The effect of iron on cognitive development and function in infants, children and adolescents: a systematic review

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Short title: Iron and cognitive development and function in infants, children and adolescents

Abstract

A systematic review was conducted to summarize the evidence currently available from randomised controlled trials (RCT) concerning the effect of iron intake of infants, children and adolescents on measures of cognitive development and function. The Cochrane Library, MEDLINE and EMBASE were searched up to and including February 2010. Studies were also identified by checking the bibliographies of the articles retrieved. All RCTs with an adequate control group in which iron supply was provided by natural food sources, fortified foods, formula, or supplements to infants, children, or adolescents until the age of 18 years were considered for inclusion. No language restrictions were applied. Twelve studies met the selection criteria. Ten out of twelve studies had a high or moderate risk of bias. A large variety of outcomes was reported. Overall, the studies suggest a modest positive effect of iron supplementation on cognition and psychomotor outcomes in anemic infants and children after supplementation periods of at least 2 months of duration.

Abbreviations: BRS, behavioural rating scale; BSID, Bayley scales of infant development; BTA, brief test of attention; CGI-S, clinical global impression- severity; CPRS, Conner's parent rating scale; CTRS, Conner's teacher rating scale; EURRECA, European recommendations aligned; HVLT, Hopkins verbal learning test; ID, iron deficiency; IDA, iron deficiency anemia; IQ, intellectual intelligence quotient; MDI, mental development index; NAID, non anemic iron deficient; PDI, psychomotor development index; RCT, randomised controlled trial; SDMT, symbol digit modalities test; VSAT, visual search and attention test.

INTRODUCTION

During the first year of life, the body iron content increases markedly. In healthy term infants, iron stores at birth comprise most of the iron requirements for the first 4–6 months. From the 4th month, the requirement for dietary iron increases to an estimated 0.78 mg/day due to the stepwise depletion of endogenous stores and rapid growth with an expansion of blood volume and increased tissue and storage iron [15]. Rapid growth with high iron needs makes infants and young children a particular risk group for iron deficiency anemia (IDA), especially those aged 6-24 months [17]. Adolescents are another risk group for development of IDA because of rapid growth and increased iron demands during puberty. This is particularly true for adolescent girls due to menstrual losses[33; 15]. In addition to inadequate intake, factors which could influence iron status may include strenuous exercise, pregnancy, low socioeconomic status and ethnicity, as well as disease-induced malabsorption and chronic blood loss [6] or polymenorrhea in girls [10; 9]. Prevalence estimates of iron deficiency (ID) in adolescent girls range from 9% to 40%, depending on the population studied and the criteria used to define ID [5]. In children below 4 years of age the estimated prevalence of ID ranges from 20% in industrialized countries to 39% in non-industrialised countries [34]. Anaemia is considered to be a public health problem when the prevalence of low haemoglobin concentrations exceeds 5% in the population. The severity of the public health problem of anaemia is classified as mild (5.0–19.9%), moderate (20.0–39.9%) or severe (≥ 40%) according to the prevalence of anaemia in the population [33]. Worldwide, the estimated prevalence of IDA among preschool-aged children is 25%; 40% among schoolchildren, and 30–55% among adolescents [35]. The prevalence of ID and IDA in infants is difficult to assess. This is because rapid physiological changes of iron status occur during infancy, and there is no agreement on cut-off values of iron status indicators for ID and IDA.

ID and IDA can have a serious impact on infants' and children's health and later development: alteration of the immune status, adverse effects on morbidity, delayed behavioural and mental development, below average school achievements and growth retardation , as well as adverse effects on cognition that may or may not be reversible with iron treatment [14; 5]. However, although various studies have been performed using neurodevelopment outcome to assess iron requirement in infancy and childhood, results have been inconclusive. Different populations have been studied at different ages with different developmental tests, which makes it difficult to compare the studies [26]. Particular interest has been given to preschool and school children. Most observational studies in children have found a significant association between IDA and poor cognitive and motor development [11; 25] showing that IDA is associated with lower scores on testing of intelligence quotients. Children 9-11 years old with IDA

obtained significantly lower scores in a standardized educational achievement test than did iron-replete children[26]. It is not clear, however, whether the iron deficiency causes the delay or merely whether the two findings are associated evidence of an underprivileged environment. It is also possible that an early neurodevelopment insult caused by IDA may not result in detectable psychomotor delay during infancy, but symptoms such as deficits in attention and school performance may appear later, in older children, young adolescents and adults [26]. In the longest follow-up study to date, children identified at 12-23 months who had been treated for severe, chronic ID in infancy still showed differences associated with IDA 19-year-olds in Costa Rica comparing to their peers who had had good iron status at infancy[22].

There is increasing evidence that low iron status, as a systemic condition, adversely influences physiological functioning not only due to reduced haemoglobin synthesis, but also because of decreased activity of iron containing enzymes in the brain[4]. Since in ID iron appears to be preferentially channelled to hemoglobin synthesis, the brain may become iron depleted when intake is insufficient even if the individual is not yet anemic [4]. A number of animal studies show that ID changes the myelination of neurones, neurometabolism, neurotransmitters and gene/protein profiles before and after iron repletion at weaning [21]. Rodent studies show effects of ID during gestation and lactation that persist into adulthood despite restoration of iron status at weaning[8]. A lack of sufficient iron intake may significantly delay the development of the central nervous system as a result of alterations in morphology, neurochemistry, and bioenergetics [3].

The role that iron plays in the neurodevelopment of anemic and non anemic iron deficient (NAID) infants, children and adolescents is not fully understood. Effect of iron treatment on cognition was not observed in most trials of children <2 years of age with IDA, but it was observed in older children[24]. In children >2 y of age and in adolescents with IDA, evidence suggests beneficial effects of iron treatment on cognitive or behavioral function; however, the insufficient number of studies, often associated with different confounders, prevents a thorough assessment.

The EURopean RECcommendations Aligned (EURRECA) Network of Excellence attempts to consolidate the basis for the definition of micronutrient requirements across Europe, taking into account relationships among intake, status and health outcomes[1]. Systematic reviews are being conducted on those micronutrients that are deemed to be of major importance for certain population groups, following a standardised methodology. This paper aims to review data from all available RCTs which met EURRECA's quality standards, to ascertain the effect of iron intake on measures of cognitive development and function in infants, children, and adolescents.

METHODS

Search methods for identification of studies

MEDLINE, EMBASE (both on Ovid) and the Cochrane Library CENTRAL database were searched until February 2010. The search strategy included terms for "[study designs in humans] AND [intake or status] AND [iron]". Both indexing and text terms were used. The search strategy was adapted for each of the individual databases. The search was not limited by language. The reference lists of retrieved articles and of published reviews were also checked for relevant studies.

Criteria for the consideration of studies for this review

Studies had to fulfil the following criteria to be included in the review: (1) investigate how iron intake affect measures of cognitive development and function (2) provide iron from supplements, fortified foods or natural dietary sources (3) be randomised controlled trials with an adequate control (placebo or no intervention) (4) study infants, children or adolescents from birth to 18 years of age at the time of the intervention (5) include apparently healthy subjects.

Some studies included interventions with more than one micronutrient. When the effect of iron was not measured separately, the studies were not considered for review. Studies had to report baseline data for the measured outcomes to be included in the review. Studies on subjects with ID or IDA but otherwise healthy were included.

Selection of studies and data extraction

First, titles and abstracts were screened to exclude any reference clearly not meeting the review criteria. Two independent reviewers screened in duplication 10% of the references. Any discrepancies at the duplicate screening step were discussed before screening the rest of the references. The potentially relevant references were then located as full texts. Full texts were double assessed for inclusion criteria by two independent reviewers. Disagreements were settled through discussion. Only papers reporting studies meeting all inclusion criteria were included in the review. Data were then extracted into a standardised database, which included bibliographic details, methodological details, population characteristics, study groups details and outcome data. Data from 10% of the total papers were extracted in duplicate. Any disagreements were discussed to settle uniform data extraction.

Assessment of risk of bias in included studies

In order to assess the quality of the study and the risk of bias, the following indicators of internal validity were collected during data extraction. These indicators are specific to the RCT methodology:

(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) dietary intake data reported, (8) outcome comparability and reproducibility, and (9) similarity at baseline of most and least exposed groups. Based on these indicators, two independent reviewers decided on the overall risk of bias. Disagreements were resolved by discussion. The criteria for judging these indicators were adapted from the Cochrane Handbook [12].

RESULTS

Twelve studies were eligible and were included in the review. Table 1 shows the key characteristics of the included studies.

Infants, toddlers and pre-school children

Six studies on infants and preschool children were included. Five of them were conducted on infants and toddlers 6-24 months of age. A supplementation trial in 24 non anemic 6-months old Turkish infants using doses of 1mg/kg&d of ferrous sulphate during 3 months showed no significant change in developmental test scores. The study used the Bayley Scales of Infant Development (BSID): Mental Development Index (MDI) scores and Psychomotor Development Index (PDI) scores[37].

One study in Indonesia included anemic and non anemic infants up to 12 months of age. The infants were treated with ferrous sulphate 10 mg/d alone, ferrous sulphate combined with zinc sulphate, zinc alone or placebo during 6 months. This study, which included a sample size of 680 subjects, indicated a small but significant positive effect of iron supplementation on motor development with single iron supplementation as assessed by BSID (PDI score) in all infants and in all groups. No significant effect was seen on cognitive development or behaviour as assed by MDI score and Behavioural Rating Scale (BRS)[18].

A trial in Guatemala that provided short term iron supplementation for 1 week to 68 anemic and not anemic infants and children until 24 months of age found no benefit of the iron supplement when testing with the BSID. A dosage of ferrous ascorbate of 5 mg/kg was used [20].

A study by Idjradinata and Pollit in anemic and non anemic 12-18 months old children showed that iron treatment (3 mg/kg&day of ferrous sulphate) during four months significantly improved BSID results in iron-deficient children, even reaching the performance level of iron-sufficient children, unlike the group treated with placebo ($p<0.001$) [14].

Two more studies on anemic toddlers and young children in European setting (England and Greece) used outcome different to BSID scales: Aukett and Parks (1986) used 24 items from the Denver developmental screening test validated by the Bayley scale in children 17-19 months old. In this treatment trial in a group of 110 anemic toddlers, 31% achieved 6 or more new skills after treatment with iron (24 mg/day ferrous sulphate combined with vitamin C) during 2 months, vs. 12% in the placebo plus vitamin C treated group ($p<0.05$), assessed by Denver developmental screening test [2].

Simple reaction time, continuous performance task and oddity learning tasks were used by Metallinos-Katsaras et al. (2004). Anemic children 3-4 years old made significantly fewer errors of commission (14% higher specificity, $p<0.05$) and exhibited 8% higher accuracy ($p<0.05$) after two months of iron treatment (15 mg elemental iron daily, given as ferrous fumarate combined with multivitamins) than those given placebo (multivitamins without iron), suggesting improved discrimination and selective attention, although no effects were found on the oddity learning task. These positive effects of iron were not seen among the children with good iron status[23].

School children and adolescents

The six studies on school children and adolescents provided iron supplements in form of ferrous sulphate alone [16; 24; 27; 28; 5; 31]. Two studies included children and adolescents from 8 to 15 years of age[16; 27]; and one study included 13-18 years old adolescents[5]. Two studies were performed on females only[16; 5]

One study was conducted in the USA[5]. The rest were conducted in Asia: two in India [16; 27], three in Indonesia [29; 28; 30] and one in Thailand [26; 31]. The dosages of supplemented iron varied widely between the studies. Doses between 2 and 60 mg of elemental iron daily in form of ferrous sulphate were used in 5 studies (see Table 1). Bruner et al used markedly higher doses: 2x2 tablets of 325 mg (1300 mg in total) ferrous sulphate daily in adolescent girls, which is equivalent to 260 mg iron daily[5]. One of the studies conducted in Indonesia used a dose of iron according to the weight of the children, 2 mg/kg&day [28], whereas the other two Indonesian studies provided iron doses of 2 mg/d[29] and 50mg/d[30]. Pollit et al. increased the dose from 10 mg/d in the first two weeks, to 20 mg/d in the following 14 weeks[24]. The duration of the interventions ranged from 2 to 4 months. In two Indian studies, girls were treated 2x60 days in a school year[16; 27]. In most of the studies, children received the iron supplement daily during the intervention, except in the study by Sungthong et al. where children received 60 mg elemental iron 5 times per week (one group) or the same dose once a week [31]. One study [16] was performed in anemic children, one study in non anemic iron deficient (NAID) girls [5], one in apparently

healthy children [31] and six studies in both anemic and non anemic children [29; 27; 28; 30], two of them including a NAID group [24; 14].

Two studies conducted in India used the same tests for assessment of cognitive function in children 8-15 years old: Clerical Task test, Digit Span test, Mazes test and Visual Memory[16; 27]. Bruner et al. used Brief Test of Attention (BTA), Symbol Digit Modalities Test (SDMT), Visual Search and Attention Test (VSAT) and Hopkins Verbal Learning Test (HVLT)[5]. Soewondo applied Discrimination Learning (DL) task, Oddity Learning (OL), and Peabody Picture Vocabulary Test in children 4 to 5 years of age[30]. Soemantri measured educational achievement and tested concentration[29]. In three studies the authors measured the intelligence quotient (IQ) in children before and after iron intervention[24; 28; 31]. The large diversity of tests employed in the different studies hampered any quantitative comparison of results or meta-analysis.

In a study by Pollitt and co-workers, the IQ and scholastic achievement significantly increased in anemic and to a lesser degree in non anemic iron deficient children 9-11 years old, after 10 mg/d iron supplementation in the first 2 weeks and 20 mg/d in the following 14 weeks [24].

Sungthong et al. reported a significantly higher increase in IQ in 6-13 years old children treated with 60 mg iron once weekly for 16 weeks (6±12 points) or placebo (6±12 points) than in children treated with the same dose of 60 mg iron 5 days a week (3±12), while no difference in learning achievement was found among groups[31].

No statistically significant improvement in IQ was found in an Indonesian study on children who received 2 mg/kg&day iron for 3 months compared to the control group, but improved learning-achievement scores were detected in anemic children treated with iron [28]. Another Indonesian study by the same authors providing 2 mg/kg&day iron for 3 months detected a significantly better school achievement by non anemic children compared to anemic children that persisted after treatment independently of iron or placebo treatment[29].

Soewondo and colleagues reported statistically significant changes for iron-depleted children treated with 50 mg/day iron during two months compared to placebo group when applying the Peabody Picture Vocabulary Test. No significant changes were seen for iron-depleted and anemic children, whereas changes in the iron-replete group were significant. When Oddity Learning (OL) test was applied, the iron-replete children learned faster before treatment than did the anemic children (statistically significant for two out of four tasks). Iron treatment did not have the same effect on the iron replete and

anemic children. After treatment, the anemic children treated with iron obtained the best scores of all groups[30].

Sixty days of supplementation with 30 or 40 mg iron per day in 8-15 years old anemic boys induced a significant improvement of all cognitive functions comparing to placebo group ($p<0.05$), except for Mazes test in the 30 mg/d group. No difference between the iron and placebo group was found in non anemic boys[27]. Girls of the same age were treated for 2x60 days with 60 mg/d iron. Significantly better scores in Clerical Task test, Digit Span test and Mazes test were reported after 8 months in the iron vs. placebo treated group ($p<0.05$) of anemic girls, but not after 4 months [16]. Similar results were found by Seshadri and Gopaldas but they also reported improved Mazes test in non anemic girls, after supplementation with iron[27]. Higher doses of 260 mg/d iron, given to NAID adolescent girls for 8 weeks, lead to significantly better results in a test of verbal learning and memory when compared with girls in the placebo group ($p<0.02$) [5].

Quality of studies included

Table 3 summarizes the internal validity of the included studies, assessed as described in the section "Methods". The results show a high risk of bias in most of the studies. Only two studies[14; 18] had a low risk of bias, and two studies had a moderate risk of bias[5; 31]. The main reasons for having a high risk of bias were an unclear adequacy of sequence generation and/or allocation, and of funders. In most cases, insufficient information related to those criteria was given.

DISCUSSION

Evidence

This review of 14 RCTs has assessed the effects of iron supplementation on measures of cognitive development and function in infants, children and adolescents. The overwhelming feature of this review is the limited number of relevant studies that could be identified and included in the review.

Only one study identified provided iron supplements for a period of time shorter than two months[20]. Based on this single study, there is no evidence of a positive effect of supplementation for one week in the mental and psychomotor development of anemic infants and children with and without IDA of 6 to 24 months of age.

For children aged 1 to 5 years of age, there is some evidence from 3 RCTs that iron supplementation during 2 to 4 months may have a positive effect on the mental and psychomotor development of anemic children [2; 14; 23] .

Eight RCTs in anemic and non anemic children over 5 years of age provided evidence for a positive effect of iron supplementation on different measures of cognition [29; 16; 24; 27; 28; 30; 5; 31]. Due to the different parameters that were tested in the studies, it was very difficult to compare studies and to get a convincing conclusion.

Given the data base available, it is not possible to derive firm evidence-based conclusions on the effect of iron interventions on cognitive development and function in infants, children and adolescents. An important reason for this poor availability is that some of the trials originally had to be excluded because they did not have an adequate control group according to our criteria. Furthermore, the presence of other confounding variables, such as other nutritional deficiencies, low socioeconomic status, studies carried out in areas with endemic malaria etc. could markedly have influenced the obtained results.

Another remarkable feature of the collected studies is the heterogeneity of study populations, which made difficult to compare and combine the available results. The heterogeneity of outcome measures precluded pooling study results quantitatively. The assessment of validity showed that most studies had a high risk of bias.

Comparison with other systematic reviews

Unlike other systematic reviews on the topic, the present systematic review was not limited to supplementation studies. However, only supplementation trials complied with our inclusion criteria. Because we selected studies independently of the baseline iron status of participants, our systematic review covers trials on non anemic, iron deficient and anemic iron deficient subjects.

Effect of iron in non anemic subjects

A recent review with meta-analysis by Szajewska et al. (2010) has analysed the effects of iron supplementation on non anemic infants and young children on the mental performance and psychomotor development of children (<3 years)[32]. The five included RCTs did not individually show a beneficial effect of iron supplementation on the MDI of the Bayley Scales of at different ages throughout the first 18 months. Three of five RCTs showed a beneficial effect of iron supplementation on the PDI at some time points, whereas two did not. The authors performed 2 meta-analyses of 3 RCTs involving 561 infants and children. It was concluded that iron supplementation in infants may have positively influenced children's psychomotor development, whereas it did not seem to alter their mental development or behaviour. Only two of the five RCTs on non anemic infants included in this review were included in our review[36; 18]. The other three were found in our search but they were

excluded because of lack of baseline data for the outcomes reported or because the exact quantity of iron supplied was not reported. Our review did not include further RCTs on non anemic infants and young children.

Effect of iron in anemic and non anemic subjects

In 2005, Sachdev and collaborators published a systematic review with a meta-analysis examining the effects of iron supplementation in relation to development in children [25]. The review included 17 trials of oral iron supplementation, fortified milks and cereal, and parenteral iron (all RCTs) involving 3646 participants. The authors concluded that iron supplementation had modest but significant beneficial effects on mental development for children who were anemic or iron deficient at baseline and for all children >7 years old, particularly for IQ scores. In younger children (aged <27 months), no effect of iron supplementation on mental development was detected. Motor development was not found to be improved through iron supplementation. Out of the 17 trials included in Sachdev's review, six were also included in our review. The rest were identified in the search by then excluded because: dose was not reported (one study), study was not randomised (two studies), no abstract available (one study), absence of control group (one study), and end values for outcomes not reported (one study).

A review by Iannotti et al. on the benefits and risks of iron supplementation of infants and children under 5 years of age in developing countries, published in 2006, concluded that providing additional iron via daily or weekly supplementation to preschool iron-deficient children may have had some positive effects on developmental indicators, especially among children who were anemic or iron deficient at baseline [13].Eight studies were included in this review for the outcome "development". Four of them were included in our review. The rest were either not found in our search (one study), results were reported in a way we could not compare groups in a good way (one study), the necessary values were not reported (one study), or there was no control group for the outcome of interest (one study).

A Cochrane review published in 2001 by Logan et al aimed to assess the effects of iron supplementation on iron deficient infants and children under 3 years of age, beginning supplementation before 1 year of age, on measures of psychomotor development or cognitive function [19]. Seven RCTs providing oral or intramuscular iron were included in this review, 5 of which assessed psychomotor development between 5 and 11 days of commencement of therapy. It was concluded that there was no convincing evidence that administration of iron improved scores on tests of psychomotor development within 6-11 days of treatment. The effect of longer interventions unfortunately remained unclear from the results of the other 2 studies where the assessment was done more than 30 days after

commencement of therapy. Three studies included in this review were also included in our review. From those not included in our review, one was not found by our search, one was an unpublished study, one was excluded by us because the relevant values were not reported, one was group-randomised, and another one did not have an adequate control group for the outcomes of interest.

Falkingham et al. recently published a systematic review assessing the effects of iron supplementation on cognition in older children (>6 years) and adults [7]. They included 14 RCTs and concluded that iron supplementation improved attention and concentration in all studies irrespective of baseline iron status. In anemic groups of children supplementation improved IQ but had no effect on non anemic participants. No effect of iron supplementation was found on memory, psychomotor skills or scholastic achievement. However, the authors emphasised the limited number of included studies, which were generally conducted in small samples of subjects, had a short duration and were methodologically weak. 10 of the studies included in Falkingham's review were performed on children 6 to 18 years old. Five of them were not included in our review because of several reasons: 1) Two of the studies were not found in our search. They were probably retrieved from the database PsychINFO, which we did not search. 2) No abstract available (one study) 3) lead exposed population (one study) 4) no baseline data reported (one study).

Strengthens and weakness of this review

In school children and adolescents, 4 out of 10 studies on cognitive function included in this review had a supplementation period shorter than 12 weeks of supplementation (Table 1), which is considered sufficient to alter the iron status. Some of the included studies lasted less than twelve weeks, and this could have possibly negated the effects of iron supplementation. However, these studies showed similar effects on cognition compared to studies with longer supplementation periods. Additionally, a 3-month long study [28] showed no effects of supplementation on IQ in anemic (and non anemic) children, which the authors explained by several factors such as mucosal block or other unidentified causes that were not detected during the study (e.g. genetic factors that control absorption). Although a much longer duration of intervention is probably needed for outcomes such as scholastic achievement, where iron status at learning may be different from iron status at assessment of performance [7], they found improved learning results after iron supplementation.

An important weakness of this review is the high risk of bias of most of the included papers. The sequence generation and/or allocation were not well addressed or not clearly reported in most papers.

The same was found for the study funders in 4 studies on cognition (Table 3). Only 2 studies were assessed as having a low risk of bias.

Development is often evaluated in a similar way in infants and young children (e.g. Bayley test). In older children, different tests were used to assess developmental outcome. Thus, comparison between studies was more difficult. In addition, different iron status at baseline (anemic, non anemic and non anemic iron deficient subjects), and different socioeconomic status of the participants make the assessment of the effects of iron interventions on cognitive functions difficult. The effects of iron might be different depending on the baseline iron status. Many of the studies included in this review had mixed populations of very different iron status.

Recommendations for practice and research

Until more convincing evidence exist that iron supplementation can significantly improve measures of cognitive function and development in infants, children and adolescents, policy should focus on prevention of iron deficiency anemia.

Randomised controlled trials in infants, children and adolescents should be conducted in a way that facilitates comparison with other studies and metaanalysis. Reporting studies in a standardised way would also contribute to a more evidence based nutrition.

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on the search strategy draft for adaptation, conducted the first screening step for 40% of the references found after search and the 10% quality control, sorted references according to population groups, assessed all full-papers (studies on infants until 12 months) according to inclusion and exclusion criteria, extracted data in the database, performed assessment of validity, and drafted the paper. V.V. assessed all full-papers (studies on children and adolescents) according to inclusion and exclusion criteria, extracted data in the database (children and adolescents), performed assessment of validity, contributed to the draft paper with all data from the children and adolescent population, and commented on following drafts. C.V. assessed all full-papers (infants) according to inclusion and exclusion criteria as second reviewer, extracted data in the database (infants), performed assessment of validity as second reviewer and commented on all drafts of the paper. A.A. extracted data in the database (children and adolescents), and performed assessment of validity as second reviewer. B.R.-V. assessed 10% of full-papers (children and adolescents) according to inclusion and exclusion criteria as second reviewer and commented on all drafts. I. I.-A. commented on all drafts. M.G. directed and supervised the work (children and adolescents) and commented on all drafts of the paper. B.K. directed and supervised the work (infants) and commented on all drafts. The authors have declared no conflict of interest.

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482 Table 1: Summary of included trials assessing cognitive development and function in infants, toddlers and pre-

483 school children: main characteristics and results

Author,year of publication, country	**Population characteristics (number of subjects, age)**	**Intervention (iron dose, number of subjects in each group)**	**Control**	**Duration of intervention (weeks of months)**	**Outcomes**	**Main results**
Lind et al. 2004 [18] Indonesia	n = 680 Anemic and non anemic infants 6 mo of age	Ferrous sulphate 10 mg/d n = 167/170 Ferrous sulphate 10 mg/d + Zinc sulphate 10 mg/d n = 160/170 Zinc sulphate n = 161/170	Placebo n = 162/170	6 mo	BSID (MDI, PDI and BRS) Assessed at 12 mo of age	Single supplementation with iron significantly improved psychomotor development Combined supplementation had no significant effect on development.
Yalcin et al. 2000 [36] Turkey	n = 24 Non anemic infants 6 mo of age	Ferrous sulphate 1mg/kg&d n = 7/11	Placebo n = 9/13	3 mo	BSID (MDI, PDI) Assessed at 9 mo of age	Iron supplementation did not change developmental test scores.
Lozoff et al. 1982 [20] Guatemala	n = 68 Mild anemic and non anemic infants 6 - 24 mo of age	Ferrous ascorbate 5 mg/kg&d 1. Anemic n = 12/15 2. Non anemic, n = 17/19	Placebo 1. Anemic n = 12/13, 2. Non anemic n = 18/21	1 w	BSID (MDI, PDI) Assessed 1 week after start of treatment	Developmental deficits in anemic group prior to treatment. Lack of rapid improvement with short term oral iron therapy. Scores improved in all groups, but iron treated anemia group did not increase more than placebo treated, anemic, or non anemic (treated or not) groups
Idjradinata and Pollitt, 1993 [14] Indonesia	n = 126 Anemic and non anemic infants/children 12-18 mo of age	Ferrous sulphate, 3 mg/d 1. IDA n = 24/25 2. Non anemic ID n = 29/29 3. Iron sufficient n = 22/24	Placebo 1. IDA n = 23/25 2. Non anemic ID n = 14/15 3. Iron sufficient n = 22/23	4 mo	BSID (MDI, PDI) Assessed 4 mo after start of treatment	The poor performance of 12-18 month-old iron deficient anaemic infants in the Bayley scales prior to the treatment. 4 mo treatment with FeSO4 improved performance to the level of performance of iron-sufficient infants
Aukett and Parks, 1986 [2] UK	n = 110 Anemic children 17-19 mo of age	Ferrous sulphate 24 mg/d + Vitamin C 10 mg/d n = 48/54	Vitamin C 10 mg/d + placebo n = 49/56	2 mo	Denver developmental screening test (24 items)	More of the children who received the iron achieved the expected rate of development as compared to those not receiving iron.

Author,year of publication, country	Population characteristics (number of subjects, age)	Intervention (iron dose, number of subjects in each group)	Control	Duration of intervention (weeks of months)	Outcomes	Main results
Metallinos-Katsaras et al. 2004 [23] Greece	n = 123 Anemic and non anemic children 3-4 y of age	Ferrous fumarate + multivitamins 15 mg Fe/d n = 27/27	Multivitamins n = 17/17	2 mo	Simple reaction time, continuous performance task, oddity learning task (ODL1), ODL2, ODL3	Iron supplementation of iron-deficient anemic preschoolers improved cognitive function, specifically discrimination and selective attention

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486 Table 2: Summary of included trials assessing cognitive development and function in school children and

487 adolescents: main characteristics and results

Author,year of publication, country	**Population characteristics (number of subjects, age)**	**Intervention (iron dose, number of subjects in each group)**	**Control**	**Duration of intervention (weeks of months)**	**Outcomes**	**Main results**
Soewondo et al 1989 [30] Indonesia	n = 139 Iron-replete, Iron-depleted, and IDA and anemic children 4-5 y of age	Ferrous sulphate 50 mg/d n = ?/77	Placebo n = ?/99	2 mo	Discrimination Learning (DL): Picture tasks and Color-form figures task Oddity learning (OL): 3 tasks Peabody Picture Vocabulary Test	Peabody Picture Vocabulary Test : Changes for iron-depleted children treated with iron were statistically significant compared to placebo group. Changes for iron-depleted and anemic children that received placebo were not significant. Changes in the iron-replete group that received either iron or placebo were significant Oddity learning: The iron-replete children learned faster before treatment than did the anemic children (statistically significant for two out of four tasks). Iron treatment did not have the same effect on the iron replete and anemic children. After treatment, the anemic children treated with iron obtained the best scores of all groups
Soemantri et al 1985 [29] Indonesia	n = 119 Non anemic (n = 41) and anemic (n= 78) children 6-11 y of age	Ferrous sulphate 2 mg/d n = ?/59	Placebo n = ?/60	3 mo	Educational achievement test Concentration test	In school achievement test, nonanemic children performed significantly better than the anemic children. No significant differences were found between children assigned to iron and placebo treatment. Post treatment evaluation indicated that the difference between iron-treated anemic and nonanemic children was still significantly different
Sungthong et al. 2004 [31] Thailand	n = 397 Apparently healthy children 6-13 y of age	Ferrous sulphate 60 mg/d 1. group: 5 days/week n = 139/140 2. group once/week n = 130/134	Placebo n = 122/123	4 mo	IQ, Thai language, Mathematika	Weekly iron supplementation increased IQ better than daily supplementation
Seshadri et al. 1989 [27] India	n = 178 Anemic and non anemic children 8-15 y of age	Ferrous sulphate 1.Boys 30 mg/d n = 16/16 2.Boys 40 mg/d n = 16/16 3.Girls 60 mg/d n = 65/65	1.Placebo boys n = 16/16 2.Placebo girls n = 65/65	2 mo	Clerical Task, Digit Span Maze test, Visual Memory	In both supplemented group of anemic boys 69% improved cognitive function, except for mazes in 30 mg Fe group. No difference in placebo and iron group. In anemic girls Clerical test, mazes and overall test were better in iron treated than in placebo. In nonanemic girls mazes was better in iron treated than in placebo group
Kashyap et al. 1987 [16] India	n = 207 Anemic school girls 8-15 y of age	Ferrous sulphate 60 mg/d n = 65/83	Placebo n = 65/83	4 mo	Clerical Task, Digit Span Maze test, Visual Memory	Prophylactic supplementation of 60 mg elemental iron for 60 days at a stretch, twice in a school year, improved concentration, discrimination, perception and visual motor coordination

Author,year of publication, country	Population characteristics (number of subjects, age)	Intervention (iron dose, number of subjects in each group)	Control	Duration of intervention (weeks of months)	Outcomes	Main results
Pollitt et al. 1989 [24] Thailand	n = 1389 Anemic, and non anemic children with ID 9-11 y of age	Ferrous sulphate 50mg Fe/d for 2 w and 100mg Fe/d for 14w No numbers per group	Placebo No numbers per group	4 mo	IQ, Thai language, Mathematika	Positive association between iron status and IQ and language school achievement test. No support for the internal validity of the hypothesis that this association is causal
Soemantri et al. 1989 [28] Indonesia	n = 130 Anemic and non anemic children from primary school 10 y of age	Ferrous sulphate 2mg kg&d 1. Anemic n = 34/34 2. Non anemic n = 37/37	Placebo n = 59/59 1. Anemic n = 24/24 2. Non anemic n = 35/35	3 mo	IQ, language scores, math scores, biology scores, social science scores	Iron supplementation for 3 mo improved learning-achievement scores but not IQ in anemic children
Bruner et al. 1996 [5] USA	n = 81 Non-anemic iron deficient adolescents 13-18 y of age	Ferrous sulphate 260 mg/d n = 37/39	Placebo n = 36/39	2 mo	BTA-auditory SDMT-visual VSAT HVLT	Girls who received iron performed better on a test of verbal learning and memory than girls in the control group

493 Table 3: Assessment of validity of included RCTs on effects of iron supply

Study (Author, year)	Adequate sequence generation	Allocation concealment adequate	Blinding adequate	Dropouts adequate and outcome data complete	Funder adequate	Lack of other potential threats to validity	Overall risk of bias
Aukett and Parks 1986 [2]	Unclear	Yes	Yes	Yes	Unclear	Yes	**High**
Bruner et al. 1996 [5]	Yes	Yes	Yes	Yes	No	Yes	**Moderate**
Idjradinata and Pollitt 1993 [14]	Yes	Yes	Yes	Yes	Yes	Yes	**Low**
Kashyap et al. 1987 [16]	Unclear	Unclear	Unclear	No	Yes	Yes	**High**
Lind et al. 2004 [18]	Yes	Yes	Yes	Yes	Yes	Unclear	**Low**
Lozoff et al. 1982 [20]	Unclear	Unclear	Yes	Yes	Yes	Unclear	**High**
Metallinos-Katsaras et al. 2004 [23]	Unclear	Yes	Yes	Yes	No	Yes	**High**
Pollitt et al. 1989 [24]	Unclear	Unclear	Yes	Unclear	Yes	Yes	**High**
Seshadri et al. 1989 [28]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	**High**
Soemantri et al. 1985 [29]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	**High**
Soemantri et al. 1989 [28]	Unclear	Unclear	Yes	Yes	Yes	Yes	**High**
Soewondo et al.1989 [30]	Unclear	Unclear	Yes	Unclear	Yes	Yes	**High**
Sungthong et al. 2004 [31]	Yes	Unclear	Yes	Yes	Yes	Yes	**Moderate**
Yalcin et al. 2000 [36]	Unclear	Unclear	No	Yes	Unclear	Unclear	**High**

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