Head circumference was measured only in infants, and only two studies with three intervention groups measuring this parameter were included in this analysis. These studies included 164 infants, 77 of whom were given iron and 87 of whom received placebo, and the duration of supplementation was 3–5 months. As shown in Figure 5, there was no significant difference in the change of the head circumference between the intervention and the control groups (overall β 0.00, 95% CI −0.01–0.01), with heterogeneity of $I^2 = 34.8\%$.

Weight at birth

Information on birth weight was available for 1,941 newborns born to 992 women who received iron during pregnancy and to 949 women in the control group (Table 2). The forest plot of the birth weight of newborns born to mothers who received daily iron intervention during pregnancy is shown in Figure 6. Pooling data from the six RCTs into one meta-analysis yielded a β random effect of 0.01 (95% CI −0.03–0.04). No significant effect was found. Due to the large heterogeneity ($I^2 = 83\%$), a subgroup analysis was performed according to the dose of supplemented iron and the duration of intervention; the resulting heterogeneity was relatively small and was found only for the highest doses of iron (Table 3).

Length of gestation

The forest plot for the overall effect of iron on length of gestation is shown in Figure 7. The primary analysis of the five trials suggested that routine daily iron supplementation during pregnancy ($n = 1{,}295$) did not exert any control on the length of gestation when compared with placebo ($n = 1{,}282$), an overall β effect of 0.00 (95% CI −0.00–0.00). The test for heterogeneity revealed no significant heterogeneity among the studies ($I^2 = 18\%$).

DISCUSSION

This systematic review with meta-analysis has documented no convincing evidence of beneficial effects of iron supplementation on the physical growth of fetuses, infants, children, or adolescents. RCTs on subjects from birth to 18 years of age were conducted on 7,574 subjects, 4,208 of whom received supplemental iron. The results showed a large heterogeneity across the included studies, for weight and MAC in particular. Thus, studies were stratified on a priori defined, potentially modifying factors. In some cases, this led to decreased heterogeneity in some of the subgroups, but considerable heterogeneity

Table 3 **Selected results from meta-analysis of iron supplementation and growth parameters in infants, children, adolescents, and pregnant women stratified by dose of supplemented iron, duration of supplementation, age of participants, and baseline iron status.**

Stratum for analysis	Weight (infants, children, adolescents)			MAC (infants, children, adolescents)			Birth weight (pregnant women)		
	No. of estimates (no. of participants)	Pooled effect size (β [95%CI])	Heterogeneity (I^2)	No. of estimates (no. of participants)	Pooled effect size (β [95%CI])	Heterogeneity (I^2)	No. of estimates (no. of participants)	Pooled effect size (β [95%CI])	Heterogeneity (I^2)
All studies	32 (4,830)	0.00 [−0.01, 0.01]	83%	13 (1,830)	0.00 [0.00, 0.01]	80.2%	6 (1,941)	0.01 [−0.01, 0.03]	68%
Dose									
≤10 mg	15 (2,901)	0.00 [−0.01, 0.01]	5.7%	2 (655)	NA	NA	0	NA	NA
11–30 mg	7 (1,064)	0.00 [−0.01, 0.01]	0	4 (707)	0.00 [−0.01, 0.01]	0	4 (1,094)	0.02 [−0.02, 0.06]	70%
40–66 mg	10 (865)	0.02* [0.00, 0.03]	71.3%	7 (468)	0.01** [0.00, 0.02]	55.5%	2 (847)	−0.00 [−0.02, 0.01]	26%
Duration of supplementation[a]									
≤12 wks, I,C,A ≤20 wks, PW	8 (653)	0.01** [0.00, 0.03]	0	4 (248)	0.01 [0.00, 0.01]	0	3 (881)	0.01 [−0.03, 0.05]	58%
>12 wks, I,C,A >20 wks, PW	24 (4,177)	0.00 [−0.01, 0.01]	86.8%	9 (1,582)	0.00 [−0.01, 0.01]	85.2%	3 (1,060)	0.01 [−0.02, 0.05]	81%
Age									
0–12 mos	14 (3,034)	0.00 [−0.01, 0.00]	7.4%	4 (1,221)	0.00 [−0.01, 0.02]	1.4%	NA	NA	NA
1–5.99 yrs	8 (695)	0.01 [−0.01, 0.03]	82.5%	6 (426)	0.01 [−0.01, 0.03]	73.8%	NA	NA	NA
≥6 yrs	10 (1,101)	0.01* [0.00, 0.02]	0	3 (183)	0.01* [0.00, 0.02]	0	NA	NA	NA
Iron status									
Anemic	10 (1,259)	0.01 [−0.01, 0.03]	79.3%	3 (251)	0.01* [0.00, 0.02]	70.6%	NA	NA	NA
Nonanemic or mixed population	22 (3,531)	0.00 [−0.01, 0.01]	12.4%	10 (1,579)	0.00 [−0.01, 0.01]	18.2%	NA	NA	NA

* $P < 0.05$ (test for overall effect).
** $P < 0.01$ (test for overall effect).
[a] Duration of supplementation used for stratification was as follows: ≤12 weeks or >12 weeks in infants, children, and adolescents, and ≤20 weeks or >20 weeks in pregnant women.
Abbreviations: CI, confidence interval; I,C,A, infants, children, and adolescents; MAC, mid-arm circumference; NA, not applicable; PW, pregnant women.

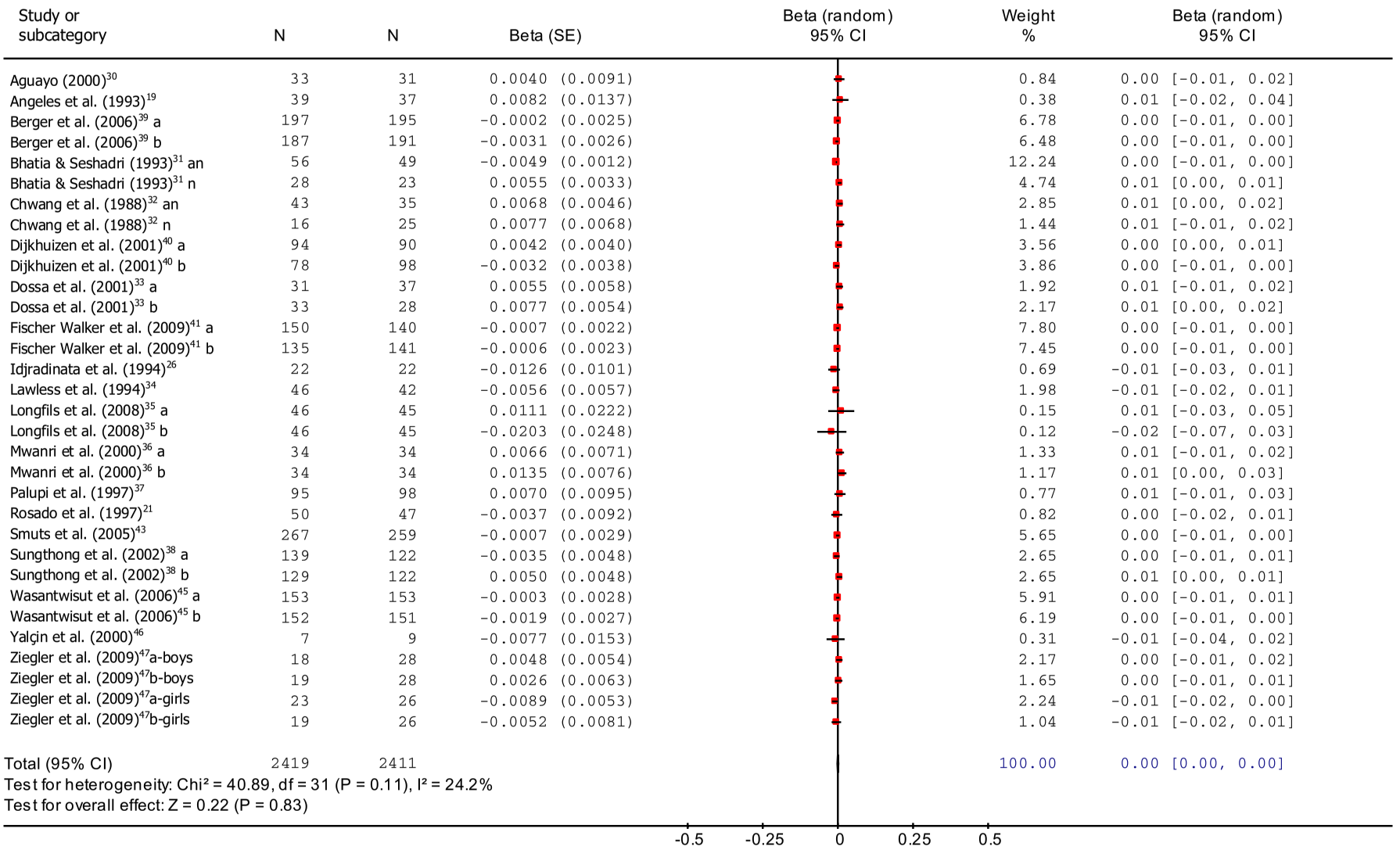

Figure 3 **Forest plot of the effect of iron supplementation on height in infants, children, and adolescents.**
Abbreviations: an, anemic children; CI, confidence interval; n, nonanemic children; SE, standard error; randomized control trial; a, first intervention group; b, second intervention group. For details see Table 1.

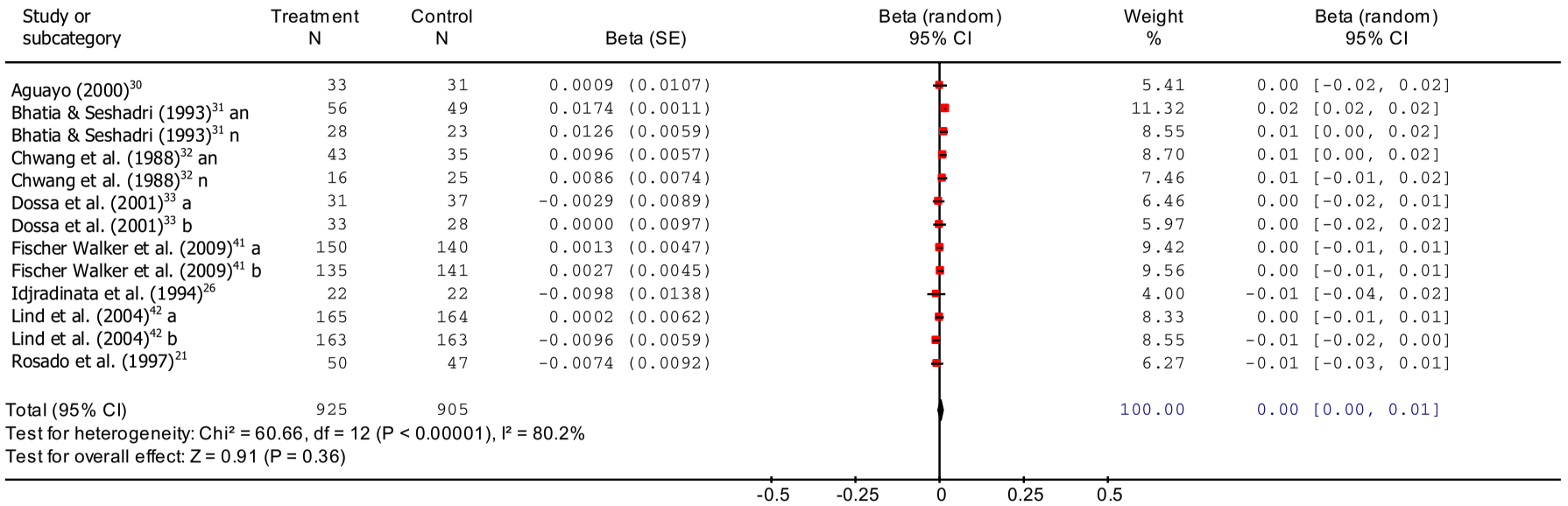

Figure 4 **Forest plot of the effect of iron supplementation on mid-arm circumference in infants, children, and adolescents.**
Abbreviations: an, anemic children; CI, confidence interval; n, nonanemic children; SE, standard error; a, first intervention group; b, second intervention group. For details see Table 1.

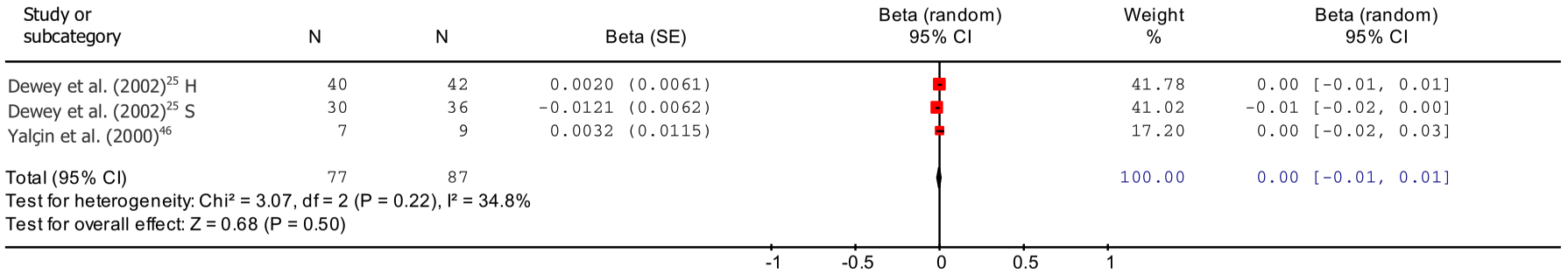

Figure 5 **Forest plot of the effect of iron supplementation on head circumference in infants.**
Abbreviations: CI, confidence interval; H, Honduras; S, Sweden; SE, standard error.

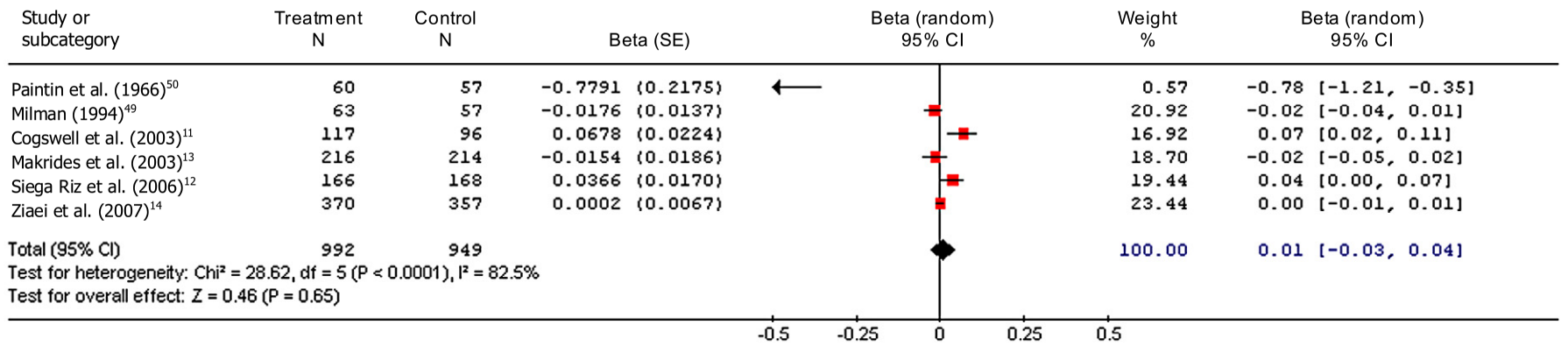

Figure 6 **Forest plot of the effects on neonatal birth weight of iron supplementation administered to iron-replete mothers during pregnancy.**
Abbreviations: CI, confidence interval; SE, standard error.

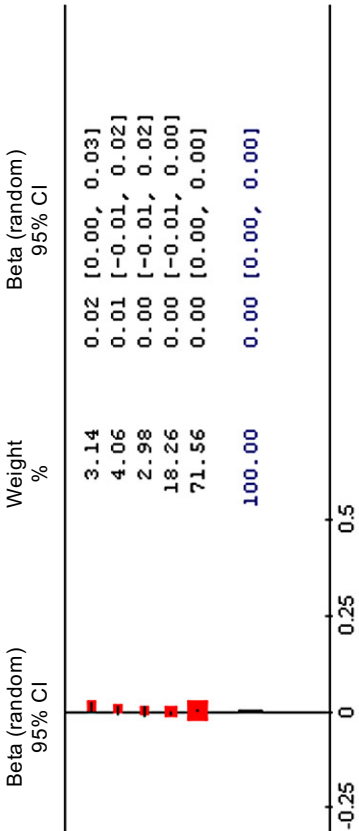

Figure 7 **Forest plot of the effects on length of gestation of iron supplementation administered to iron-replete mothers during pregnancy.**
Abbreviations: CI, confidence interval; SE, standard error.

remained. Moreover, the effect estimates were unaffected and, after stratification, remained around 0 as well. Stratification of studies on height across age, baseline iron status, dose of supplemental iron, or duration of studies showed no effect of iron on height (data not shown). A small but significant effect of iron on weight and MAC in children 0–18 years of age was found only for doses of 40–66 mg of elemental iron per day. Since a base *e* logarithmic transformation on the iron intake and parameters of growth was applied, the overall β value represents the difference in the ln-transformed predicted value of weight for each one-unit difference in the ln-transformed value in iron intake. An overall β of 0.02 from pooling of trials on children supplemented with 40–66 mg iron daily means that for every one-unit difference in iron intake (a multiplication of the constant *e*), the difference in weight is e^{β} (= $e^{0.02}$ = 1.02), which is 2%. This means, for example, that a child with an iron intake of approximately 40 mg/day has a weight that is 2% higher than one who has an iron intake of approximately 14.7 mg/day.

Furthermore, the pooled estimate was significant for a study duration of ≤12 weeks and for children ≥6 years of age, but here it should be noted that these studies are mostly the same as those that used doses 40–66 mg of iron for intervention, so it is possible that it was the effect of the dose, rather than the age of participants. The results of the meta-analysis on anemic children showed a slight impact of iron supplementation on MAC only. Since only three studies used supplements other than ferrous sulfate, it was not possible to assess the impact of the other types of supplement, and exclusion of these studies from the meta-analysis (i.e., inclusion of only studies using ferrous sulfate) did not change the results. These data suggest that duration of supplementation, baseline iron status, and the type of supplement do not influence the effect of iron on physical growth. Dose of supplemental iron is probably an important factor, judging by the results.

As for infants, children, and adolescents, no significant increase of either the weight at birth or the length of gestation in response to iron supplementation was detected through the meta-analysis. These results are in line with the results provided by the original RCTs. The majority of the studies could at most show a positive trend for both birth weight and gestational length after iron supplementation, with percentages of the adverse outcomes lower among pregnant women supplied with iron than among those belonging to the control groups. Only two RCTs found a significant difference in the outcomes of interest between iron-supplemented pregnant women and the control group: Cogswell et al.[11] found that both the birth weight of newborns ($P = 0.01$) and the length of gestation ($P = 0.049$) were significantly higher in iron-supplemented women than in women taking

placebo; Siega-Riz et al.[12] measured a significantly higher ($P = 0.03$) birth weight after iron supplementation.

Even if prophylactic prenatal iron supplementation is recommended in many countries and effectiveness on iron status is recognized, some concerns exist about a lack of adequate benefit of this approach in iron-sufficient women.[7,51,52] There was an overall lack of studies that were specifically designed to determine the real benefits of routine iron supplementation in iron-replete pregnant women. In this context, RCTs that included anemic women or that supplied elemental iron $\geq$100 mg/day were excluded. In addition, the number of available trials supplying low doses of iron was insufficient to run a meta-analysis by different doses in order to quantify their effect. Moreover, there were no relevant RCTs found that evaluated the effects on pregnancy outcomes of iron supplementation started in the second half of gestation, even though the timing of maternal nutritional intake and status may impact embryonal/fetal organ development specifically and differently.[53] Thus, the time of initiation and the dose of prenatal supplementation are important issues to be considered. In addition, only limited information related to clinical maternal and infant outcomes was found. The lack of this information does not allow critical evaluation of the clinical effectiveness of routine iron supplementation.

The results presented here are in line with those of two other systematic reviews, which also concluded that iron intervention had no significant effect on growth in children, even after stratification across age, duration of supplementation, dosage of supplemental iron, and baseline iron or anthropometric status.[17,54] Although several studies were included in this review as well as in the other two reviews, the present review considers updated references as well, while some studies included in the other two reviews were excluded from the search in this review due to the presence of malaria or the other severe diseases in the study population. Unlike the present review, the review of Sachdev et al.[17] focused on weight-for-age, weight-for-height, and height-for-age parameters, and none of the other systematic reviews included pregnant women, e.g., fetal growth. Furthermore, in this review, estimation of the slope of the dose-response relationship was attempted for the first time by calculating an overall pooled estimate.

The influence of iron on the physical growth of fetuses, infants, and children can be modified by many other factors, e.g., low socioeconomic status, energy and micronutrient inadequacy, iron bioavailability, and the presence of infections. These factors were often present in the studies included in this review. Studies varied with respect to the dietary data available: in several studies, dietary intake was not reported or the assessment method was not validated in low-income populations.[55] It is worthwhile to note that diet composition could markedly influence iron bioavailability, and therefore the potential effect of differences in bioavailability can also be a confounding factor. Because of the adverse effects of disease on iron status, all studies in subjects with malaria or other severe diseases were excluded; however, hookworm infections were the rule rather than the exception in the included trials. In all studies that reported parasitic infections in participants, a deworming treatment was applied before intervention to eliminate the possible effects of hookworm infections on the results obtained.

The strengths of this review include the selection of data from double-blind RCTs and from different vulnerable population groups as well as the comprehensive evaluation of the methodological quality of the studies included. All RCTs included in this review had a placebo group, ensuring that all effects can be attributed to iron. An important limitation of this review is the quality of the RCTs included, since only 6 of 28 studies were of a high quality, as assessed using the recommended criteria. The exclusion of studies with a high or moderate risk of bias made it impossible to perform a meta-analysis of MAC or head circumference or in pregnant women; nevertheless, even after the exclusion of all such studies, the results of meta-analysis of height and weight in infants and children remained unchanged.

CONCLUSION

In summary, the meta-analyses presented here demonstrate that iron supplementation did not exert a significant beneficial effect on the overall physical growth of fetuses, infants, children, or adolescents. A slight effect was found only on weight and MAC in children supplemented with 40–66 mg of iron. No effect in fetuses or infants was detected, even after stratification across baseline iron status, dose, and duration of supplementation.

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REFERENCES

1. Asobayire FS, Adou P, Davidsson L, et al. Prevalence of iron deficiency with and without concurrent anemia in population groups with high prevalences of malaria and other infections: a study in Cote d'Ivoire. Am J Clin Nutr. 2001;74:776–782.
2. World Health Organization. *Worldwide prevalence of anaemia 1993–2005*. Global Database on Anaemia. Geneva, Switzerland. 2008; Available at: http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf. Accessed 24 March 2013.
3. Clark SF. Iron deficiency anemia. Nutr Clin Pract. 2008;23:128–141.
4. Ferrara M, Coppola L, Coppola A, et al. Iron deficiency in childhood and adolescence: retrospective review. Hematology. 2006;11:183–186.
5. Iglesia I, Doets EL, Bel-Serrat S, et al. Physiological and public health basis for assessing micronutrient requirements in children and adolescents. The EURRECA network. Matern Child Nutr. 2010;6:84–99.
6. Leung AK, Chan KW. Iron deficiency anemia. Adv Pediatr. 2001;48:385–408.
7. Allen LH. Anemia and iron deficiency: effects on pregnancy outcome. Am J Clin Nutr. 2000;71(Suppl 5):S1280–S1284.
8. Ronnenberg AG, Wood RJ, Wang X, et al. Preconception hemoglobin and ferritin concentrations are associated with pregnancy outcome in a prospective cohort of Chinese women. J Nutr. 2004;134:2586–2591.
9. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Cochrane Database Syst Rev. 2009;(4):CD004736.
10. Casanueva E, Viteri FE. Iron and oxidative stress in pregnancy. J Nutr. 2003;133(Suppl 5 2):S1700–S1708.
11. Cogswell ME, Parvanta I, Ickes L, et al. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. Am J Clin Nutr. 2003;78:773–781.
12. Siega-Riz AM, Hartzema AG, Turnbull C, et al. The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. Am J Obstet Gynecol. 2006;194:512–519.
13. Makrides M, Crowther CA, Gibson RA, et al. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. Am J Clin Nutr. 2003;78:145–153.
14. Ziaei S, Norrozi M, Faghihzadeh S, et al. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin ≥13.2 g/dl. BJOG. 2007;114:684–688.
15. Owen GM, Lubin AH, Garry PJ. Preschool children in the United States: who has iron deficiency? J Pediatr. 1971;79:563–568.
16. Rao MR, Hediger ML, Levine RJ, et al. Effect of breastfeeding on cognitive development of infants born small for gestational age. Acta Paediatr. 2002;91:267–274.
17. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on physical growth in children: systematic review of randomised controlled trials. Public Health Nutr. 2006;9:904–920.
18. Aukett MA, Parks YA, Scott PH, et al. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child. 1986;61:849–857.
19. Angeles IT, Schultink WJ, Matulessi P, et al. Decreased rate of stunting among anemic Indonesian preschool children through iron supplementation. Am J Clin Nutr. 1993;58:339–342.
20. Morais MB, Ferrari AA, Fisberg M. Effect of oral iron therapy on physical growth. Rev Paul Med. 1993;111:439–444.
21. Rosado JL, Lopez P, Munoz E, et al. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. Am J Clin Nutr. 1997;65:13–19.
22. Daly A, MacDonald A, Aukett A, et al. Prevention of anaemia in inner city toddlers by an iron supplemented cows' milk formula. Arch Dis Child. 1996;75:9–16.
23. Moffatt ME, Longstaffe S, Besant J, et al. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomized clinical trial. J Pediatr. 1994;125:527–534.
24. Morley R, Abbott R, Fairweather-Tait S, et al. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial. Arch Dis Child. 1999;81:247–252.
25. Dewey KG, Domellof M, Cohen RJ, et al. Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. J Nutr. 2002;132:3249–3255.
26. Idjradinata P, Watkins WE, Pollitt E. Adverse effect of iron supplementation on weight gain of iron-replete young children. Lancet. 1994;343:1252–1254.
27. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.2 [updated September 2009]. Oxford, UK: The Cochrane Collaboration; 2009; Available at: http://www.cochrane-handbook.org. Accessed 24 March 2013.
28. Hermoso M, Vucic V, Vollhardt C, et al. The effect of iron on cognitive development and function in infants, children and adolescents: a systematic review. Ann Nutr Metab. 2011;59:154–165.
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188.
30. Aguayo VM. School-administered weekly iron supplementation – effect on the growth and hemoglobin status of non-anemic Bolivian school-age children. A randomized placebo-controlled trial. Eur J Nutr. 2000;39:263–269.
31. Bhatia D, Seshadri S. Growth performance in anemia and following iron supplementation. Indian Pediatr. 1993;30:195–200.
32. Chwang LC, Soemantri AG, Pollitt E. Iron supplementation and physical growth of rural Indonesian children. Am J Clin Nutr. 1988;47:496–501.
33. Dossa RA, Ategbo EA, de Koning FL, et al. Impact of iron supplementation and deworming on growth performance in preschool Beninese children. Eur J Clin Nutr. 2001;55:223–228.
34. Lawless JW, Latham MC, Stephenson LS, et al. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr. 1994;124:645–654.
35. Longfils P, Monchy D, Weinheimer H, et al. A comparative intervention trial on fish sauce fortified with NaFe-EDTA and FeSO4+citrate in iron deficiency anemic school children in Kampot, Cambodia. Asia Pac J Clin Nutr. 2008;17:250–257.
36. Mwanri L, Worsley A, Ryan P, et al. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. J Nutr. 2000;130:2691–2696.
37. Palupi L, Schultink W, Achadi E, et al. Effective community intervention to improve hemoglobin status in preschoolers receiving once-weekly iron supplementation. Am J Clin Nutr. 1997;65:1057–1061.
38. Sungthong R, Mo-Suwan L, Chongsuvivatwong V, et al. Once weekly is superior to daily iron supplementation on height gain but not on hematological improvement among schoolchildren in Thailand. J Nutr. 2002;132:418–422.
39. Berger J, Ninh NX, Khan NC, et al. Efficacy of combined iron and zinc supplementation on micronutrient status and growth in Vietnamese infants. Eur J Clin Nutr. 2006;60:443–454.
40. Dijkhuizen MA, Wieringa FT, West CE, et al. Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. J Nutr. 2001;131:2860–2865.
41. Fischer Walker CL, Baqui AH, Ahmed S, et al. Low-dose weekly supplementation of iron and/or zinc does not affect growth among Bangladeshi infants. Eur J Clin Nutr. 2009;63:87–92.
42. Lind T, Lonnerdal B, Stenlund H, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. Am J Clin Nutr. 2004;80:729–736.
43. Smuts CM, Lombard CJ, Spinnler Benade AJ, et al. Efficacy of a foodlet-based multiple micronutrient supplement for preventing growth faltering, anemia, and micronutrient deficiency of infants: the four country IRIS trial pooled data analysis. J Nutr. 2005;135:S631–S638.
44. Lopez De Romana G, Cusirramos S, Lopez De Romana D, et al. Efficacy of multiple micronutrient supplementation for improving anemia, micronutrient status, growth, and morbidity of Peruvian infants. J Nutr. 2005;135:S646–S652.
45. Wasantwisut E, Winichagoon P, Chitchumroonchokchai C, et al. Iron and zinc supplementation improved iron and zinc status, but not physical growth, of apparently healthy, breast-fed infants in rural communities of northeast Thailand. J Nutr. 2006;136:2405–2411.
46. Yalçin SS, Yurdakok K, Acikgoz D, et al. Short-term developmental outcome of iron prophylaxis in infants. Pediatr Int. 2000;42:625–630.
47. Ziegler EE, Nelson SE, Jeter JM. Iron status of breastfed infants is improved equally by medicinal iron and iron-fortified cereal. Am J Clin Nutr. 2009;90:76–87.

48. Chan KK, Chan BC, Lam KF, et al. Iron supplement in pregnancy and development of gestational diabetes – a randomised placebo-controlled trial. BJOG. 2009;116:789–797.
49. Milman N, Agger AO, Nielsen OJ. Iron status markers and serum erythropoietin in 120 mothers and newborn infants. Effect of iron supplementation in normal pregnancy. Acta Obstet Gynecol Scand. 1994;73:200–204.
50. Paintin DB, Thomson AM, Hytten FE. Iron and haemoglobin level in pregnancy. J Obstet Gynaecol Br Commonw. 1966;73:181–190.
51. Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. Am J Clin Nutr. 2000;71(Suppl 5):S1288–S1294.
52. Berti C, Biesalski HK, Gartner R, et al. Micronutrients in pregnancy: current knowledge and unresolved questions. Clin Nutr. 2011;30:689–701.
53. Berti C, Decsi T, Dykes F, et al. Critical issues in setting micronutrient recommendations for pregnant women: an insight. Matern Child Nutr. 2010;6(Suppl 2):S5–S22.
54. Ramakrishnan U, Aburto N, McCabe G, et al. Multimicronutrient interventions but not vitamin A or iron interventions alone improve child growth: results of 3 meta-analyses. J Nutr. 2004;134:2592–2602.
55. Vucic V, Glibetic M, Novakovic R, et al. Dietary assessment methods used for low-income populations in food consumption surveys: a literature review. Br J Nutr. 2009;101(Suppl 2):S95–S101.